Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, April 4, 2024 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333.

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	A. Gibler (OHA)
	E. Legislative update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Vascular Endothelial Growth Factor Class Update and New Drug Evaluation	
	B. Insulins Literature Scan	
	C. PDL OLD BUSINESS: Inhalers for Asthma and COPD Class Update	
	D. Oncology Prior Authorization Updates	
	1. Public Comment	

III. DUR NEW BUSINESS

1:25 PM	A. Orphan Drug Policy Updates	S. Servid (OSU)
	1. Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
1:30 PM	B. Tepezza® (Teprotumumab) Prior Authorization Update	S. Fletcher (OSU)
	1. Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

IV. PREFERRED DRUG LIST NEW BUSINESS

1:40 PM	C. Drugs for Weight Loss DERP Summary and GLP-1 Receptor Agonists Literature Scan	
	1. Weight Loss Coverage State Plan Overview	D. Weston (OHA)
	2. GLP-1 Receptor Agonists Literature Scan	K. Sentena (OSU)

3. Weight Loss DERP Summary/Prior Authorization Criteria
4. Public Comment
5. Discussion and Clinical Recommendations to OHA

2:20 PM D. Drugs for Bowel Prep Class Review — D. Moretz (OSU)
1. Class Review
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

2:35 PM E. Antivirals for SARS-CoV2 Class Review — D. Moretz (OSU)
1. Class Review
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

2:55 PM BREAK

3:10 PM F. Syfovre® (pegcetacoplan) and Izervay™ (avacincaptad pegol) New Drug Evaluations — D. Engen (OSU)
1. New Drug Evaluations/Prior Authorization Criteria
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

3:30 PM G. Phosphorus Binder Class Update and New Drug Evaluation — D. Moretz (OSU)
1. Class Update/Prior Authorization Criteria
2. Xphozah® (tenapanor) New Drug Evaluation
3. Public Comment
4. Discussion and Clinical Recommendations to OHA

3:50 PM V. EXECUTIVE SESSION

4:50 PM VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2024
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2024
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2024
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2025
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2025
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2025
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2026
Bridget Bradley, PharmD, BCPP	Pharmacist	OHSU Clinical Pharmacist	Beaverton	December 2026
Vacant	Physician			December 2026
Vacant	Public			December 2026

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, February 1st, 2024
1:05 PM - 4:45 PM
Via Zoom webinar

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence, and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee, and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333

Members Present: Stacy Ramirez, PharmD; Patrick DeMartino, MD; Bridget Bradley, PharmD; Douglas Carr, MD; Tim Langford, PharmD; Eriko Onishi, MD; Eddie Saito, PharmD; **Ad-Hoc: Erika Finanger, MD**

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Megan Herink, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Lan Starkweather, PharmD; Kendal Pucik, PharmD Candidate 2024; Brandon Wells; Trevor Douglass, DC; Jennifer Bowen; Kyle Hamilton

Audience: Craig Sexton*, GSK; Nirmal Ghuman*, J&J; Tao Wang*, Climate Works; Brian Denger *, Parent Project Muscular Dystrophy; Adam Gold*, NS Pharma; Armen Khachatourian*, Sarepta; Mark Kantor, AllCare Health; Robin Wells, NS Pharma; Suzanne Morgan, NS Pharma; Melissa Abbott, Eisai; Lori McDermott, Viking HCS; Mike Donabedian, Sarepta; Jim Cromwell, Sarepta; Shirley Kim, Sarepta; Leslie Zanetti, Sarepta; Mindy Cameron; Chris VanWynen, Sarepta; Leif Bruce, Novo Nordisk; Gary Parenteau, Dexcom; Brielle Dozier, Artia Solutions; Tracy Copeland, Sarepta; Brandie Ferger, Advanced Health; Yesina Camacho, PharmD Candidate w/ Umpqua Health; Saghi Maleki, Takeda; Lisa Pulver, J&J; Chris Ferrin, IHN; Leanne Yantis, AllCare; Robert Pearce, Karuna; Uche Mordi, Karuna; Cheryl Bondy, Sobi; Emily Cooper; Alexandria Jarvais, Sobi; Matt Worthy, OHSU; Tiina Andrews, UHA; Mark England, Mercer; Daria Meleshkina, Moda/EOCCO; Samyukta Vendrachi; Long Nguyen; Philip Santa Maria; Bryan Armstrong, CareOregon; Melissa Bailey Hall; Susan Lakey Kevo; Melissa Snider, Gilead; Michele Sabados, Alkermes; Paul Thompson, Alkermes; Shauna Wick, Trillium; Jeff White, Sumitomo; Amy Aikins, Little Hercules Foundation; Richie Kahn, Canary Advisors; Kate Ogden

(*) Provided verbal testimony

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I. CALL TO ORDER

A. Roll Call & Introductions
- Called to order at approx. 1:05 p.m., introductions by Committee and staff

B. Conflict of Interest Declaration – no new conflicts of interest were declared

C. Election of Chair and Vice Chair
Dr. Ramirez volunteered to serve as Chair and Dr. DeMartino as Vice-Chair
ACTION: Motion to approve, 2nd, all in favor

D. Approval of Agenda and December 2023 Minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd, all in favor with one abstention

E. Department Update provided by Andrew Gibler, PharmD

F. Legislative Update provided by Trevor Douglass, DC, MPH

II. CONSENT AGENDA TOPICS

A. **Preferred Drug List (PDL): Insulin Literature Scan -** Deferred to April P&T Meeting

B. **P&T Evidence Methods**

C. **P&T Operating Procedures**

D. **Oncology Prior Authorization (PA) Updates**
Recommendation:
- Add: Akeega ™ (abiraterone acetate/niraparib tosylate); Truqap™ (capivasertib); Xalkori® (crizotinib); Fruzaqla™ (fruquintinib); Hepzato Kit™ (Melphalan HCl/hepatic delivery kit (HDS)); Ogsiveo™ (nirogacestat hydrobromide); Augtyro™ (repotrectinib); and Loqtorzi™ (toripalimab-tpzi) to Table 1 in the Oncology Agents PA criteria

E. **Orphan Drug Policy Updates**
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Reblozyl ® (luspatercept-aamt); and Bylvay™ (odevixibat) based on FDA-approved label
ACTION: Motion to approve, 2nd, all in favor

III. DUR ACTIVITIES

A. **Quarterly Utilization Report:** Roger Citron, RPh

B. **ProDUR Report**: Lan Starkweather, PharmD

C. **RetroDUR Report**: Dave Engen, PharmD

D. **Oregon State Drug Review**: Kathy Sentena, PharmD
1. **An Update in Weight Loss Therapies-Including FDA Approved GLP-1 Receptor Agonists**
2. **Prevention of Respiratory Syncytial Virus (RSV) Infection: New Products and Recommendations**

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IV. DUR OLD BUSINESS

A. Spravato® (esketamine) PA Update: Sarah Servid, PharmD
Recommendation:
- Update the safety edit for esketamine to include outpatient initiation for people with suicidal ideation who have optimized first-line alternative treatments for depression
Public Comment: Nirmal Ghuman, J&J
ACTION: The Committee recommended ensuring the approved doses match the FDA approved labeling for each indication
Motion to approve, 2nd, all in favor

V. DUR NEW BUSINESS

A. Antipsychotics in Children Policy Evaluation: Sarah Servid, PharmD
Recommendation:
- Update the Antipsychotics in Children safety edit to include assessment of rapid weight gain for members without glucose monitoring, consider allowing longer initial therapy before PA is required, and apply the policy to members who are three to six years of age
ACTION: The Committee recommended allowing up to 60 days initial therapy before PA is required and to explore options to notify providers about the policy before members have a denied claim
Motion to approve, 2nd, all in favor

B. Melatonin Policy Evaluation:
Kendal Pucik, PharmD Candidate 2024 and Megan Herink, PharmD
Recommendations:
- No policy changes recommended based on the policy evaluation
ACTION: Motion to approve, 2nd, all in favor

VI. PREFERRED DRUG LIST (PDL) NEW BUSINESS

A. Lantidra™ (donislecel) New Drug Evaluation: Kathy Sentena, PharmD
Recommendations:
- Implement the proposed PA for donislecel to ensure that it is used in patients in which the benefits outweigh the risks of transplant
ACTION: Motion to approve, 2nd, all in favor

B. Maintenance Inhalers for Asthma/COPD: Deanna Moretz, PharmD

Recommendations:

- Designate at least one long-acting muscarinic antagonist-long-acting beta agonist (LAMA-LABA) combination agent preferred on the PMPDP PDL changes recommended based on the review of recently published evidence
- Remove PA requirements for preferred LAMA-LABA and preferred long-acting muscarinic antagonistlong-acting beta agonist-inhaled corticosteroid (LAMA-LABA-ICS) combination products
- Maintain Airsupra™ (albuterol-budesonide) and Symbicort® Aerosphere™ (budesonide 160 mcg-formoterol 4.8 mcg) as non-preferred inhalers on the PMPDP
- Evaluate costs in executive session

Public Comment: Craig Sexton, GSK

ACTION: Motion to approve, 2nd, all in favor

C. Duchenne Muscular Dystrophy DERP Report and NDE: Sarah Servid, PharmD

Recommendations:

- Implement the proposed PA criteria for delandistrogene moxeparvovec (Elevidys™) to limit use to the FDA-approved indication
- Based on the review of recently published evidence no PDL changes to the preferred corticosteroids were recommended
- Update the DMD PA criteria to apply to all non-preferred corticosteroids for DMD
- Evaluate costs in executive session

Public Comment: Tao Wang, parent; Brian Denger, Parent Project Muscular Dystrophy; Adam Gold, NS Pharma; Armen Khachatourian, Sarepta

ACTION: The Committee modified the proposed PA criteria to require prescribing by a neuromuscular specialist and to require documentation of informed consent for members with deletions of exons 1-17 or 59-71

Motion to approve, 2nd, all in favor with one abstention

D. Antivirals for SARS-CoV2 Class Review: Deferred to April P&T Meeting

VII. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Patrick DeMartino, MD; Bridget Bradley, PharmD; Douglas Carr, MD; Eriko Onishi, MD; Eddie Saito, PharmD; **Ad-Hoc: Erika Finanger, MD**

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VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Maintenance Inhalers for Asthma/COPD
Recommendation: Make Arnuity™ Ellipta® (fluticasone furoate) preferred
ACTION: Motion to approve, 2nd, all in favor

B. Duchenne Muscular Dystrophy (DMD)
Recommendations: Designate all targeted DMD therapies as non-preferred and make Emflaza® (deflazacort) and Agamree® (vamorolone) non-preferred
ACTION: Motion to approve, 2nd, all in favor with one abstention

IX. ADJOURN

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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Drug Class Update with New Drug Evaluation: Vascular Endothelial Growth Factor (VEGF) Inhibitors

Date of Review: April 2024

Date of Last Review: August 2020
Dates of Literature Search: 01/01/2020 - 02/01/2024
Brand Name (Manufacturer): Vabysmo (Genentech, Inc)
Dossier Received: yes

Generic Name: faricimab-svoa

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose for this class update is to evaluate new comparative evidence for vascular endothelial growth factor (VEGF) inhibitors and place in therapy for faricimab which was approved by the Food and Drug Administration (FDA) in 2022.

Plain Language Summary:

- VEGF is a protein produced by cells in the body that helps create new blood vessels. When cells produce too much VEGF, abnormal blood vessels can grow in the eye. These new blood vessels cause fluid accumulation (called macular edema) and damage to the retina of the eye leading to reduced vision and blindness.
- VEGF inhibitors are medicines injected into the eye that slow growth of blood vessels. VEGF inhibitors improve vision when macular edema or growth of new blood vessels is related to:
    - advanced age (called age-related macular degeneration)
    - diabetes or high blood sugar levels (called diabetic macular edema or diabetic retinopathy)
    - blocked blood vessels in the eye (called retinal vein occlusion)
    - changes in the shape of the eye (called myopic choroidal neovascularization)
    - premature birth in very small infants (called retinopathy of prematurity)
- There is no evidence that one specific VEGF inhibitor improves vision better than another. Studies usually evaluate vision over 1-2 years, but some have studied VEGF inhibitors up to 4 years.
- OHP will pay for VEGF inhibitors when prescribed and injected by a healthcare professional. We do not recommend any changes to the current policy.

Research Questions:
1. What is the comparative efficacy or effectiveness of VEGF inhibitors in people with macular edema related to ocular conditions?
2. What is the comparative safety of VEGF inhibitors in people with ocular conditions?

Author: Sarah Servid, PharmD

3. Is there evidence to show that individual VEGF inhibitors are more effective or safe in certain populations of people (based on diagnoses, disease characteristics, or baseline visual acuity)?

Conclusions:

- Updated systematic reviews in neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) continue to demonstrate no clinical differences in best corrected visual acuity (BCVA) between VEGF inhibitors after 1 to 2 years.[1,2] Certainty in evidence ranged from moderate to low quality depending on the comparison and population.
- Faricimab is a new VEGF inhibitor approved in neovascular AMD, DME, and macular edema due to retinal vein occlusion. Faricimab was non-inferior to aflibercept for changes in BCVA based on results of 2 trials in each condition (moderate certainty evidence for retinal vein occlusion and low certainty evidence for AMD and DME). All trials evaluated efficacy within 1 year; and long-term data evaluating durability of response is currently lacking. Data was supported by phase 2 dose-finding studies evaluating faricimab to ranibizumab, which generally showed no difference in BCVA between therapies (insufficient evidence).
- Aflibercept was approved by the Food and Drug Administration (FDA) for retinopathy of prematurity (ROP) based on 2 open-label, non-inferiority RCTs comparing aflibercept to laser photocoagulation therapy.[3] Laser photocoagulation to cauterize and destroy abnormal blood vessels is one of the currently available treatment strategies in infants with retinopathy of prematurity and is preferred over cryotherapy because of better visual outcomes.[4] Compared to laser photocoagulation therapy, there was no difference in the proportion of infants without active retinopathy of prematurity at 1 year in either study (79.6% vs. 77.8%; mean difference [MD] 1.81% [95% confidence interval [CI] -15.7 to 19.3] and 78.7% vs. 81.6%; MD -1.88% [95% CI -17.0 to 13.2]; low certainty evidence).[3] However, confidence intervals were wide, and the analysis failed to meet pre-established criteria for non-inferiority of aflibercept (pre-specified as a difference of 5%). Neither trial demonstrated that aflibercept was superior or inferior to laser photocoagulation therapy.
- New formulations approved by the FDA include a ranibizumab port delivery system with administration every 6 months,[5] high-dose (8 mg) aflibercept administered every 8 to 16 weeks,[6] and 2 biosimilars of ranibizumab.[7,8]
- Evidence for safety outcomes related to use of VEGF inhibitors (including all-cause mortality, arterial thromboembolic events, and serious ocular events) was graded as low certainty. For people with DME, there was no difference in all-cause mortality or thromboembolic events compared to control therapies, but clinically relevant increases in safety outcomes could not be ruled out.[2] Evidence was limited by inconsistency and imprecision. In people with AMD, serious events and mortality was rare with no differences between VEGF inhibitors (low to very low certainty evidence).[1]
- FDA labeling for brolucizumab was updated to include risk for retinal vasculitis and retinal vascular occlusion.[9] Because of this risk, brolucizumab should not be administered more frequently than every 8 weeks.[9] Events appear to be immune mediated and correlate with increased intraocular inflammation. Compared to aflibercept, patients treated with brolucizumab every 8 to 12 weeks had a higher rate of intraocular inflammation (4% vs. 1%).[9] Trials evaluating every 4-week dosing of brolucizumab were discontinued early due to increased incidence of these serious adverse events.[10] Compared to aflibercept, patients with neovascular AMD treated with brolucizumab every 4 weeks had higher rates of inflammation (9.3% vs. 4.5%), retinal vasculitis (0.8% vs. 0%), and retinal occlusion (2% vs. 0%), and all-cause mortality (n=6, 1.7% vs. 0%).[10]

Recommendations:

- No PDL recommendations based on clinical evidence. Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Current evidence indicates that there is no clinically meaningful difference in BCVA between ranibizumab, bevacizumab, or aflibercept in patients treated for DME, neovascular AMD, or macular edema associated with retinal vein occlusion based on moderate to high quality evidence. There is moderate quality evidence that brolucizumab is non-inferior to aflibercept at 48 weeks based on BCVA in patients with neovascular AMD with limited long-term evidence beyond 2 years.
- There is low quality evidence of no difference in visual acuity between ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularization.
- There is no difference in serious ocular events between ranibizumab, bevacizumab or aflibercept (low quality evidence). Evidence regarding comparative risk of thrombotic events and serious adverse effects with anti-VEGF agents is mixed, though higher quality observational studies and systematic reviews of RCTs failed to demonstrate any difference in cardiovascular events between agents. Overall, differences in rate of cardiovascular events or mortality between agents is likely small (moderate quality evidence).
- Bevacizumab is the current preferred product. All other VEGF inhibitors are non-preferred. The majority of claims are billed via medical claims and administered in a provider setting.

Background:

Vascular endothelial growth factor (VEGF) inhibitors are indicated for a wide variety of ocular conditions. FDA-approved indications differ between agents, but commonly include macular edema associated with diabetic retinopathy or retinal vein occlusion, neovascular AMD, and myopic choroidal neovascularization. In these diseases, vascular damage can trigger inflammatory responses, expression of VEGF, and formation of new blood vessels in the choroid layer of the eye located between the retina and sclera.[11,12] Accompanying features of choroidal neovascularization include sub-retinal exudation and hemorrhage, lipid deposits, retinal pigment epithelium detachment, and fibrotic scarring which cause progressive vision impairment and blindness.[11,12] Intraocular injections of VEGF inhibitors work to prevent vascular endothelial growth factor expression in late stage disease, thereby preventing further choroidal neovascularization and preserving vision in these populations.[11,12]

These ocular conditions are often categorized according to the type of retinal abnormalities present including presence or absence of neovascularization or macular edema. Macular edema is usually evaluated via optical coherence tomography. A larger central subfield thickness upon optical coherence tomography represents presence of macular edema and decreases in the central subfield thickness have been correlated with improvements in macular edema.

With presence of neovascularization or macular edema, VEGF inhibitors are typically indicated as a first-line treatment option. Guidelines from the American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first-line therapy for macular edema associated with branched or central retinal vein occlusion, neovascular AMD, and clinically significant DME associated with vision loss.[13] No recommendations are made for any specific agent. Similar guidelines are available from National Institute for Health and Care Excellence (NICE) which recommend VEGF inhibitors as first-line therapy for neovascular AMD, myopic choroidal neovascularization, and macular edema due to retinal vein occlusion or diabetes.[14-17] Alternative treatment options vary by condition and disease characteristics, but can include intraocular steroids, laser photocoagulation, and panretinal photocoagulation. In patients with other associated complications of diabetic retinopathy, these non-pharmacological options may be preferred or used in combination with VEGF inhibitors.[12,18] For example, panretinal photocoagulation is a laser treatment usually recommended for people with proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy to slow growth of new blood vessels.[12]

Recently, VEGF inhibitors have also been studied for treatment of retinopathy of prematurity (ROP). In premature infants, birth interrupts the normal development of vasculature in the eye.[4] As a result, VEGF is upregulated which can result in growth of new blood vessels, macular edema, and damage to the

eye.[4] Retinopathy of prematurity is most common in infants born at less than or equal to 30 weeks gestational age, infants with very low birth weight (<1500 g or about 3.3 lbs), or infants who need supplemental oxygen.[4] Disease is categorized based on location (zone 1 to 3 from the central to peripheral retina), pathologic changes (stage 0 to 5 with higher numbers indicating worsening involvement), and presence of abnormal (e.g., dilated or twisted) blood vessels in the posterior pole of the eye in at least 2 quadrants (plus [+] disease).[4] In about 90% of infants, retinopathy of prematurity is classified as mild disease which does not require treatment.[4] Prompt ablative treatment (usually laser photocoagulation within 72 hours) to destroy abnormal blood vessels is recommended by the American Academy of Pediatrics for the following groups:[4]

- Zone 1: stage 0-5+ disease
- Zone 1: stage 3 disease
- Zone 2: stage 2+ or 3+ disease

VEGF inhibitors used most commonly in practice in the United States (US) include bevacizumab, ranibizumab and aflibercept. Newer agents include brolucizumab and faricimab which were FDA approved in 2019 and 2022, respectively. See **Table 1** for a list of common ocular indications. While bevacizumab is not FDA-approved for any ophthalmic indications, there is a substantial body of evidence supporting off-label use.

Table 1. FDA-approved and compendia-supported ophthalmic indications for VEGF inhibitors

Generic Drug Name (Brand)	Neovascular AMD	Macular Edema Following RVO	Diabetic Retinopathy	DME	ROP	Myopic Choroidal Neovascularization
Aflibercept (Eylea®)	**FDA**	**FDA**	**FDA**	**FDA**	**FDA**	
Bevacizumab (Avastin®)	**compendia**	**compendia**	**compendia**	**compendia**	**compendia**	**compendia**
Brolucizumab (Beovu®)	**FDA**			**FDA**		
Faricimab (Vabysmo®)	**FDA**	**FDA**		**FDA**		
Ranibizumab (Lucentis®) and biosimilars (Cimerli®, Byooviz®)	**FDA**	**FDA**	**FDA***	**FDA***	**compendia**	**FDA**

Abbreviations: AMD = age related macular degeneration; DME = diabetic macular edema; FDA = Food and Drug Administration; RVO = retinal vein occlusion; ROP = retinopathy of prematurity

*Not FDA-approved for Byooviz®

In clinical trials, visual acuity changes are often evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart. The minimal clinically important difference referenced in the literature can vary, but a change of 5 letters (corresponding to 1 line on the chart or 0.1 logMAR) is typically considered to be the minimum clinically detectable change.[14] For many conditions, moderate visual gains or losses are defined as changes of at least 10 to 15 letters (corresponding to approximately 2-3 lines).[14] Many trials also report improvements in central subfield thickness or central retinal thickness as a secondary surrogate outcome. However, in changes in central retinal thickness may not correlate with changes in visual acuity.[19]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high

quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Age-related Macular Degeneration (AMD)

A 2022 AHRQ review evaluated the efficacy and safety of screening and treatments for impaired visual acuity in older adults.[1] The review was used to inform vision screening recommendations for the US Preventative Services Task Force. The review focused on uncorrected refractive errors, cataracts, and AMD and did not include screening for diabetic retinopathy.[1] RCTs comparing VEGF inhibitors to placebo, sham injection (use of a syringe without a needle pressed against the anesthetized eye) or active treatment with an alternative VEGF inhibitor were included. BCVA was the primary efficacy outcome evaluated by gain or loss of at least 15 ETDRS letters or having vision 20/200 or better (the current legal threshold for blindness in the US). Four RCTs (n=2086) compared a VEGF inhibitor (ranibizumab or pegaptanib) to sham injection over 1-2 years. After 1 year of treatment, use of VEGF inhibitors was associated with improved BCVA for the following outcomes:[1]

- gain in visual acuity of at least 15 letters (RR, 2.92, 95% CI 1.20 to 7.12, I2=76%; absolute risk difference [ARD] 10%),
- less than 15 letters of visual acuity loss (RR, 1.46, 95% CI 1.22 to 1.75, I2=80%; ARD 27%), and
- having vision 20/200 or better (RR, 1.47, 95% CI 1.30 to 1.66, I2=42%; ARD 24%).[1]

Results were comparable when evaluating ranibizumab or pegaptanib separately. Mean age in these trials ranged from 75 to 78 years and 54-68% of patients were female.[1] Mean baseline visual acuity was about 20/80 in 3 trials and most patients enrolled in the fourth study had a visual acuity between 20/40 and 20/200. Only one trial evaluated functional outcomes with ranibizumab at 2 years. Vision-related function and quality of life measures at 1 and 2 years had a small, but clinically significant, improvement with VEGF inhibitors compared to sham injection (8 points on a 0-100 point scale; published MCID of 4-6 points).[1] In a subgroup of people who were driving at baseline, there was also an increased likelihood that patients treated with ranibizumab 0.3 or 0.5 mg would continue to be driving after 2 years compared to sham injection (78-81% vs. 67%), though there was no difference in the subgroup of patients who were not driving at baseline.[1] Deaths and serious ocular adverse events were infrequently reported in these trials and were comparable between groups.[1] There was no difference compared to sham injection in the number of patients who withdrew due to adverse events.

This systematic review also evaluated evidence of newer VEGF inhibitors (aflibercept and brolucizumab) compared to older agents (ranibizumab or bevacizumab). Trials which compared brolucizumab and aflibercept did not meet prespecified inclusion criteria for the review and were excluded. Three trials were identified which compared aflibercept and ranibizumab.[1] Included patients were on average 73 to 79 years of age and 53-57% were female. Average baseline visual acuity was 20/80 for 2 studies and 20/50 in the third trial.[1] Patients were followed for 1-4 years. Dosing frequency varied among trials and included fixed monthly dosing, dosing every 8 weeks, or dosing at least every 12 weeks with frequency based on disease activity. After one year of treatment, aflibercept and ranibizumab had comparable improvement in BCVA outcomes:[1]

- gain in visual acuity of at least 15 letters (31.4% vs. 32%)
- less than 15 letters of visual acuity loss (94.9% vs. 94.3%)
- having vision 20/40 or better (35.2% vs. 35.1%).[1]

Both drugs also had comparable improvement in vision-related functional scores with an average improvement from baseline of 4.5 to 6.7 points (range 0-100) at 1 year. Change in BCVA remained similar between groups at 2 years. Deaths and serious adverse events were infrequently reported and comparable between groups.[1]

Diabetic Macular Edema (DME)

A 2023 update of a Cochrane review evaluated use of VEGF inhibitors for DME.[2] Previous Cochrane reviews on this topic have identified only small differences between VEGF inhibitors which did not achieve thresholds for clinically important differences in visual acuity.[2] The primary outcome for this review was BCVA between VEGF inhibitors at 24 months. Secondary outcomes of interest included BCVA at 12 months, gain of at least 3 ETDRS lines from baseline to 24 months, and change in central retinal thickness at 24 months. Safety outcomes included all-cause mortality, and arterial thromboembolic events and serious ocular adverse events at the longest available follow-up. Laser therapy, observation, sham procedures were used as control groups for safety outcomes. A systematic review of the literature through July 2022 identified 23 RCTs (n=3513) which met inclusion criteria.[2] Nine studies were industry sponsored, 7 were independent RCTs, and 2 were publicly funded. Only 9 RCTs maintained randomization at 2 years.[2] People included in these trials had DME with a mean central thickness of 460 microns and an average BCVA of 0.48 logMAR (Snellen equivalent of about 20/60) corresponding to moderate vision loss.[2] Most studies excluded participants with a central subfield thickness (CST) below 400 microns.[2] A difference of 0.1 logMAR (corresponding to one ETDRS line or 5 letters) was used for the minimum clinically important difference for non-inferiority trials.[2] On average, patients enrolled in trials received 7 to 10 injections per year (which is higher than many clinical settings).[2] In practice, many VEGF inhibitors are administered at longer dosing intervals for people with stable disease under a "treat and extend" protocol in which injections are given at increasingly extended intervals in people whose disease has remained stable.[20-23] VEGF inhibitors evaluated in RCTs included ranibizumab (n=13 RCTs), bevacizumab (n=5), aflibercept (n=6), brolucizumab (n=2) and faricimab (n=2). There was high or unclear risk of bias for random sequence generation (5 RCTs), allocation concealment (8 RCTs), blinding of patients and personnel (9 RCTs) or outcome assessment (9 RCTs), attrition bias (8 RCTs), and selective reporting (5 RCTs).[2] A network meta-analysis was conducted for efficacy outcomes. Statistical analyses demonstrated inconsistency (with difference in treatment effects for direct and indirect analyses) for the following comparisons: bevacizumab vs. ranibizumab for the outcome of BCVA at 24 months; aflibercept versus control for the outcome of all-cause mortality; for aflibercept and ranibizumab versus control and each other for arterial thromboembolic events.[2] No inconsistency was identified for other comparisons or outcomes.

- The median change in BCVA at 24 months was improved by -0.19 logMAR (8 RCTs) with no difference when comparing ranibizumab to aflibercept (moderate quality evidence), brolucizumab (low quality evidence), or bevacizumab (low quality evidence). A change of 0.1 logMAR typically corresponds to a change of 5 letters or 1 line on the ETDRS chart.[14] At 12 months compared to ranibizumab (20 RCTs), there were small differences in BCVA favoring faricimab (MD −0.08 logMAR, 95% CI −0.12 to −0.05), aflibercept (MD −0.07 logMAR, 95% CI −0.10 to −0.04), and brolucizumab (MD −0.07, 95% CI −0.10 to −0.03), but the average difference did not reach thresholds for minimum clinically important changes (moderate quality evidence).[2]
- Thirty-four percent of people treated with ranibizumab gained 3 or more ETDRS lines at 24 months with no difference compared to aflibercept (moderate quality evidence) or bevacizumab (low or very low quality evidence).[2] There was no data for comparisons of brolucizumab or faricimab at 24 months.
- Compared to control (e.g., laser therapy, observation, or sham procedures), there was no statistical differences in all-cause mortality with any VEGF inhibitor (20 RCTs; low quality evidence).[2] The average mortality in control groups was 1.8% at the longest available follow-up.[2] However, all trials of VEGF inhibitors demonstrated a trend toward increased mortality. While statistical analyses did not demonstrate increases in mortality, clinically relevant increases in mortality could also not be ruled out. Similarly, there was no difference in arterial thromboembolic events with VEGF inhibitors compared to control, but analyses were limited by inconsistency and imprecision (low to very low quality evidence for all VEGF inhibitors).[2] Serious ocular events were rare and definitions varied across trials. Endophthalmitis (related to intraocular injections) occurred in 0.24% to 0.8% of participants; vascular disorders, retinal vein occlusion, and retinal artery occlusion occurred on 0% to 0.54% of participants treated with VEGF inhibitors, and intraocular inflammation occurred in 0.12% to 2.72% of participants.[2] Overall, authors highlighted the need for additional long-term safety data.

Proliferative Diabetic Retinopathy

A 2023 Cochrane systematic review evaluated evidence of efficacy and safety of VEGF inhibitors for proliferative diabetic retinopathy.[24] The review evaluated literature through June 2022 and included RCTs of VEGF inhibitors compared to other active therapy (e.g., panretinal photocoagulation), sham treatment, or no treatment.[24] The review identified 23 RCTs (12 evaluating bevacizumab, 7 evaluating ranibizumab, and 1 evaluating aflibercept). [24] Most included studies had high or unclear risk of performance and detection bias due to blinding of participants and outcome assessors. Most trials also had unclear risk for selection bias from random sequence generation and allocation concealment.[24] Seven studies were industry funded and 11 did not report a funding source. The average age of participants was 56 years (range 48 to 77 years) and average HbA1c was 8.25 to 8.45%.[24] About half of studies enrolled participants with proliferative diabetic retinopathy and half included people with high-risk proliferative diabetic retinopathy.[24] The average follow-up period was 8 months, and all except 2 RCTs evaluated VEGF inhibitors in combination with panretinal photocoagulation compared to panretinal photocoagulation alone. Panretinal photocoagulation is a laser treatment recommended by the American Academy of Opthamology as a preferred option in people with high-risk proliferative diabetic retinopathy.[12,18] VEGF inhibitors with or without panretinal photocoagulation improved visual acuity compared to panretinal photocoagulation alone (MD -0.08 logMAR; 95% CI -0.12 to -0.04; moderate quality evidence), but differences were generally small corresponding to an average difference of 4 letters (95% CI 2.5 to 5 letters).[24] There was also moderate quality evidence that VEGF inhibitors reduced the need for additional laser photocoagulation (RR 0.18, 95% CI 0.11 to 0.28; I2=0%; 2 RCTs, 464 eyes; moderate-certainty evidence) or vitrectomy (RR 0.67, 95% CI 0.49 to 0.93; I2= 43%; 8 RCTs, 1248 eyes; low-certainty evidence) compared to panretinal photocoagulation.[24] Comparisons between VEGF inhibitors were not reported. All safety outcomes were graded as very low quality indicating substantial uncertainty in the treatment effect.[24]

Neovascular glaucoma

A 2020 Cochrane systematic review evaluated VEGF inhibitors for treatment of neovascular glaucoma.[25] Four RCTs (n=263) published prior to March 2019 were included in the review.[25] Trials compared bevacizumab, aflibercept, or ranibizumab as monotherapy in one study or combined with Ahmed valve implantation or panretinal photocoagulation in 3 studies. All studies used anti-glaucoma medications to control intraocular pressure. The primary outcome was control of intraocular pressure reported as the proportion of patients with intraocular pressure less than or equal to 21 mmHg.[25] No study reported changes in visual acuity. Trials were conducted in China, Brazil, Egypt and Japan. Two studies included participants with central retinal vein occlusion or proliferative diabetic retinopathy as the underlying cause of the neovascular glaucoma.[25] Heterogeneity in study designs precluded combination of results in a meta-analysis. Efficacy outcomes were graded with low certainty of evidence due to unclear risk of bias for most categories, inconsistency in treatment effects between studies, and imprecision.[25] Overall authors concluded that there is not enough evidence to determine whether adjunct use of VEGF inhibitors improve intraocular pressure in people with neovascular glaucoma compared to conventional glaucoma treatments.[25]

After review, 42 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., non-VEGF inhibitor), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Since the last review, NICE has evaluated evidence and made recommendations for faricimab and brolucizumab for treatment of neovascular AMD and DME in 2020 and 2022.

- Brolucizumab and faricimab are recommended as treatment options for DME in adults when the eye has a central retinal thickness of 400 micrometers or more prior to treatment.[26,27] A review of available evidence demonstrated similar efficacy when compared to aflibercept. Indirect comparisons of these agents to ranibizumab also showed similar clinical effectiveness, although these results are less certain.[26,27]

- Brolucizumab and faricimab are recommended as treatment options for neovascular AMD when the patient meets the following criteria:[28,29]
    - The eye has a BCVA between 6/12 and 6/96 prior to treatment,
    - There is no permanent structural damage to the central fovea,
    - Lesion size is 12 disc areas or less, AND
    - There are recent signs of disease progression (e.g., visual acuity changes or blood vessel growth)
- Brolucizumab and faricimab should only be continued for patients with neovascular AMD if they maintain adequate response to therapy.[28,29] Discontinuation is recommended if there are persistent visual acuity changes or anatomical changes to the retina despite treatment which would indicate inadequate response. Recommendations were based on clinical trial evidence and network meta-analyses which demonstrated comparable net health benefits with these drugs versus aflibercept and ranibizumab.[28,29]

CADTH evaluated evidence and made recommendations for faricimab for treatment of neovascular AMD and DME in 2022.[30,31]

- Faricimab was recommended as an option for the treatment of neovascular AMD or DME when the patient is under the care of an ophthalmologist experienced in managing neovascular AMD or DME and when the cost does not exceed alternative VEGF inhibitors.[30,31] This recommendation was based on clinical trials which demonstrated non-inferiority to aflibercept in people with neovascular AMD (2 RCTs) and DME (2 RCTs). Phase 2 trials compared faricimab to ranibizumab in neovascular AMD, but study designs prevented definitive conclusions regarding comparative efficacy. Based on available evidence, it is unknown whether faricimab is associated with fewer injections than other VEGF inhibitors.[30,31]

New Formulations or Indications:

<u>New Formulations</u>

A new formulation of ranibizumab (SUSVIMO) was FDA approved in October 2021. This formulation is administered via a port delivery system in which a surgically planted, permanent, refillable ocular implant is used to deliver intraocular ranibizumab over 24 weeks. Approval was primarily based on a single, open-label, study comparing ranibizumab monthly injections to the port delivery system in patients with neovascular AMD who were previously responsive to a VEGF inhibitor (**Table 3**). Outcomes were evaluated at 36-40 weeks after at least one refill of the port delivery system (at 24 weeks). Subsequent results were published with about 2 years of follow-up, and results were supported by a smaller phase 2, dose-finding, study. The port delivery system met prespecified margins for non-inferiority and equivalence compared to ranibizumab monthly injections.[32] In November 2022, a voluntary recall was issued for SUSVIMO due to manufacturing issues associated with the port delivery system resulting in leaking of the drug after injection and/or repeated dosing (**Table 2**). The timeframe for resolution of these manufacturing issues is unknown at this time.

Since the last review, 2 biosimilars have been approved for ranibizumab. BYOOVIZ (ranibizumab-nuna) was approved by the FDA in September 2021 and has indications for treatment of neovascular AMD, macular edema associated with retinal vein occlusion and myopic choroidal neovascularization. CIMERLI (ranibizumab-eqrn) was approved by the FDA in August 2022 for neovascular AMD, DME, diabetic retinopathy, macular edema associated with retinal vein occlusion and myopic choroidal neovascularization. CIMERLI is interchangeable with the originator product (LUCENTIS).[7]

A new dosage form of aflibercept (EYLEA HD®) was FDA approved in August 2023 for indications of AMD, DME, and diabetic retinopathy.[6] The recommended dosing regimen is 8 mg intravitreal injection every 4 weeks for the first 3 weeks followed by maintenance injections once every 8 to 16 weeks in people with AMD or DME and every 8 to 12 weeks for people with diabetic retinopathy.[6] Approval was based 2 multi-center, double-blind non-inferiority RCT in patients with AMD and DME (PULSAR and PHOTON) which evaluated 3 maintenance regimens of aflibercept: 8 mg every 12 weeks, 8 mg every 16 weeks, and 2 mg every 8 weeks. In patients receiving treatment every 12 or 16 weeks, dose interval could be increased to every 8 weeks based on pre-specified visual and anatomic

criteria. In people with AMD, the average number of doses administered was 5.2 for patients randomized to treatment every 16 week group, 6.1 injections for patients in the 12 week group, and 6.9 injections for patients in the 8 week group.[6] At 48 weeks, both groups randomized to 8 mg doses met non-inferiority criteria for BCVA (4 ETDRS letters) compared to patients given 2 mg every 8 weeks (MD of -1.0 letters, 95% CI -2.9 to 0.9 for 8 mg every 12 weeks and MD of -1.1 letters, 95% CI -3.0 to 0.7 for 8 mg every 16 weeks.[6] The chosen non-inferiority margin was within the minimum clinically important difference referenced in the literature (5 ETDRS letters). Non-inferiority was also achieved in people with DME. Compared to aflibercept 2 mg every 8 weeks, aflibercept 8 mg every 12 weeks (MD -0.6, 95% CI -2.3 to 1.1) and aflibercept 8 mg every 16 weeks (MD -1.4, 95% CI -3.3 to 0.4) had similar changes in visual acuity at 48 weeks.[6]A key secondary outcome for people with DME was the proportion of patients with at least a 2 step improvement in DRSS score at 48 weeks (with a non-inferiority margin of 10%). The proportion of people with a 2 step improvement in DDRS score was similar for people treated with aflibercept 2 mg every 8 weeks (27%) and aflibercept 8 mg every 12 weeks (29%; MD 2%, 95% CI -6.6 to 10.6) but not aflibercept 8 mg every 16 weeks (20%; MD -8%, 95% CI -16.9 to 1.8).[6] Thus, for people with diabetic retinopathy, maintenance dosing every 16 weeks is not included in the FDA label.

New Indications

Brolucizumab for DME

In May 2022, brolucizumab was FDA approved for the treatment of DME based on results from 2, phase 3 trials which compared treatment to aflibercept (KITE and KESTREL).[33] Brolucizumab was previously approved for AMD. Loading doses of brolucizumab were studied every 6 weeks for 5 doses (compared to 3 doses studied for AMD) before switching to maintenance administration every 8-12 weeks.[33] Aflibercept loading doses were given every 4 weeks for 5 doses, then every 8 weeks. The primary outcome was BCVA at 52 weeks. Enrolled patients had an HbA1c of less than or equal to 10%, BCVA between 78 and 23 ETDRS letters (~20/32 to 20/320 Snellen equivalent), and central-involved DME based on a central subfield thickness of at least 320 µm at screening.[33] Patients were excluded if they had active proliferative diabetic retinopathy, had recent intraocular steroid treatment or any prior VEGF treatment.[33]

Multiple methodological limitations limit interpretation of results in these studies. Sham injections were used to mask treatment groups when study treatments were administered at different times.[33] However, patients can often determine when they are receiving a sham injection which may lead to unmasking of treatment groups and increase risk of performance bias, particularly for outcomes like BCVA which are dependent on patient effort. A different masked investigator administered outcome and disease activity assessment. Missing or censored data was imputed using a last observation carried forward methodology and slightly more patients discontinued treatment in brolucizumab 6 mg groups compared to aflibercept in each study (18.5% vs. 13.4% and 19% vs. 16%).[33] This could result in an overestimation of the treatment effect. Non-inferiority analysis was performed using all enrolled patients which may bias groups toward no difference.[33] There were slight imbalances in baseline characteristics which increases risk of selection bias. In KITE, mean BCVA at baseline was slightly lower in aflibercept treatment group (63.7 vs. 66 ETDRS letters).[33] Patients randomized to brolucizumab were also more commonly male (67% vs. 63.5%), had an HbA1c over 7.5% (54.2% vs. 47%), and had a lower incidence of subretinal fluid (31.3% vs. 37%). In KESTREL, patients randomized to brolucizumab 6 mg were slightly younger (mean 62 vs. 64 years), less commonly male (58% vs. 67%), had a HbA1c of at least 7.5% (60% vs. 43%), and had a lower average central subfield thickness at baseline (453 vs. 476 µm).[33]

Brolucizumab 6mg was non-inferior to aflibercept for mean BCVA at 52 weeks in both studies (9.2 vs. 10.5 ETDRS letters; MD-1.3 [95% CI -2.9 to 0.3] and 10.6 vs. 9.4 ETDRS letters; MD 1.2 [95% CI -0.6 to 3.1]).[33] The non-inferiority margin (4 ETDRS letters) was also achieved for the key secondary endpoint which evaluated average change in BCVA over 40-52 weeks.[33] The proportion of patients who gained at least 15 letters or reached a BCVA of 84 letters was comparable in one study (37% vs. 39%) and improved with brolucizumab treatment in KITE compared to aflibercept (46.4% vs. 37.6%).[33] However, results in KITE may have been influenced by imbalances in baseline characteristics as there were a greater proportion of patients randomized to brolucizumab with a higher visual acuity compared to the aflibercept group (45.8% in brolucizumab group with a BCVA ≥ 70 letters at baseline vs. 32% with aflibercept).[33] Overall rates of serious ocular

adverse events were infrequent and similar between groups (1.1 to 2.2%).[33] Rates of intraocular inflammation occurred more frequently with brolucizumab compared to aflibercept in KESTREL (3.7% vs. 0.5%) and at similar rates in KITE (1.7% in each group).[33] Retinal artery occlusion and endophthalmitis were infrequent and occurred at similar rates between groups.

Aflibercept for Retinopathy of Prematurity (ROP)

In February 2023, aflibercept was FDA approved for retinopathy of prematurity.[3] FDA approval was based on 2, open-label, non-inferiority RCTs comparing aflibercept to laser photocoagulation therapy (BUTTERFLEYE [n=120] and FIREFLEYE [n=113]). FIREFLEYE enrolled participants in Europe, Asia, and South America.[34] BUTTERFLEYE was completed in 2022 and enrolled participants in the United States, South America, Europe, and Asia but remains unpublished.[35] Aflibercept 0.4 mg was administered up to three times in each eye with at least 28 days between injections.[3] Rescue therapy could be provided based on pre-specified criteria. In BUTTERFLEYE, 18.5% of infants randomized to laser photocoagulation and 15.1% of participants randomized to aflibercept received rescue therapy from baseline to 52 weeks.[35] In FIREFLEYE, rescue therapy was administered for 12.5 % and 8.2% of infants randomized to laser photocoagulation and aflibercept, respectively.[34] In people treated with aflibercept, 92% received injections in both eyes.[3] Pre-term infants enrolled in the study had a max gestational birth of 32 weeks, max birth weight of 1500 g (about 3.3 lbs) and weighed at least 800 g on the day of treatment.[3] Retinopathy of prematurity was defined according to international guidelines and could include zone 1 (stage 1+, 2+, 3, or 3+), zone 2 (stage 2+ or 3+), or aggressive posterior retinopathy of prematurity.[3] Zone 1 is defined as the innermost zone of the retina around the optic disc and is more likely to progress and become more severe than retinopathy of prematurity in zone 2 (which is a more peripheral retinal zone).[34] Advanced stages of retinopathy of prematurity with complete or partial retinal detachment were excluded (stage 4 and 5) and retinopathy of prematurity only involving zone 3 were excluded.[35] Participants were on average 10 weeks old at enrollment. In BUTTERFLEYE, 26% had zone 1 involvement.[35] In FIREFLEYE, 20% had zone 1 involvement, and aggressive posterior retinopathy of prematurity was present in 13 and 19% of members in the aflibercept and laser groups, respectively.[34]

The primary outcome was absence of active retinopathy of prematurity or unfavorable structural ocular outcomes (such as retinal detachment, macular dragging, macular fold, or retrolental opacity) at 1 year.[3] The non-inferiority margin was pre-specified at 5%.[34] For infants who received bilateral treatment, both eyes were required to meet the primary endpoint. Compared to laser photocoagulation therapy, there was no difference in the proportion of people without active retinopathy of prematurity at 1 year in either study (79.6% vs. 77.8%; MD 1.81% [95% CI -15.7 to 19.3] and 78.7% vs. 81.6%; MD -1.88% [95% CI -17.0 to 13.2]).[3] However, the analysis failed to meet pre-established criteria for non-inferiority of aflibercept compared to laser photocoagulation therapy. Neither trial demonstrated that aflibercept was superior or inferior to laser photocoagulation therapy.[3]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ranibizumab[5]	SUSVIMO	April 2022	Warnings/ Precautions	Septum dislodgement, implant damage where the septum has dislodged into the implant body, has been reported in clinical trials. During administration, avoid twisting and/or rotating the refill in order to minimize risk of septum dislodgement. Manufacturer labeling recommends evaluation by dilated slit lamp exam and/or dilated indirect ophthalmoscopy to evaluate whether septum dislodgement has occurred.

				Voluntary recall issued November 2022 related to manufacturing of the seal on the port delivery system which could result in leaking after injection and/or repeated dosing.
Brolucizumab-dbbl[9]	BEOVU	2020-2022	Warnings/ Precautions	Retinal Vasculitis and/or Retinal Vascular Occlusion have occurred in post-marketing studies and subsequent phase 3 clinical trials following administration of brolucizumab. These events are immune-mediated, have typically occurred in the presence of intraocular inflammation, and can occur after the first injection. Patients with intraocular inflammation should be closely monitored and treatment discontinuation is recommended if retinal vasculitis or vascular occlusion occurs.[9] In clinical trials of patients treated with brolucizumab every 8-12 weeks, intraocular inflammation occurred in 4% of patients with AMD and 2% of patients with DME compared to 1% with aflibercept.[9] Compared to aflibercept, patients with neovascular AMD treated with brolucizumab every 4 weeks had higher rates of inflammation (9.3% vs. 4.5%), retinal vasculitis (0.8% vs. 0%), and retinal occlusion (2% vs. 0%).[10] Trials evaluating every 4 week dosing were discontinued early due to increased incidence of these serious adverse events (see **Table 3**). Overall incidence of events for patients treated every 4 weeks was more common than studies of patients treated every 8 or 12 weeks. Based on these trials labeling was updated to specify that doses for maintenance treatment should not occur more frequently than every 8 weeks.[9]

Randomized Controlled Trials:

A total of 427 citations were manually reviewed from the initial literature search. After further review, 421 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., non-VEGF inhibitor), or outcome studied (e.g., non-clinical). The remaining 6 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr><td>1. Khanani, et al. 2022.[10]

MERLIN NCT03710564

MC, DB, NI, phase 3 RCT</td><td>1. Brolucizumab 6 mg every 4 weeks (n=356)
2. Aflibercept 2 mg every 4 weeks (n=179)

*Intensive dose regimen (FDA labeled dose is brolucizumab 6 mg every 6 weeks for 5 doses then</td><td>Patients ≥50 years of age who had active CNV secondary to neovascular AMD and persistent fluid affecting the central subfield despite prior treatment with VEGF inhibitors. Patients</td><td>Mean change in BCVA at 52 weeks (non-inferiority margin 4 ETDRS letters)</td><td>Change in BCVA from baseline to week 52
1. 0.3 letters (SE 0.44)
2. 0.9 letters (SE 0.62)
MD -0.6 ETDRS letters (95% CI -2.1 to 0.9); non-inferiority margin met

BCVA gain or loss from baseline to week 52
<table>
<tr><th></th><th>Gain ≥ 15 letters</th><th>Loss ≥ 15 letters</th></tr>
<tr><td>1.</td><td>16.9%</td><td>4.8%</td></tr>
<tr><td>2.</td><td>17.4%</td><td>1.7%</td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td>Duration: 104 weeks

Early study termination after 52 weeks</td>
<td>every 8-12 weeks and aflibercept 2 mg every 4 weeks for 5 doses then every 8 weeks)</td>
<td>had BCVA of ≥ 55 letters (about ≥ 20/80).

Patients with active intraocular inflammation or infection were excluded.</td>
<td></td>
<td>
<table>
<tr><td>MD</td><td>-0.5% (95% CI -9.5 to 8.4)</td><td>3.1% (95% CI -5.9 to 12.1)</td></tr>
</table>
Intraocular inflammation
1. 33 (9.3%)
2. 8 (4.5%)

Study terminated early due to increased incidence of adverse events with brolucizumab including serious ocular events, intraocular inflammation, retinal vasculitis and retinal vascular occlusion. All-cause mortality also occurred in more patients receiving brolucizumab compared to aflibercept (n=6, 1.7% vs. 0%).
</td>
</tr>
<tr>
<td>Vader, et al. 2020.[36]

BRDME Study NCT01635790

MC, DB, NI, RCT

Duration: 26 weeks</td>
<td>1. Bevacizumab 1.25 mg (n=86) every 4 weeks
2. Ranibizumab 0.5 mg (n=84) every 4 weeks

N=170</td>
<td>Adults with DME with HbA1c ≤12%, CST ≥ 325 µm and BCVA of 24-78 ETDRS letters

Location: Netherlands from June 2012 to February 2018</td>
<td>Change in BCVA at 6 months (non-inferiority margin of -3.5 ETDRS letters)</td>
<td>Change in BCVA at 6 months
1. 4.9 (SD 6.7)
2. 6.7 (SD 8.7)
Lower bound of 90% CI was -3.626. Non-inferiority was not achieved.</td>
</tr>
<tr>
<td>Singh, et al. 2023.[37]

KINGFISHER; NCT03917472

MC, DB, NI, phase 3 RCT

Duration: 52 weeks</td>
<td>1. Brolucizumab 6 mg every 4 weeks*
2. Aflibercept 2 mg every 4 weeks*

N = 517

*Intensive dose regimen (FDA labeled dose is brolucizumab 6 mg every 6 weeks for 5 doses then every 8-12 weeks and aflibercept 2mg every 4 weeks for 5 doses then every 8 weeks)</td>
<td>Adults with DME with HbA1c ≤12% and not treated with a VEGF inhibitor within 3 months. Participants excluded if they had stroke or myocardial infarction in the prior 6 months, ocular disorders, or uncontrolled glaucoma

Location: Hungary, Israel, Slovakia, and the US from September 2019 to March 2020.</td>
<td>Change in BCVA at 52 weeks (NI margin of -4 ETDRS letters)</td>
<td>Change in BCVA at 6 months
1. 12.2 letters
2. 11.0 letters
MD 1.1 letters; 95% CI,−0.6 to 2.9
p < 0.001 for non-inferiority; p = 0.10 for superiority

Brolucizumab 6 mg every 4 weeks was non-inferior but not superior to aflibercept 2 mg every 4 weeks.

BCVA gain or loss from baseline to week 52
<table>
<tr><td></td><td>Gain ≥15 letters or BCVA ≥84 letters</td><td>Loss ≥15 letters (at any visit)</td></tr>
<tr><td>1.</td><td>43.6%</td><td>3.2%</td></tr>
<tr><td>2.</td><td>40.4%</td><td>2.9%</td></tr>
<tr><td>MD</td><td>5.5% (95% CI -2.7 to 14.3)</td><td>NR</td></tr>
</table>
Safety
<table>
<tr><td></td><td>Serious Ocular AEs</td><td>Intraocular inflammation</td></tr>
<tr><td>1.</td><td>0.9%</td><td>14 (4.0%)</td></tr>
</table>
</td>
</tr>
</table>

				2. 0% 5 (2.9%) All 13 injections were given for 55% of the brolucizumab group and 55% of the aflibercept group. Protocol deviations due to COVID-19 pandemic (primarily missed visits) were noted for ~25% of people in each group.
Jhaveri, et al. 2022.[38] PROTOCOL AC NCT03321513 MC, DB, NI, RCT Duration: 2 years	1. Aflibercept 2mg every 4 weeks for 1 year then every 4-16 weeks as needed 2. Bevacizumab 1.25 mg every 4 weeks for 1 year then every 4-16 weeks as needed After 12 weeks patients in the bevacizumab group could switch to aflibercept based on pre-specified criteria including persistent DME, visual acuity change of <5 letters, change in central subfield thickness of <10%, and visual acuity below 20/50 at 24 weeks or later N = 270 (312 eyes)	Adults with DME and visual acuity of 20/320 to 20/50 Location: 54 sites in the US between December 2017 and November 2019	Change in BCVA (time-averaged over 2 years); NI margin 3.5 letters	BCVA at 2 years 1. 15.0 (SD 8.5) letters 2. 14.0 (SD 8.8) letters MD 0.8 letters, 95% CI -0.9 to 2.5, p=0.37 70% of people who started bevacizumab met pre-defined criteria and switched to aflibercept over 2 years. 30% of people prescribed aflibercept met pre-defined criteria and continued treatment. Serious AE 1. 52% 2. 36% Hospitalization for AE 1. 48% 2. 32%
Regillo, et al. 2023.[39] Holekamp, et al. 2022.[40] ARCHWAY NCT03677934 MC, NI, OL, phase 3, RCT	1. Ranibizumab port delivery system, filled every 24 weeks (n=248) 2. Ranibizumab 0.5 mg injections every 4 weeks (n=167) N=415	Adults with neovascular AMD diagnosed within 9 months and with prior treatment response to VEGF inhibitors Location: 78 sites in the US from	Change in BCVA at 36-40 weeks (9 months) and 88 to 92 weeks (1.7 years); NI margin of	BCVA at 36-40 weeks 1. 0.2 (SE 0.5) ETDRS letters 2. 0.5 (SE 0.6) ERDRS letters MD -0.3 ETDRS letters (95% CI -1.7 to 1.1) BCVA at 88 to 92 weeks 1. -1.1 (SE 0.61) ETDRS letters 2. -0.5 (SE 0.75) ETDRS letters MD -0.6 ETDRS letters (95% CI -2.5 to 1.3)

Duration: 2 years		September 2018 to June 2021	3.9 ETDRS letters	
Vader, et al. 2020.[41] NCT01635803 DB, NI, MC, RCT Duration: 6 months	1. Bevacizumab 1.25 mg every 4 weeks (n=139) 2. Ranibizumab 0.5 mg every 4 weeks (n=138)	Adults with macular edema secondary to branch, hemi or central RVO Location: The Netherlands from June 2012 to February 2018	Change in BCVA at 6 months (NI margin of 4 letters)	Change in BCVA 1. 15.3 (SD 13.0) ETDRS letters 2. 15.5 (SD 13.3) ETDRS letters Lower bound of 90% CI was -1.724. Non-inferiority criteria were met.

Abbreviations: AE = adverse events; AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; CST = central subfield thickness; DB = double blind; DME = diabetic macular edema; ETDRS = early treatment diabetic retinopathy study; FDA = Food and Drug Administration; HbA1c = hemoglobin A1c; MC = multicenter, MD = mean difference; NI = non-inferiority; OL = open label; RCT = randomized controlled trial; RVO = retinal vein occlusion; SD = standard deviation; SE = standard error; US = United States; VEGF = vascular endothelial growth factor

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Faricimab was approved by the FDA in 2022 for the treatment of neovascular AMD, DME, and macular edema following retinal vein occlusion. Approval for each condition was based on 2 identically designed, phase 3 trials comparing faricimab to aflibercept with supporting data from phase 2 trials comparing faricimab to ranibizumab in AMD[42,43] and DME.[44] Clinical outcomes focused on improvements in BCVA after about 1 year of treatment for AMD and DME and after 6 months for people with retinal vein occlusion.

Faricimab is a monoclonal antibody with a dual mechanism of action. It inhibits both VEGF and Ang-2. The effect of Ang-2 inhibition on macular edema has yet to be established. In AMD and DME, trials evaluated dosing as needed based on disease activity for faricimab, but the comparator, aflibercept, was only evaluated at fixed dosing every 8 weeks. Studies were not designed to compare faricimab to treat-and-extend dosing for aflibercept, and conclusions regarding less frequent dosing of faricimab compared to aflibercept cannot be made.[45] Because currently available studies were not designed to evaluate dosing frequency compared to an appropriate comparison regimen, it is not clear if Ang-2 inhibition has any effect on the durability of therapy in these conditions.[45] Fixed monthly dosing was evaluated in people with macular edema due to retinal vein occlusion. In AMD and DME, the FDA approved dose for faricimab is 6 mg given every 4 weeks for at least the first 4 doses then frequency of injections is determined based on treatment response.[46] In patients with AMD, dose frequency could be adjusted every 8, 12, or 16 weeks based on optical coherence tomography and visual acuity evaluations.[46] In patients with DME, dose could be adjusted as needed to regimens every 4, 8, 12, or 16 weeks based central subfield thickness (CST) and visual acuity evaluations. Some patients with active disease may need

more frequent dosing every 4 weeks.[46] Fixed monthly dosing for up to 6 months is recommended in people with macular edema due to retinal vein occlusion as there is no comparative data for treat-and-extend regimens.[46]

In both phase 3 trials, patients were randomized with adequate methods and allocation concealment with baseline characteristics generally well balanced between groups. Risk of performance and detection bias was high in trials for AMD and DME due to unblinding. Because frequency of administration differed between groups, patients and providers were blinded with use of sham injections (use of a syringe without a needle pressed against the anesthetized eye). However, often patients can identify if they are receiving a sham injection, which likely led to unblinding of groups at 16 to 24 weeks. Unblinded groups is of particular concern for outcomes such as BCVA where patient effort may significantly impact results. The method of blinding was not reported in clinical trials evaluating retinal vein occlusion leading to unclear risk for performance bias.

Major limitations in the evidence include lack on long-term data to evaluate durability of response or safety beyond one year. There is limited data comparing faricimab to other VEGF inhibitors or comparing faricimab to other treatment regimens of aflibercept. Phase 2 studies comparing faricimab to ranibizumab had small sample sizes with generally high or unclear risk of bias which limits ability to draw conclusions in efficacy or safety.

<u>Diabetic Macular Edema</u>

In phase 3 trials for DME, patients were required to have center-involving DME with central subfield thickness of at least 325 µm and BCVA 25-73 ETDRS letters (approximate Snellen equivalent of 20/320 to 20/40).[47] Patients were excluded if they had an A1C greater than 10%, were recently initiated on DM treatment, had blood pressure over 180/100 mmHg, or had a stroke or MI in the previous 6 months. Patients with a variety of other ocular conditions were also excluded. About 38% and 44% of patients screened for these trials were excluded.[47] Some of the most common reasons for exclusion were retinal complications (such as presence of tractional retinal detachment, pre-retinal fibrosis and epiretinal membrane; 6-8%), failure to meet BCVA criteria (7-8%), and failure to meet central subfield thickness criteria for macular thickening of the central fovea (7-8%).[47] The majority of patients enrolled were White (77-81%), had DM that was reasonably well-controlled (average HbA1c 7.6 to 7.7%), and were treatment naïve (76-80%).[47] A little more than half of patients did not have diabetic retinopathy or had diabetic retinopathy that was questionable upon exam. Average BCVA at baseline was 62 letters, and average central subfield thickness was 466-492 µm.[47]

Average improvement in BCVA In patients with DME after 1 year was similar upon comparison of aflibercept and faricimab (average gain of 10-12 letters).[47] About one-third of patients (29-35%) had a gain of 15 or more ETDRS letters which was comparable between groups.[47] In the group of patients with faricimab dose adjusted based on disease activity, a little over 50% of patients were receiving treatment every 16 weeks, 20% had dosing every 12 weeks, and 15% were on faricimab every 8 weeks.[47] A smaller, phase 2 trial comparing faricimab and ranibizumab in treatment-naïve patients demonstrated similar magnitude of benefit with an average gain of 13.9 ETDRS letters (80% CI 12.2 to 15.6) at 24 weeks with faricimab 6 mg monthly compared to 10.3 ETDRS letters (80% CI 8.8 to 11.9) with ranibizumab monthly (MD 3.6 letters; 80% CI 1.5 to 5.6).[44] Difference in BCVA did not achieve MCIDs referenced in the literature (5 ETDRS letters or approximately 1 line on the Snellen chart), and data were limited by imbalances in baseline characteristics and lack of methodological reporting for masking treatment groups. Results from these trials are generally applicable to patients with early disease and diabetes that is relatively well-controlled. The majority of patients had never received treatment for DME and had an average BCVA of 62 letters. Patients with retinal complications or DME which didn't involve the central fovea were excluded. Despite the fact that diabetes affects a large number of populations and communities that have been most impacted by historic and contemporary injustices and health inequities, people who identified as races other than white were underrepresented in these trials. Of patients with diabetes, population studies show that diabetic retinopathy is more prevalent in people of African or Asian or descent compared to patients identifying as White.[48] However, in these trials, only 8-11% identified as Asian and 4-8% identified as black.[47]

Age-related Macular Degeneration

In phase 3 trials for AMD, enrolled patients were at least 50 years of age and had treatment-naïve neovascular AMD with active choroidal neovascularization with a subfoveal component (involving the central portion of the macula).[49] Lesion size was required to be less than 9 disc areas, and choroidal neovascularization component area had to be less than 50% of the total session size.[49] Patients were excluded if they had uncontrolled blood pressure greater than 180/100 mmHg or uncontrolled glaucoma, or other eye conditions related to choroidal neovascularization or macular pathology. Patients with recent stroke, cancer, cataract surgery, or a history of uveitis were also excluded. The most common reasons for exclusion were lack of subfoveal involvement, inability to meet choroidal neovascularization lesion characteristics, BCVA outside of specified range (24-78 ETDRS letters), or the patient met other ocular exclusion criteria.[49]

Patients enrolled in the phase 3 trials were on average 75-76 years of age.[49] Most patients identified as White (83-90%); 8-11% identified as Asian and 8-14% identified Hispanic.[49] AMD is generally more common in patients who are White. This is generally representative of disease prevalence estimates. More than half of patients and average BCVA was 59-61 letters were within 1 month of diagnosis. Most patients had presence of intra-retinal (43-47%) or subretinal fluid (65-68%). After 40-48 weeks, about 45-46% of patients in the faricimab group were receiving treatment every 16 weeks. About 33-34% of patients received faricimab every 12 weeks.[49]

There was no difference between faricimab and aflibercept for the primary outcome (change in BCVA) at 40 to 48 weeks in both trials.[49] Average improvement from baseline was 5-7 ETDRS letters for both groups.[49] Similarly there was no difference in the proportion of patients gaining 15 or more ETDRS letters. The proportion of patients with a gain of 15 or more ETDRS letters was 20% for faricimab and 15.7% for aflibercept (MD 4.3% [95% CI −1.6 to 10.1]) in the first trial and 20% for faricimab and 22% for aflibercept (MD −2.0% [95% CI −8.3 to 4.3]) in the second trial.[49] Two phase 2 trials evaluated faricimab every 4, 12, or 16 weeks compared to ranibizumab 0.5 mg every 4 weeks.[42,43] Both trials recruited similar patients as phase 3 trials. Data from phase 2 trials were limited by small sample sizes, imbalances in baseline characteristics, and unclear reporting of trial methods. However, results are generally supportive of magnitude of benefit observed in phase 3 trials. In both trials, the average change in BCVA from baseline to 36 or 40 weeks was similar upon comparison of ranibizumab and faricimab at FDA approved doses (about 6-8 ETDRS letters in one trial and 9-12 letters in the second trial).[42,43]

Macular edema due to retinal vein occlusion

Phase 3 RCTs evaluating retinal vein occlusion enrolled participants with center-involved macular edema due to branched, central or hemi-retinal vein occlusion.[50] Participants were newly diagnosed with macular edema (within the past 4 months) and were excluded if they had prior treatment for macular edema. Other exclusion criteria included uncontrolled blood pressure, history of other systemic or ocular disease, macular neovascularization, or vitreomacular-interface abnormalities.[50] Participants were on average 65 years of age and primarily identified as white, Asian or Hispanic; other races were under-represented. The average BCVA at baseline was 50 and 57 ETDRS letters in each trial and participants were required to have a central subfield thickness of at least 325 µm.[50]

A 6 months, BCVA was improved by an average of 17 ETDRS letters with no difference between aflibercept 2 mg or faricimab 6 mg every 4 weeks in both RCTs.[50] Faricimab met the pre-specified non-inferiority margin of 4 ETDRS letters.[50] Similarly there was no difference between groups in the proportion of patients gaining 15 or more ETDRS letters. In each trial, 56.1% and 56.6% of patients treated with faricimab gained at least 15 ETDRS letters compared to 60.4% and 58.1% of patients treated with aflibercept.[50] In people with retinal vein occlusion, there is no comparative data on treat-and-extend dosing intervals with faricimab or comparative data beyond 6 months.

Clinical Safety:
In clinical trials, the most common adverse effects in patients receiving faricimab were cataracts and conjunctival hemorrhage.[46] Incidence of adverse events varied depending on the population studied (**Table 4**). Like other VEGF inhibitors, warnings and precautions in the labeling for faricimab include risk for endophthalmitis and retinal detachments, increases in intraocular pressure, thromboembolic events, retinal vasculitis and retinal vascular occlusion.[46] Faricimab is contraindicated in people with periocular infection or intraocular inflammation.[46]

Based on the mechanism of action, faricimab may impact reproductive capacity and embryo-fetal development.[46] Use of an effective contraceptive is recommended for anyone with reproductive potential during therapy and for at least 3 months following the last dose. In animals studies, an increased risk of pregnancy loss was observed with intravenous exposure at 158 times the recommended human dose of 6 mg monthly.[46]

Table 4. Adverse events occurring in more than 1% of patients during phase 3 clinical trials[46]

	Faricimab			Aflibercept		
	AMD N=664	DME N=1262	RVO N=641	AMD N=662	DME N=625	RVO N=635
Cataracts	3%	15%	<1%	2%	12%	1%
Conjunctival hemorrhage	7%	8%	3%	8%	7%	4%
Vitreous detachment	3%	5%	2%	3%	4%	2%
Vitreous floaters	3%	4%	2%	2%	3%	2%
Retinal pigment epithelial tear	3%	0%	0%	1%	0%	0%
Intraocular pressure increased	3%	4%	1%	2%	3%	3%
Eye pain	3%	3%	<1%	3%	3%	<1%
Intraocular inflammation	2%	1%	1%	1%	1%	<1%

Abbreviations: AMD = age-related macular edema; BCVA = best corrected visual acuity; DME = diabetic macular edema; RVO = retinal vein occlusion

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual acuity
2) Quality of life
3) Function (e.g., ability to drive, read, perform activities of daily living, etc)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in best corrected visual acuity (BCVA)

Table 5. Pharmacology and Pharmacokinetic Properties.[46]

Parameter	
Mechanism of Action	Inhibitor of angiopoietin 2 and vascular endothelial growth factor-A which promotes vascular stability, decreases vascular leakage, and prevents inflammation
Oral Bioavailability	Not applicable

Distribution and Protein Binding	C_{max} of about 0.2 mcg/mL in plasma at 2 days post-dose Mean plasma free trough concentrations of 0.02-0.03 mcg/mL for every 4-week dosing
Elimination	Not fully characterized; expected to be renally eliminated
Half-Life	7.5 days
Metabolism	Not fully characterized; expected to be catabolized into small peptides and amino acids which are renally eliminated

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Wykoff, et al. 2022.[47] YOSEMITE NCT03622580 Phase 3, DB, NI and superiority RCT	1. faricimab 6mg every 8 weeks (with every 4 week dosing up to week 20; 6 injections) 2. faricimab 6mg every 4 weeks through week 12 (4 injections) and until CST < 325 um. Dose was then adjusted to every 4, 8, 12, or 16 weeks per personalized treatment intervals at 4 week intervals. 3. aflibercept 2mg every 8 weeks (with every 4	Demographics: - Female: 37-43% - White 77-81% - Asian 8-10% - Black: 4-7% - BMI: 31 kg/m2 - HbA1c 7.6 (SD 1.1) - T2DM 92-96% - BCVA: 62 letters - CST: 484-492 um - Time since diagnosis: 14-17 months - Treatment-naïve:76-78% - Macular leakage 94-97% - DR absent or questionable: 55-60% - Proliferative DR: 6-7% Key Inclusion Criteria: - Age ≥18 years - T1DM or T2DM on treatment - HbA1c ≤10% - Center-involving DME - CST ≥ 325 um - BCVA 25-73 EDTRS letters (Snellen ~20/320 to 20/40) Key Exclusion Criteria: - VEGF therapy within 3 months - Recent initiation of DM treatment within prior 3 months - Active cancer in past year	ITT: 1. 315 2. 313 3. 312 PP (without major protocol deviations): 1. 251 2. 275 3. 274 Attrition: 1. 31 (9.8%) 2. 30 (9.6%) 3. 26 (8.3%)	Primary Endpoint: Change in BCVA at 1 year (averaged from weeks 48 to 56) 1. 10.7 letters (97.52% CI 9.4 to 12.0) 2. 11.6 letters (97.52% CI 10.3 to 12.9) 3. 10.9 letters (97.52% CI 9.6 to 12.2) 1. vs. 3: -0.2 (97.52% CI -2.0 to 1.6) 2. vs. 3: 0.7 (97.52% CI -1.1 to 2.5) non-inferiority met (margin of 4 letters) superiority criteria not met Secondary Endpoints: Dosing at 1 year (personalized therapy group) Every 4 weeks: 31 (11%) Every 8 weeks: 44 (15%) Every 12 weeks: 60 (21%) Every 16 weeks: 151 (53%) BCVA - gain in ETDRS letters (PP analysis) | | ≥15 | ≥10 | ≥5 | |---|---|---|---| | 1 | 29% | 57% | 79% | | 2 | 35% | 58% | 80% | | 3 | 32% | 58% | 81% | Difference between groups NR BCVA - no loss in ETDRS letters (PP analysis) | | ≥15 | ≥10 | ≥5 | |---|---|---|---| | 1 | 98% | 96% | 95% | | 2 | 99% | 98% | 97% | | 3 | 99% | 98% | 96% | BCVA gain ≥ 15 letters or Snellen ≥ 20/40 1. 32.1% (95% CI 26.6–37.6)	NA	Death 1.7 2.9 3.4 Non-fatal MI, stroke or death 1.9 (3%) 2.10 (3%) 3.9 (3%) Serious AEs 1. 171 2. 114 3. 96 Serious ocular AEs 1.6 (2%) 2.9 (3%) 3.2 (1%) Ocular AEs of interest* 1.6 (2%) 2.8 (3%) 3.1 (<1%) DC due to AEs 1. 6 (2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized via IVRS. Slight differences in time since DME diagnosis with a shorter time in faricimab 6 mg every 8 week group (difference of 3 months). Performance Bias: High. Patients, study site personnel, BCVA examiners, study vendors, central reading center personnel, and the sponsor and its agents were blinded via sham injections for non-active dosing visits. Differences in dosing regimens at weeks 16-24 unmasked patients and investigators to treatment groups. Detection Bias: High. BCVA examiners were blinded with use of sham injections. Differences in dosing regimens at weeks 16-24 unmasked patients and investigators to treatment groups.[45] Attrition Bias: Low. Primary analysis based on ITT and included only treatment-naïve patients. Mixed model for repeated measured used. Missing data imputed based on a missing at random mechanism. Data was censored after events due to the COVID pandemic (e.g., use of prohibited medications, missing doses, treatment discontinuation, death). Sensitivity analyses (including a per protocol analysis) conducted with various methods for missing data demonstrated similar results. Type 1 error were controlled for the primary outcome for NI analysis and superiority analyses in the treatment naïve and ITT populations.

	week dosing up to week 16; 5 injections) Screening period of up to 28 days	- Systemic treatment for suspected or active infection - Renal failure - Uncontrolled BP > 180/100 mmHg - Stroke or MI within prior 6 months - Other ocular conditions including tractional retinal detachment, pre-retinal fibrosis, active rubeosis, epiretinal membrane, vitreomacular traction, high-risk proliferative DR, uncontrolled glaucoma, history of retinal detachment or macular hole, other retinal disease-causing macular edema, history of immune-mediated uveitis, active ocular inflammation - Other conditions which could lead to vision loss (foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions) - Other ocular treatments including PRP, macular laser, anti-VEGF, intraocular surgery in prior 3 months; corticosteroid injections or implants in prior 6 months		2. 39.1% (95% CI 33.5–44.7) 3. 37.0% (95% CI 31.5–42.5) Snellen ≥ 20/40 1. 71.6 (95% CI 66.5–76.6) 2. 77.1 (95% CI 72.4–81.8) 3. 74.8 (95% CI 69.9–79.6) Patients with ≥ 2 step improvement in ETDRS DRSS 1. 46.0% (97.52% CI 38.8–53.1) 2. 42.5% (97.52% CI 35.5–49.5) 3. 35.8% (97.52% CI 29.1–42.5) NI margin of -10% met		2. 8 (3%) 3. 3 (1%)		Reporting Bias: Unclear. Statistical analyses between groups for secondary endpoints were not included. Pre-specified endpoint evaluating visual functioning and quality of life was not reported. Other Bias: Unclear. F Hoffmann-La Roche participated in the study design, data collection, analysis and interpretation, and report writing. **Applicability**: Patient: Majority of participants identified as White and on average had DM that was controlled. Patients with HbA1c >10% and high-risk proliferative diabetic retinopathy, groups commonly treated in clinical practice, were excluded. Inclusion criteria limited enrollment to a subset of patients. Data is most applicable to patients who have mild vision loss, were treatment naïve, and had well-controlled diabetes without diabetic retinopathy. Intervention: Evaluations every 4 weeks which is likely more frequent than standard practice. Disease activity criteria used to determine dosing frequency is unvalidated.[45] Comparator: Aflibercept at FDA-approved dose and treatment intervals. Study was not designed to compare faricimab to treat-and-extend dosing for aflibercept. Since studies were not designed to evaluate durability of response, conclusions regarding less frequent dosing of faricimab compared to aflibercept cannot be made.[45] Outcomes: BCVA is a well-studied outcome to evaluate visual acuity. A difference of about 5 letters is typically considered clinically significant and corresponds to about one line on the ETDRS chart. Prespecified NI margin established at 4 letters which is reasonable based on prior studies and the MCID. Setting: 179 sites in 16 countries. Enrollment in the US or Canada: 54%

<table>
<tr>
<td>2. Wykoff, et al. 2022.[47]

RHINE

Phase 3, DB, NI and superiority RCT</td>
<td>1. faricimab 6mg every 8 weeks (with every 4 week dosing up to week 20)

2. faricimab 6mg every 4 weeks through week 12 and until CST < 325 um. Dose was then adjusted per personalized treatment intervals at 4 week intervals.

3. aflibercept 2mg every 8 weeks (with every 4 week dosing up to week 16)

See YOSEMITE</td>
<td><u>Demographics</u>:
- Female: 38-41%
- White: 78-80%
- Asian 10-11%
- Black: 6-8%
- BMI: 30 kg/m2
- HbA1c: 7.7%
- T2DM: 94-95%
- BCVA: 62 letters
- CST: 466-477 um
- Time since diagnosis: 19-20 months
- Treatment-naïve:79-80%
- Macular leakage 95-97%
- DR absent or questionable: 56-58%
- Proliferative DR: 6-12%

<u>Key Inclusion Criteria</u>:
- See YOSEMITE

<u>Key Exclusion Criteria</u>:
- See YOSEMITE</td>
<td><u>ITT</u>:
1. 317
2. 319
3. 315

<u>PP:</u>
1. 258
2. 271
3. 273

<u>Attrition</u>:
1. 24 (7.6%)
2. 11 (3.5%)
3. 19 (6.0%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at 1 year (averaged from weeks 48 to 56)
1. 11.8 letters (97.52% CI 10.6 to 13.0)
2. 10.8 letters (97.52% CI 9.6 to 11.9)
3. 10.3 letters (97.52% CI 9.1 to 11.4)
1. vs. 3: 1.5 (97.52% CI -0.1 to 3.2)
2. vs. 3: 0.5 (97.52% CI -1.1 to 2.1)
non-inferiority met (margin of 4 letters)
superiority criteria not met

<u>Secondary Endpoints</u>:
Dosing at 1 year (personalized therapy group)
Every 4 weeks: 41 (13%)
Every 8 weeks: 48 (16%)
Every 12 weeks: 62 (20%)
Every 16 weeks: 157 (51%)

BCVA - gain in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>34%</td><td>59%</td><td>82%</td></tr><tr><td>2</td><td>29%</td><td>53%</td><td>77%</td></tr><tr><td>3</td><td>30%</td><td>54%</td><td>78%</td></tr></table>Difference between groups NR

BCVA - no loss in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>99%</td><td>98%</td><td>97%</td></tr><tr><td>2</td><td>99%</td><td>98%</td><td>97%</td></tr><tr><td>3</td><td>99%</td><td>98%</td><td>95%</td></tr></table>BCVA gain ≥ 15 letters or Snellen ≥ 20/40
1. 38.3 (95% CI 32.6–44.0)
2. 32.4 (95% CI 27.2–37.6)
3. 33.5 (95% CI 28.1–38.9)

Snellen ≥ 20/40
1. 73.2 (95% CI 68.2–78.3)
2. 71.6 (95% CI 66.7–76.4)
3. 68.5 (95% CI 63.6–73.5)

BCVA ≥ 2 step improvement in ETDRS
1. 44.2% (97.52% CI 37.1–51.4)
2. 43.7% (97.52% CI 36.8–50.7)
3. 46.8% (97.52% CI 39.8–53.8)
NI margin of -10% not met</td>
<td>NA</td>
<td><u>Death</u>
1. 5
2. 0
3. 5

<u>Non-fatal MI, stroke, or death</u>
1. 4 (1%)
2. 2 (1%)
3. 5 (2%)

<u>Serious Non-ocular AEs</u>
1. 101
2. 79
3. 95

<u>Serious ocular AEs</u>
1. 9 (3%)
2. 10 (3%)
3. 6 (2%)

<u>Ocular AEs of interest*</u>
1. 9 (3%)
2. 9 (3%)
3. 5 (2%)

<u>DC due to AEs</u>
1. 4 (1%)
2. 4 (1%)
3. 4 (1%)</td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. See YOSEMITE
<u>Performance Bias</u>: High. See YOSEMITE
<u>Detection Bias</u>: High. See YOSEMITE
<u>Attrition Bias</u>: Low. See YOSEMITE
<u>Reporting Bias</u>: Unclear. See YOSEMITE
<u>Other Bias:</u> Unclear. See YOSEMITE

Applicability:
<u>Patient</u>: See YOSEMITE
<u>Intervention</u>: See YOSEMITE
<u>Comparator</u>: See YOSEMITE
<u>Outcomes</u>: See YOSEMITE
<u>Setting</u>: 174 sites in 24 countries. Enrollment in the US or Canada: 35%.</td>
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<tr>
<td>3. Heier, et al. 2022.[49]

TENAYA
NCT03823287

DB, NI, MC, AC, RCT

Duration: 112 weeks</td>
<td>1. faricimab 6.0 mg every 4 weeks (4 injections) then every 8, 12, or 16 weeks based on disease activity at 20 or 24 weeks

2. Aflibercept 2.0 mg every 4 weeks for 3 injection then every 8 weeks

48 weeks with fixed treatment regimen. After 60 weeks dosing could be adjusted based on disease activity from 8 to 16 weeks.</td>
<td><u>Demographics</u>:
- Age: 76 years
- Female: 57-63%
- White: 90-91%
- Asian: 8%
- Hispanic: 8%
- BCVA 61 letters
- CST: 356-360 µm
- IOP: 15 mmHg
- Time since diagnosis ≤ 1 month: 74%
- Phakic: 55-58%
- Intraretinal fluid: 44-47%
- Subretinal fluid: 67-65%
- CNV location
Subfoveal 55-60%
Juxtafoveal: 26%
Extrafoveal: 12-16%
- CNV lesion type
Occult 52-53%
Classic 22-25%

<u>Key Inclusion Criteria</u>:
- Age ≥ 50 years
- Treatment-naïve
- CNV secondary to neovascular AMD
- Subfoveal CNV or other CNV with subfoveal component
- CNV lesion size ≤ 9 disc areas
- CNV component area ≥50% total lesion area
- Active CNV with exudation (fluid)
- BCVA 78-24 ETDRS letters (~20/32−20/320 Snellen equivalent)

<u>Key Exclusion Criteria</u>:
- Any prior CNV treatment or intraocular surgery
- Uncontrolled blood pressure >180/100 mmHg
- Stroke in prior 6 months
- Uncontrolled glaucoma</td>
<td><u>ITT</u>:
1. 334
2. 337

<u>PP</u> (at least one non-missing BVCA at 40-48 weeks)
1. 292
2. 300

<u>Attrition</u>:
1. 26 (8%)
2. 15 (5%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at 40-48 weeks
1. 5.8 letters (95% CI 4.6 to 7.1)
2. 5.1 letters (95% CI 3.9 to 6.4)
MD 0.7 letters (95% CI −1.1 to 2.5)

<u>Secondary Endpoints</u>:
Dosing interval
Every 8 weeks: 64 (20%)
Every 12 weeks: 107 (34%)
Every 16 weeks: 144 (46%)

BCVA - gain in ETDRS letters (PP analysis)
<table><tr><th></th><th>≥15</th><th>≥10</th><th>≥5</th><th>≥0</th></tr><tr><td>1</td><td>20.0</td><td>37.1</td><td>59.2</td><td>75.6</td></tr><tr><td>2</td><td>15.7</td><td>31.7</td><td>58.0</td><td>76.8</td></tr></table>MD ≥15 letters: 4.3 (95% CI −1.6 to 10.1)
MD ≥10 letters: 5.4 (95% CI −2.0 to 12.7)
MD ≥5 letters: 1.2 (95% CI −6.6 to 8.9)
MD ≥0 letters: −1.2 (95% CI −7.9 to 5.4)

BCVA – no loss in ETDRS letters (PP analysis)
<table><tr><th></th><th>≥15</th><th>≥10</th><th>≥5</th></tr><tr><td>1</td><td>95.4</td><td>91.6</td><td>88.0</td></tr><tr><td>2</td><td>94.1</td><td>92.0</td><td>86.8</td></tr></table>MD ≥15 letters: 1.3 (95% CI −2.2 to 4.8)
MD ≥10 letters: −0.4 (95% CI −4.6 to 3.9)
MD ≥5 letters: 1.2 (95% CI −4.0 to 6.4)

BCVA- gain of ≥ 15 ETDRS letters OR BCVA ≥84 ETDRS letters
1. 24.3 (95% CI 19.5, 29.1)
2. 21.3 (95% CI 16.8, 25.7)
MD 3.0 (95% CI −3.6, 9.5)

BCVA Snellen equivalent ≥ 20/40
1. 56.4 (95% CI 51.5, 61.4)
2. 57.0 (95% CI 51.9, 62.1)
MD −0.5 (95% CI −7.7, 6.6)

BCVA Snellen equivalent ≤20/200
1. 6.4 (95% CI 3.7, 9.1)
2. 6.9 (95% CI 4.2, 9.5)
MD −0.5 (95% CI −4.2, 3.3)

Change in CST at 40-48 weeks</td>
<td></td>
<td><u>Serious non-ocular AEs</u>
1. 30 (9%)
2. 34 (10%)

<u>Serious Ocular AEs</u>
1. 4 (1%)
2. 6 (2%)

<u>Intra-ocular inflam-mation</u>
1. 5 (2%)
2. 2 (1%)

<u>Death, Non-fatal MI, stroke</u>
1. 3 (1%)
2. 3 (1%)

<u>DC due to AEs</u>
1. 3 (1%)
2. 3 (1%)</td>
<td></td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. Randomized via interactive voice or web-based response system. Baseline characteristics generally balanced between groups.
<u>Performance Bias</u>: High. Blinded with use of sham injections at non-active dosing visits. Differences in treatment regimen resulted in unmasking of treatment groups at week 12.[45]
<u>Detection Bias</u>: High. BCVA examiners masked to treatment with use of sham injections. Differences in treatment regimen resulted in unmasking of treatment groups at week 12.[45]
<u>Attrition Bias</u>: Low. ITT analysis used for primary and secondary endpoints. PP analysis was consistent with ITT analysis. Missing data were imputed using MMRM analysis assuming a missing at random mechanism. At least one missing outcome assessment from 36-48 weeks in 22% of aflibercept and 17% of faricimab patients. Clinical rationale and justification provided for non-inferiority margin of 4 letters. No adjustment for multiplicity of secondary outcomes.
<u>Reporting Bias</u>: Low. Outcomes reported as pre-specified.
<u>Other Bias:</u> Unclear. F Hoffmann-La Roche participated in the study design, data collection, analysis and interpretation, and report writing.

Applicability:
<u>Patient</u>: Most applicable to patients who are treatment-naïve with mild vision loss and a recent diagnosis. Majority of people identified as white; other races were under-represented. People with comorbid ocular conditions or recent major illness were excluded.
<u>Intervention</u>: Study visits every 4 weeks. Lack of randomization for faricimab dosing intervals prevents evaluations on comparative efficacy of each regimen (e.g., injections given every 8, 12 or 16 weeks).[45]
<u>Comparator</u>: Aflibercept administered at FDA-approved dose and intervals. Treat-and-</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>- Cataract surgery within prior 3 months
- History of uveitis
- Other eye conditions related to CNV or macular pathology including myopia with refractory error >8 diopters, central serous chorioretinopathy, retinal pigment epithelial tear involving the macula, subretinal hemorrhage or fibrosis/atrophy > 50% of total lesion size, vitreous hemorrhage
- Cancer within prior 12 months
- Major illness, infection, surgery in prior 1 month</td>
<td></td>
<td>1. −136.8 µm (95% CI −142.6 to −131.0)
2. −129.4 µm (95% CI −135.2 to −123.5)
MD −7.4 µm (95% CI −15.7 to 0.8)</td>
<td></td>
<td></td>
<td></td>
<td>extend dosing regimens which are common in clinical practice were not evaluated for aflibercept.
Outcomes: Long-term outcomes are unknown, and up to 2-3 years of data may be needed to assess durability.
Setting: 149 sites in 15 countries. Enrollment in US and Canada: 54-55%.</td>
</tr>
<tr>
<td>4. Heier, et al. 2022.[49]

LUCERNE NCT03823300</td>
<td>1. faricimab 6.0 mg every 4 weeks (4 injections) then every 8, 12, or 16 weeks based on disease activity at 20 or 24 weeks

2. Aflibercept 2.0 mg every 4 weeks for 3 injection then every 8 weeks

See TENAYA</td>
<td>Demographics:
- Age: 75-76 years
- Female: 57-61%
- White: 83-84%
- Asian: 10-11%
- Hispanic: 11-14%
- BCVA 59 letters
- CST: 353-359 µm
- IOP: 15 mmHg
- Time since diagnosis ≤ 1 month: 64-67%
- Phakic: 57%
- Intraretinal fluid: 43-47%
- Subretinal fluid: 67-68%
- CNV location
Subfoveal 58-63%
Juxtafoveal: 22-26%
Extrafoveal: 13%
- CNV lesion type
Occult 43-52%
Classic 30-33%

Key Inclusion Criteria:
See TENAYA

Key Exclusion Criteria:
See TENAYA</td>
<td>ITT:
1. 331
2. 327

PP (at least one non-missing BVCA at 40-48 weeks)
1. 302
2. 291

Attrition:
1. 18 (5%)
2. 22 (7%)</td>
<td>Primary Endpoint:
Change in BCVA at 40-48 weeks (NI margin of 4 letters)
1. 6.6 letters (95% CI 5.3 to 7.8)
2. 6.6 letters (95% CI 5.3 to 7.8)
MD 0.0 letters (95% CI –1.7 to 1.8)

Secondary Endpoints:
Dosing interval
Every 8 weeks: 70 (22%)
Every 12 weeks: 104 (33%)
Every 16 weeks: 142 (45%)

BCVA - gain in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td><td>≥0</td></tr><tr><td>1</td><td>20.2</td><td>39.2</td><td>60.5</td><td>82.2</td></tr><tr><td>2</td><td>22.2</td><td>35.8</td><td>59.4</td><td>79.1</td></tr></table>MD ≥15 letters: −2.0 (95% CI −8.3 to 4.3)
MD ≥10 letters: 3.4 (95% CI −3.9 to 10.7)
MD ≥5 letters: 1.0 (95% CI −6.6 to 8.6)
MD ≥0 letters: 3.1 (95% CI −3.1 to 9.3)

BCVA - no loss in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>95.8</td><td>93.8</td><td>91.2</td></tr><tr><td>2</td><td>97.3</td><td>94.6</td><td>88.5</td></tr></table>MD ≥15 letters: −1.5 (95% CI −4.4 to 1.3)
MD ≥10 letters: −0.9 (95% CI −4.5 to 2.8)</td>
<td></td>
<td>Serious non-ocular AEs
1. 38 (11%)
2. 48 (15%)

Serious Ocular AEs
1. 7 (2%)
2. 7 (2%)

Intra-ocular inflam-mation
1. 8 (2%)
2. 6 (2%)

Death, Non-fatal MI, stroke
1. 4 (1%)
2. 3 (1%)

DC due to AEs
1. 8 (2%)</td>
<td></td>
<td>Risk of Bias (low/high/unclear):
Selection Bias: Low; See TENAYA. Most baseline characteristics balanced. Imbalances in time since diagnosis and proportion of patients with occult choroidal neovascularization lesions. It’s unclear if or how these imbalances may impact results.
Performance Bias: High. See TENAYA.
Detection Bias: High See TENAYA.
Attrition Bias: Low. See TENAYA. At least one missing outcome assessment from 36-48 weeks in 16% of aflibercept and 17% of faricimab patients. Results from per protocol analysis were consistent with ITT analysis.
Reporting Bias: Low. See TENAYA.
Other Bias: Unclear. See TENAYA.

Applicability:
Patient: See TENAYA.
Intervention: See TENAYA.
Comparator: See TENAYA.
Outcomes: See TENAYA.
Setting: 122 sites in 20 countries. Enrollment in US and Canada: 40-41%</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MD ≥5 letters: 2.6 (95% CI −2.1 to 7.3)

BCVA- gain of ≥ 15 ETDRS letters OR BCVA ≥84 ETDRS letters
1. 24.5 (95% CI 19.8, 29.2)
2. 26.2 (95% CI 21.2, 31.1)
MD − 1.7 (95% CI −8.5, 5.1)

BCVA Snellen equivalent ≥ 20/40
1. 55.2 (95% CI 50.1, 60.2)
2. 49.4 (95% CI 44.4, 54.4)
MD 5.7 (95% CI −1.4, 12.9)

BCVA Snellen equivalent ≤20/200
1. 7.9 (95% CI 5.0, 10.8)
2. 7.5 (95% CI 4.7, 10.3)
MD 0.4 (95% CI −3.6, 4.4)

Change in CST at 40-48 weeks
1. −137.1 µm (95% CI −143.1 to −131.2)
2. −130.8 µm (95% CI −136.8 to −124.8)
MD −6.4 µm (95% CI −14.8 to 2.1)</td>
<td></td>
<td>2. 1 (<1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Tadayoni, et al. 2024.[50]

Hattenbach, et al. 2023.[51]

BALATON NCT04740 905

MC, DB, phase 3 RCT

Duration: 72 weeks</td>
<td>1. faricimab 6 mg every 4 weeks

2. Aflibercept 2 mg every 4 weeks

After 24 weeks, all participants transitioned to faricimab with treat and extend dosing where dose interval (from 4-16 weeks) was determined based on</td>
<td><u>Demographics</u>:
- Age 64-65 years
- Female 48-53%
- White: 62%
- Asian: 33-34%
- Hispanic 17-18%
- Mean BCVA: 57 letters
- BCVA ≥55 letters: 68%
- Mean CST 558 µm
- Time since diagnosis: 1.3-1.7 months

<u>Key Inclusion Criteria</u>:
- Age ≥18 years
- Center-involved macular edema due to RVO (branched)
- BCVA 73 to 19 ETDRS letters
- CST≥325 µm

<u>Key Exclusion Criteria</u>:
- Prior treatment for macular edema (e.g., VEGF inhibitors,</td>
<td><u>ITT</u>:
1. 276
2. 277

PP:
1. 241
2. 243

<u>Attrition</u>:
1. 9 (3%)
2. 3 (1%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at week 24 (NI margin: 4 letters)
1. 16.9 ETDRS letters (95% CI 15.7 to 18.1)
2. 17.5 ETDRS letters (95% CI 16.3 to 18.6)
MD -0.6 ETDRS (95% CI -2.2 to 1.1)

<u>Secondary Endpoints</u>:
Change in CST
1. -311.4 µm (95% CI -316.4 to -306.4)
2. -304.4 µm (95% CI -309.3 to -299.4)
Differences not reported

BCVA - gain in ETDRS letters
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td><td>≥0</td></tr><tr><td>1</td><td>56.1%</td><td>77.5%</td><td>90.9%</td><td>97.1%</td></tr><tr><td>2</td><td>60.4%</td><td>77.3%</td><td>89.6%</td><td>95.7%</td></tr></table>Differences not reported

BCVA - no loss in ETDRS letters
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>99.6%</td><td>99.6%</td><td>98.6%</td></tr><tr><td>2</td><td>98.6%</td><td>98.2%</td><td>97.5%</td></tr></table>Differences not reported</td>
<td>NS</td>
<td><u>Non-ocular serious AE</u>
1. 9
2. 16

<u>Serious ocular AE</u>
1. 3 (1.1%)
2. 2 (0.7%)

<u>Death, stroke, or MI</u>
1. 3 (1.1%)
2. 4 (1.5%)

<u>DC due to ocular AE</u>
None

<u>Intraocular Inflam-mation</u></td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. Adequate randomization and allocation concealment with use of IVRS. Stratified by baseline BCVA and geographic region. Baseline characteristics were generally balanced between groups.
<u>Performance Bias</u>: Unclear. Patients and providers were masked to treatment (method not described).
<u>Detection Bias</u>: Unclear. BCVA examiners were masked to treatment and study eye. Imaging technicians and central reading center graders were masked to study treatment. Method of blinding not described.
<u>Attrition Bias</u>: Low. Low rate of patients who discontinued treatment. Primary outcome was assessed using a mixed model for repeated measures analysis with missing data imputed assuming a missing at random mechanism. Protocol deviations occurred in 26.8% of visits (missed visits accounted for 15.7%); 6% were related to COVID-19. Sensitivity analyses performed with similar results in the PP population and using various</td>
</tr>
</table>

	changes in CST and BCVA	steroids, macular laser, or panretinal coagulation) - Diagnosis > 4 months before screening - Uncontrolled blood pressure - History of other systemic or ocular disease - Macular neovascularization - Vitreomacular-interface abnormalities				None		imputation methods including imputation based on non-random data with worse outcomes. Reporting Bias: Unclear. Most outcomes reported as pre-specified. Statistical differences between groups were not reported for secondary endpoints. The National Eye Institute Visual Function Questionnaire 25 score was pre-specified as a patient-reported secondary endpoint but results were not described. Other Bias: Unclear. Funded by the manufacturer of faricimab who was involved in study design, data collection, analysis, interpretation and writing of the report. **Applicability**: Patient: Data is most applicable to people newly diagnosed with macular edema due to RVO who are treatment naïve. Most study participants identified as White (62%), Asian (33%), or Hispanic (18%). Other races were under-represented. Intervention: Monthly dosing interval is consistent with FDA-label. No comparative data available on durability of response with extended dosing intervals. Comparator: Aflibercept administered every 4 weeks is consistent with FDA-labeled dosing, but may be more frequent than dosing in clinical practice. Outcomes: Short treatment duration (~6 months) makes it difficult to assess long-term comparative durability. Setting: 22 countries; 149 sites from March 2021 to February 2022. ~22-23% of patients were in the United States or Canada.

<table>
<tr>
<td>6. Tadayoni, et al. 2024.[50]

Hattenbach, et al. 2023.[51]

COMINO NCT04740931

MC, DB, phase 3 RCT

Duration: 72 weeks</td>
<td>1. faricimab 6 mg every 4 weeks

2. Aflibercept 2 mg every 4 weeks

After 24 weeks, all participants transitioned to faricimab with treat and extend dosing where dose interval (from 4-16 weeks) was determined based on changes in CST and BCVA</td>
<td><u>Demographics</u>:
- Mean age: 65 years
- Female 45-47%
- White: 66-69%
- Asian: 24%
- Hispanic: 18-20%
- Mean BCVA: 50-51 letters
- BCVA ≥ 55 letters: 49%
- Mean CST 702-721 µm
- Time since diagnosis 1.1-1.6 months

<u>Key Inclusion Criteria</u>:
- See BALATON
- Center-involved macular edema due to RVO (central or hemiretinal)

<u>Key Exclusion Criteria</u>:
- See BALATON</td>
<td><u>ITT</u>:
1. 366
2. 363

PP:
1. 328
2. 311

<u>Attrition</u>:
1. 11 (3%)
2. 15 (4%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at week 24 (NI margin: 4 letters)
1. 16.9 ETDRS letters (95% CI 15.4 to 18.3)
2. 17.3 ETDRS letters (95% CI 15.9 to 18.8)
MD -0.4 ETDRS letters (95% CI -2.5 to 1.6)

<u>Secondary Endpoints</u>:
Change in CST
1. -461.6 µm (95% CI -471.4 to -451.9)
2. -448.8 µm (95% CI -458.6 to -439.0)
Difference not reported

BCVA - gain in ETDRS letters
<table>
<tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td><td>≥0</td></tr>
<tr><td>1</td><td>56.6%</td><td>72.2%</td><td>85.3%</td><td>91.6%</td></tr>
<tr><td>2</td><td>58.1%</td><td>73.3%</td><td>84.6%</td><td>89.8%</td></tr>
</table>
Differences not reported

BCVA - no loss in ETDRS letters
<table>
<tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr>
<tr><td>1</td><td>96.2%</td><td>95.1%</td><td>94.0%</td></tr>
<tr><td>2</td><td>96.7%</td><td>95.9%</td><td>93.7%</td></tr>
</table>
Differences not reported</td>
<td>NS</td>
<td><u>Non-ocular serious AE</u>
1. 22
2. 23

<u>Serious ocular AEs</u>
1. 9 (2.5%)
2. 12 (3.3%)

<u>Death, stroke, or MI</u>
1. 4 (1.1%)
2. 5 (1.4%)

<u>DC due to ocular AE</u>
1. 3
2. 2

<u>Intraocular inflam-mation</u>
1. 8 (2.2%)
2. 4 (1.1%)</td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. See BALATON. Slight differences in CST between groups but the clinical significance of these differences is unclear.
<u>Performance Bias</u>: Unclear. See BALATON
<u>Detection Bias</u>: Unclear. See BALATON
<u>Attrition Bias</u>: Low. See BALATON. Protocol deviations occurred in 29.8% of visits (missed visits accounted for 17.1%); 7% were related to COVID-19.
<u>Reporting Bias</u>: Unclear. See BALATON
<u>Other Bias:</u> Unclear. See BALATON

Applicability:
<u>Patient</u>: See BALATON
<u>Intervention</u>: See BALATON
<u>Comparator</u>: See BALATON
<u>Outcomes</u>: See BALATON
<u>Setting</u>: 22 countries; 149 sites from March 2021 to February 2022. ~25-26% of patients were in the United States or Canada.</td>
</tr>
<tr>
<td colspan="8"><u>Abbreviations</u> [alphabetical order]: AC = active comparison; ARR = absolute risk reduction; BCVA = best corrected visual acuity; BMI = body mass index; CI = confidence interval; CNV = choroidal neovascularization; CST = central subfield thickness; DB = double blind; DC = discontinuation; DME = diabetic macular edema; DR = diabetic retinopathy; DRSS = diabetic retinopathy severity scale; ETDRS=early treatment diabetic retinopathy study; HbA1c = glycated hemoglobin IOP = intraocular pressure; ITT = intention to treat; MC = multicenter; MD = mean difference; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; nAMD = neovascular age-related macular degeneration; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; PRP = panretinal photocoagulation; RCT = randomized clinical trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; VEGF = vascular endothelial growth factor
*Ocular AEs of interest were defined as events associated with severe intraocular inflammation, events requiring surgical or medical intervention to prevent permanent loss of sight, or events associated with BCVA loss of 30 ETDRS letters or more for more than 1 hour.</td>
</tr>
</table>

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
bevacizumab	AVASTIN	VIAL	INTRAVEN	Y
aflibercept	EYLEA	SYRINGE	INTRAOCULR	N
aflibercept	EYLEA	VIAL	INTRAOCULR	N
brolucizumab-dbll	BEOVU	SYRINGE	INTRAOCULR	N
brolucizumab-dbll	BEOVU	VIAL	INTRAOCULR	N
faricimab-svoa	VABYSMO	VIAL	INTRAOCULR	N
ranibizumab	LUCENTIS	SYRINGE	INTRAOCULR	N
ranibizumab	LUCENTIS	VIAL	INTRAOCULR	N
ranibizumab	SUSVIMO	VIAL	IMPLANT	N
ranibizumab/init fill needle	SUSVIMO	VIAL	IMPLANT	N
ranibizumab-nuna	BYOOVIZ	VIAL	INTRAOCULR	N

Appendix 2: Abstracts of Comparative Clinical Trials

Jhaveri CD, Glassman AR, Ferris FL, 3rd, et al. Aflibercept Monotherapy or Bevacizumab First for Diabetic Macular Edema. *The New England journal of medicine.* 2022;387(8):692-703.

BACKGROUND: In eyes with diabetic macular edema, the relative efficacy of administering aflibercept monotherapy as compared with bevacizumab first with a switch to aflibercept if the eye condition does not improve sufficiently (a form of step therapy) is unclear., METHODS: At 54 clinical sites, we randomly assigned eyes in adults who had diabetic macular edema involving the macular center and a visual-acuity letter score of 24 to 69 (on a scale from 0 to 100, with higher scores indicating better visual acuity; Snellen equivalent, 20/320 to 20/50) to receive either 2.0 mg of intravitreous aflibercept or 1.25 mg of intravitreous bevacizumab. The drug was administered at randomization and thereafter according to the prespecified retreatment protocol. Beginning at 12 weeks, eyes in the bevacizumab-first group were switched to aflibercept therapy if protocol-specified criteria were met. The primary outcome was the mean change in visual acuity over the 2-year trial period. Retinal central subfield thickness and visual acuity at 2 years and safety were also assessed., RESULTS: A total of 312 eyes (in 270 adults) underwent randomization; 158 eyes were assigned to receive aflibercept monotherapy and 154 to receive bevacizumab first. Over the 2-year period, 70% of the eyes in the bevacizumab-first group were switched to aflibercept therapy. The mean improvement in visual acuity was 15.0 letters in the aflibercept-monotherapy group and 14.0 letters in the bevacizumab-first group (adjusted difference, 0.8 letters; 95% confidence interval, -0.9 to 2.5; P = 0.37). At 2 years, the mean changes in visual acuity and retinal central subfield thickness were similar in the two groups. Serious adverse events (in 52% of the patients in the aflibercept-monotherapy group and in 36% of those in the bevacizumab-first group) and hospitalizations for adverse events (in 48% and 32%, respectively) were more common in the aflibercept-monotherapy group., CONCLUSIONS: In this trial of treatment of moderate vision loss due to diabetic macular edema involving the center of the macula, we found no evidence of a significant difference in visual outcomes over a 2-year period between aflibercept monotherapy and treatment with bevacizumab first with a switch to aflibercept in the case of suboptimal response. (Funded by the National Institutes of Health; Protocol AC ClinicalTrials.gov number, NCT03321513.).

Khanani AM, Brown DM, Jaffe GJ, et al. MERLIN: Phase 3a, Multicenter, Randomized, Double-Masked Trial of Brolucizumab in Participants with Neovascular Age-Related Macular Degeneration and Persistent Retinal Fluid. *Ophthalmology.* 2022;129(9):974-985.

PURPOSE: To assess the 52-week efficacy and safety of brolucizumab 6 mg administered every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks in eyes with neovascular age-related macular degeneration (nAMD) and persistent retinal fluid. DESIGN: Multicenter, randomized, double-masked phase 3a study. PARTICIPANTS: Participants with recalcitrant nAMD (persistent residual retinal fluid despite previous frequent anti-vascular endothelial growth factor treatment). METHODS: Eyes were randomized (2:1) to intravitreal brolucizumab 6 mg or aflibercept 2 mg every 4 weeks up to and including week 100. MAIN OUTCOME MEASURES: The primary end point was analysis of noninferiority in mean best-corrected visual acuity (BCVA) change from baseline to week 52 (margin, 4 letters). Other key end points included change in central subfield thickness (CST) from baseline to week 52, fluid-free status (no intraretinal fluid and no subretinal fluid), and safety. RESULTS: At week 52, brolucizumab was noninferior to aflibercept in BCVA change from baseline (least squares mean difference, -0.6 Early Treatment Diabetic Retinopathy Study letters; 95% confidence interval [CI], -2.1 to 0.9; P < 0.001). A total of 4.8% and 1.7% of participants reported a 15-letter or more BCVA loss from baseline at week 52 in the brolucizumab and aflibercept groups, respectively. In eyes treated with brolucizumab compared with those treated with aflibercept, the CST was reduced significantly (P < 0.001), and a significantly greater proportion of eyes were fluid free at week 52 (40.4% brolucizumab vs. 19.0% aflibercept; 95% CI, 13.9-29.0; P < 0.001). Incidence of intraocular inflammation (IOI), including retinal vasculitis and retinal vascular occlusion, were 9.3% (0.8% and 2.0%) for brolucizumab versus 4.5% (0% and 0%) for aflibercept, respectively. CONCLUSIONS: Visual acuity outcomes in previously treated participants with nAMD and persistent retinal fluid receiving brolucizumab 6 mg dosed every 4 weeks were noninferior to aflibercept 2 mg dosed every 4 weeks, with superior anatomic outcomes. However, incidences of IOI, including retinal vasculitis and retinal vascular occlusion, also were higher, leading to study termination.

Regillo C, Berger B, Brooks L, et al. Archway Phase 3 Trial of the Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration 2-Year Results. *Ophthalmology.* 2023;130(7):735-747.

PURPOSE: To report 2-year results from the Archway clinical trial of the Port Delivery System with ranibizumab (PDS) for treatment of neovascular age-related macular degeneration (nAMD)., DESIGN: Phase 3, randomized, multicenter, open-label, active-comparator-controlled trial., PARTICIPANTS: Patients with previously treated nAMD diagnosed within 9 months of screening and responsive to anti-vascular endothelial growth factor therapy., METHODS: Patients were randomized 3:2 to PDS with ranibizumab 100 mg/ml with fixed refill-exchanges every 24 weeks (PDS Q24W) or intravitreal ranibizumab 0.5 mg injections every 4 weeks (monthly ranibizumab).

Patients were followed through 4 complete refill-exchange intervals (~2 years)., MAIN OUTCOME MEASURES: Change in best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score from baseline averaged over weeks 44 and 48, weeks 60 and 64, and weeks 88 and 92 (noninferiority margin, -3.9 ETDRS letters)., RESULTS: The PDS Q24W was noninferior to monthly ranibizumab, with differences in adjusted mean change in BCVA score from baseline averaged over weeks 44/48, 60/64 and 88/92 of -0.2 (95% confidence interval [CI], -1.8 to +1.3), +0.4 (95% CI, -1.4 to +2.1) and -0.6 ETDRS letters (95% CI, -2.5 to +1.3), respectively. Anatomic outcomes were generally comparable between arms through week 96. Through each of 4 PDS refill-exchange intervals, 98.4%, 94.6%, 94.8%, and 94.7% of PDS Q24W patients assessed did not receive supplemental ranibizumab treatment. The PDS ocular safety profile was generally unchanged from primary analysis. Prespecified ocular adverse events of special interest (AESI) were reported in 59 (23.8%) PDS and 17 (10.2%) monthly ranibizumab patients. The most common AESI reported in both arms was cataract (PDS Q24W, 22 [8.9%]; monthly ranibizumab, 10 [6.0%]). Events in the PDS Q24W arm included (patient incidence) 10 (4.0%) conjunctival erosions, 6 (2.4%) conjunctival retractions, 4 (1.6%) endophthalmitis cases, and 4 (1.6%) implant dislocations. Serum ranibizumab sampling showed that the PDS continuously released ranibizumab over the 24-week refill-exchange interval and ranibizumab serum concentrations were within the range experienced with monthly ranibizumab., CONCLUSIONS: The PDS Q24W showed noninferior efficacy to monthly ranibizumab through approximately 2 years, with approximately 95% of PDS Q24W patients not receiving supplemental ranibizumab treatment in each refill-exchange interval. The AESIs were generally manageable, with learnings continually implemented to minimize PDS-related AEs., FINANCIAL DISCLOSURE(S): Proprietary or commercial disclosure may be found after the references.

Singh RP, Barakat MR, Ip MS, et al. Efficacy and Safety of Brolucizumab for Diabetic Macular Edema: The KINGFISHER Randomized Clinical Trial. *JAMA ophthalmology.* 2023;141(12):1152-1160.

Importance: Despite the effectiveness of existing anti-vascular endothelial growth factor (VEGF) therapies, a need remains for further treatment options to improve response rates and/or reduce injection or monitoring frequency in patients with diabetic macular edema (DME)., Objective: To evaluate the efficacy and safety of brolucizumab vs aflibercept dosed every 4 weeks in participants with DME., Design, Participants, and Setting: This 52-week, double-masked, phase 3 randomized clinical trial included treatment-naive adults and adults who had previously received anti-VEGF therapy. Data were collected from September 2019 to March 2020, and data were analyzed from April 2020 to February 2021., Intervention: Brolucizumab, 6 mg, intravitreal injection every 4 weeks or aflibercept, 2 mg, intravitreal injection every 4 weeks., Main Outcomes and Measures: Participants were randomized 2:1 to brolucizumab, 6 mg, or aflibercept, 2 mg. The primary end point was change from baseline in best-corrected visual acuity at week 52. Secondary end points were the proportion of participants with a 2-step improvement or greater from baseline in Diabetic Retinopathy Severity Scale score, the proportion of eyes with absence of both subretinal fluid and intraretinal fluid, change from baseline in central subfield thickness, and safety at week 52., Results: A total of 517 participants were randomized to brolucizumab (n = 346) or aflibercept (n = 171); 299 (57.8%) were male, and the mean (SD) age was 60.7 (10.2) years. Brolucizumab was noninferior to aflibercept in best-corrected visual acuity (Early Treatment Diabetic Retinopathy Study letter score) change from baseline at week 52 (brolucizumab, 12.2-letter improvement; aflibercept, 11.0-letter improvement; difference, 1.1; 95% CI, -0.6 to 2.9; noninferiority margin, 4; P < .001). Brolucizumab was superior to aflibercept for the proportion of eyes without subretinal and intraretinal fluid (brolucizumab, 144 of 346 [41.6%]; aflibercept, 38 of 171 [22.2%]; difference, 20.0%; 95% CI, 12.5to 28.6; P < .001) and mean central subfield thickness change from baseline at week 52 (brolucizumab, -237.8 mum; aflibercept, -196.5 mum; difference, -41.4; 95% CI, -58.9 to -23.8; P < .001). Incidence of intraocular inflammation was 4.0% (14 of 346) in the brolucizumab arm and 2.9% (5 of 171) in the aflibercept arm, incidence of retinal vasculitis was 0.9% (3 of 346) and 0.6% (1 of 171), respectively, and incidence of retinal vascular occlusion was 0.3% (1 of 346) and 0.6% (1 of 171). One participant in the brolucizumab arm had retinal artery occlusion., Conclusions and Relevance: In these study participants with DME, no clinically meaningful differences in visual outcomes were noted between the brolucizumab and aflibercept arms; some superior anatomic improvements were noted in the brolucizumab arm. No new safety concerns were identified., Trial Registration: ClinicalTrials.gov Identifier: NCT03917472.

Vader MJC, Schauwvlieghe A-SME, Verbraak FD, et al. Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Retinal Vein Occlusion: The Bevacizumab to Ranibizumab in Retinal Vein Occlusions (BRVO) study, a Randomized Trial. *Ophthalmology Retina.* 2020;4(6):576-587.

PURPOSE: Comparing the efficacy of intravitreal injections of bevacizumab to ranibizumab in the treatment of macular edema (ME) resulting from retinal vein occlusion (RVO)., DESIGN: Comparative, randomized, double-masked, multicenter, noninferiority clinical trial. The noninferiority margin was 4 letters., PARTICIPANTS: Patients with vision loss resulting from ME secondary to a branch or (hemi) central RVO who might benefit from anti-vascular endothelial growth factor treatment were eligible for participation., METHODS: From June 2012 through February 2018, 277 participants were randomized to receive injections of 1.25 mg bevacizumab (n = 139) or 0.5

mg ranibizumab (n = 138). The follow-up was 6 months with a monthly dosing interval., MAIN OUTCOME MEASURES: The primary outcome was a change in visual acuity from baseline at 6 months. Changes in the central area thickness and safety were studied as secondary outcomes., RESULTS: The mean visual acuity (+/-standard deviation) improved, with 15.3+/-13.0 letters for bevacizumab and 15.5+/-13.3 letters for ranibizumab after 6 months of monthly treatment. The lower limit of the 2-sided 90% confidence interval was -1.724 letters, which is within the noninferiority margin of 4 letters. Even in the branch and (hemi-)central RVO subgroups, minimal differences were found in visual acuity outcomes between treatment arms. Changes in central area thickness on OCT at 6 months did not differ significantly between treatment groups, with a decrease of 287.0+/-231.3 mum in the bevacizumab group and 300.8+/-224.8 mum in the ranibizumab group. Severe adverse events (SAEs) were also distributed equally over both treatment groups: 10 participants (7.1%) in the bevacizumab group and 13 participants (9.2%) in the ranibizumab group experienced SAEs., CONCLUSIONS: This study showed, based on the change in visual acuity, that bevacizumab is noninferior to ranibizumab for patients with ME resulting from RVO of either subtype when receiving monthly injections for a period of 6 months. In addition, anatomic and safety outcomes did not differ between treatment groups. Based on our findings, bevacizumab may be an effective alternative to ranibizumab.

Vader MJC, Schauwvlieghe A-SME, Verbraak FD, et al. Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Diabetic Macular Edema (BRDME): The BRDME Study, a Randomized Trial. *Ophthalmology Retina.* 2020;4(8):777-788.

PURPOSE: To generate conclusive evidence regarding the noninferiority of intravitreal bevacizumab compared with ranibizumab in patients with diabetic macular edema (DME)., DESIGN: Comparative, randomized, double-masked, multicenter, noninferiority clinical trial., PARTICIPANTS: Eligible patients were older than 18 years, diagnosed with type 1 or type 2 diabetes mellitus, with glycosylated hemoglobin of less than 12%, central area thickness of more than 325 mum, and visual impairment from DME with a best-corrected visual acuity (BCVA) between 24 letters and 78 letters., METHODS: From June 2012 through February 2018, a total of 170 participants were randomized to receive 6 monthly injections of either 1.25 mg bevacizumab (n = 86) or 0.5 mg ranibizumab (n = 84)., MAIN OUTCOME MEASURES: Primary outcome was change in BCVA from baseline to month 6 compared between the 2 treatment arms. The noninferiority margin was 3.5 letters., RESULTS: The difference in mean BCVA between treatment arms was 1.8 letters in favor of ranibizumab after 6 months of follow-up; BCVA improved by 4.9+/-6.7 letters in the bevacizumab group and 6.7+/-8.7 letters in the ranibizumab group. The lower bound of the 2-sided 90% confidence interval (CI) was -3.626 letters, exceeding the noninferiority margin of 3.5 letters. Central area thickness decreased more with ranibizumab (138.2+/-114.3 mum) compared with bevacizumab (64.2+/-104.2 mum). In a post hoc subgroup analysis, participants with a worse BCVA at baseline (<=69 letters) improved by 6.7+/-7.0 letters with bevacizumab and 10.4+/-10.0 letters with ranibizumab, and central area thickness decreased significantly more in the ranibizumab arm of this subgroup compared with the bevacizumab arm. Participants with an initially better BCVA at baseline (>=70 letters) did not demonstrate differences in BCVA or OCT outcomes between treatment arms., CONCLUSIONS: Based on change in BCVA from baseline to month 6, the noninferiority of 1.25 mg bevacizumab to 0.5 mg ranibizumab was not confirmed. Only the subgroup of patients with a lower BCVA at baseline showed better visual acuity and anatomic outcomes with ranibizumab. Our study confirmed the potential differential efficacy of anti-vascular endothelial growth factor agents in the treatment of DME as well as the difference in response between patient groups with different baseline visual acuities.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to February 01, 2024

1	exp bevacizumab/ or exp ranibizumab/	16610
2	aflibercept.mp.	3072
3	brolucizumab.mp.	220
4	pegaptanib.mp.	665
5	exp vascular endothelial growth factors/	62006
6	faricimab.mp.	48
7	exp Retinal Degeneration/	49090
8	exp Retinal Diseases/	147642
9	1 or 2 or 3 or 4 or 5 or 6	73918
10	7 or 8	147642
11	9 and 10	10607
12	limit 11 to yr="2020 -Current"	2090
13	limit 12 to (english language and humans)	1897
14	limit 13 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or "systematic review")	427

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VABYSMO safely and effectively. See full prescribing information for VABYSMO.

VABYSMO® (faricimab-svoa) injection, for intravitreal use

Initial U.S. Approval: 2022

RECENT MAJOR CHANGES

Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.3)	10/2023
Dosage and Administration, Diabetic Macular Edema (2.3)	1/2023
Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (2.4)	10/2023
Warnings and Precautions, Retinal Vasculitis and/or Retinal Vascular Occlusion (5.4)	10/2023

INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD) (1.1)
- Diabetic Macular Edema (DME) (1.2)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.3)

DOSAGE AND ADMINISTRATION

For intravitreal injection. (2.1)

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
  - The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to inform whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48; or 3) Weeks 20, 28, 36 and 44. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.2)

- Diabetic Macular Edema (DME)
  - VABYSMO is recommended to be dosed by following one of these two dose regimens: 1) 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, monthly) for at least 4 doses. If after at least 4 doses, resolution of edema based on the central subfield thickness (CST) of the macula as measured by optical coherence tomography is achieved, then the interval of dosing may be modified by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments based on CST and visual acuity evaluations; or 2) 6 mg dose of VABYSMO can be administered every 4 weeks for the first 6 doses, followed by 6 mg dose via intravitreal injection at intervals of every 8 weeks (2 months). Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.3)

- Macular Edema Following Retinal Vein Occlusion (RVO)
  - The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for 6 months. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL solution in a single-dose vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2023

Appendix 5: Key Inclusion Criteria

Population	Ocular conditions associated with macular edema
Intervention	VEGF inhibitor in Appendix 1
Comparator	VEGF inhibitor in Appendix 1
Outcomes	Visual acuity, function, quality of life, thromboembolic events, serious ocular events
Setting	Outpatient treatment

Appendix 6: Prior Authorization Criteria

Ocular Vascular Endothelial Growth Factors

Goal(s):

- Promote use of preferred drugs and ensure that non-preferred drugs are used appropriately for OHP-funded conditions
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes**: Go to #3	**No**: Go to #4

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve for 12 months, or for length of the prescription, whichever is less
4. RPh only: All other indications need to be evaluated as to whether they are funded or contribute to a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve for 12 months, or for length of the prescription, whichever is less. If not funded: • Current age ≥ 21 years: Deny; not funded by the OHP • Current age < 21 years: If clinic provides supporting literature, and documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) then approve for 12 months, or for length of the prescription, whichever is less. •		

P&T / DUR Review: *8/20 (SS); 3/17*
Implementation: *TBD*

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Drug Class Literature Scan: Insulin Class

Date of Review: February 2024

Date of Last Review: February 2020
Literature Search: 1/1/20 – 11/20/23

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This scan looks at new research for medicine called insulin. Insulin is produced by the pancreas and keeps the body's blood sugar in a healthy range. In people with diabetes, their body cannot make enough insulin or their body cannot use insulin as well as it should. When there is not enough insulin or cells stop responding to insulin, too much blood sugar stays in the blood stream. Over time, this can cause serious health issues such as heart diease, vision loss, and kidney disease. Insulin is a medicine that is used to treat almost all patients with type 1 diabetes mellitus, and some patients with type 2 diabetes mellitus or gestational diabetes to help the body use the glucose (sugar) in the blood.
- Some kinds of insulins work quickly but do not last long in the body and are given near mealtime. These are called bolus or prandial insulins. Other kinds work very slowly over a longer period of time, these are called basal insulins. Some patients may need both basal and bolus insulin.
- A high quality guideline from the Department of Veterans Affairs and Department of Defense does not make recommendations for any particular insulin over another in people with type 2 diabetes.
- A high-quality guideline from the American Diabetes Association recommends certain long acting insulins combined with rapid or ultrarapid insulins as the preferred choice for patients with type 1 diabetes who inject insulin multiple times a day. In patients who have type 2 diabetes, the choice of insulin is more individualized and often used in combination with other types of medicines.
- One of the side effects of taking insulin is hypoglycemia, which is very low blood sugar. Symptoms of low blood sugar include shakiness, sweating, headache, dizziness, or confusion. If someone has these symptoms, eating a high-sugar food or drinking juice helps get blood sugar into normal range. Some evidence shows that patients with type 1 or 2 diabetes using certain long-acting basal insulins may have fewer cases of hypoglycemia than patients taking an intermediate-acting insulin.
- Three new insulin products were recently approved. Two of them, SEMGLEE and REZVOGLAR, are interchangeable biosimilars with insulin glargine (LANTUS). This means they are very similar insulin glargine (LANTUS) and switching from one to the other is not expected to cause changes in blood glucose control. The third new insulin, insulin lispro-aabc (LYUMJEV) is not a biosimilar and starts working a little bit faster than insulin lispro (HUMALOG). It is not designated as interchangeable with HUMALOG.
- New government rules starting January 1, 2024 will affect the prices of many insulin medicines.
- Insulin detemir, a preferred product, will start to become difficult for pharmacies to order in January 2024 and become unavailable by the end of 2024.
- Drug Use Research and Management recommends that no changes be made to coverage of insulins based on new evidence, but that costs of preferred and non-preferred products and formulations should be reviewed.

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Conclusions:

- Three high quality systematic reviews, 2 guidelines, and 9 randomized controlled trials (RCTs) are included in this update.
- A Cochrane review comparing the efficacy and safety of basal insulin formulations found that patients with type 1 diabetes mellitus (T1DM) may have fewer episodes of hypoglycemia with insulin detemir than with neutral protamine Hagedorn (NPH) insulin (detemir 79/1000 vs. NPH 115/1000; relative risk [RR] 0.69, 95% confidence interval [CI] 0.52 to 0.92; moderate certainty evidence).[1] Hemoglobin A1c (HbA1c) and other outcomes of interest and comparisons found no difference or lack of evidence to assess differences between insulin detemir and NPH insulin.
- A Cochrane review comparing the efficacy and safety of basal insulin formulations in patients with type 2 diabetes mellitus (T2DM) showed less hypoglycemia with insulin glargine or insulin detemir when either product was compared to NPH insulin.[2] Evidence certainty varied for each type of hypoglycemia, but was generally better for insulin glargine (very low to moderate certainty, depending on hypoglycemia type) when compared to NPH insulin than detemir compared to NPH (very-low to low certainty, depending on hypoglycemia type).[2]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) committee commissioned a network meta-analysis (NMA) to compare the safety and efficacy of different basal insulin formulations in patients with T1DM. For the primary outcome of hemoglobin A1c (HbA1c) with basal insulins, long-acting insulin had a greater HbA1c decrease compared to intermediate insulin (mean difference [MD] - 0.14%, 95% CI -0.22% to -0.06%, n=8327, 25 trials).[3] The reduction in fasting plasma glucose (FPG) (n=7685, 21 trials) was statistically significant for both long-acting insulin compared to intermediate insulin (MD -1.03, 95% CI -1.33 to -0.73) and ultra-long-acting insulin compared to intermediate-acting insulin (MD -1.45, 95% CI -2.12 to -0.79).[3]
- The Department of Veterans Affairs and Department of Defense updated the 2017 guidelines for the management of T2DM in 2023.[4] It is intended for use in adult patients with T2DM. There were no recommendations related to specific insulin formulations or preferences for one formulation or biosimilar over another.[4]
- The American Diabetes Association updated guidelines in 2023.[5] Patients with T1DM should receive a rapid acting insulin analogue to reduce hypoglycemia risk (Grade A: high-quality evidence).[5] The preferred regimen for most patients with T1DM is a long-acting insulin analogue combined with a rapid-acting or ultra-rapid acting analogue. Patients with T2DM should receive a more person-centered approach to guide the choice of pharmacologic agents considering the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (Grade E: expert consensus).[5]
- Nine recently published, comparative RCTs are summarized in **Appendix 2, Table 1**. No new evidence was identified that would result in changes to the preferred drug list (PDL).
- Three new insulin products have been approved to improve glycemic control in adults and pediatric patients with diabetes mellitus (DM).
    - Insulin glargine-yfgn (SEMGLEE) and insulin glargine-aglr (REZVOGLAR) are interchangeable biosimilars for LANTUS.
    - Insulin Lispro-aabc (LYUMJEV) has a faster onset than HUMALOG and is not interchangeable.

Recommendations:

- No changes to the PDL are recommended based on the clinical review of efficacy and safety.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

- Current PDL status available in **Appendix 1**. Non-preferred products are subject to prior authorization (PA).
- The insulin class was last reviewed in 2020 and 2019. Neither review found clinically significant differences in glucose lowering between long-acting insulin products or between short-acting insulin products.

- After executive session in 2020, the prior authorization (PA) for insulin detemir pens (LEVEMIR FLEXTOUCH) was removed. All forms of insulin lispro, except ADMELOG, were designated as preferred.
- The American Rescue Plan (ARP) Act of 2021 included a provision that eliminates the statutory cap on rebates paid to Medicaid by drug manufacturers. Beginning January 1st, 2024, rebates will no longer be capped at 100% of the quarterly average manufacturer price (AMP). This cap previously reduced the amount of rebates paid, particularly for drugs with significant price increases over time. This "AMP CAP" removal has the potential to significantly affect drug rebate amounts. Significant price fluctuations are anticipated in response to this provision, particularly in certain drug classes, including insulins, which have seen large prices increases over time.[6-8]
- Insulin detemir products will be phased out with injection pens being discontinued in April 2024 and vials to be discontinued by the end of 2024. Supply disruptions are anticipated to begin in mid-January 2024. LEVEMIR vials, LEVEMIR FLEXPEN, and LEVEMIR FLEXTOUCH pen are all preferred on the PDL.[9] Insulin glargine (LANTUS vials and LANTUS SOLOSTAR pens) are designated preferred on the PDL and available on the market as an alternative long-acting basal insulin.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>(Ultra-) Long-Acting Insulin Analogues For People With Type 1 Diabetes Mellitus[1]</u>

A 2021 Cochrane review evaluated the long-term effects of the use of long-acting or ultra-long-acting insulin analogues compared to each other or NPH insulin in people with T1DM.[1] The review included 24 published and 2 unpublished RCTs of 24 to 104 week duration and including 8784 participants.[1] Eight of the 26 studies included, and 21% of all participants were children.[1] The literature search included materials published through August 24, 2020.[1] The outcomes of interest were all-cause mortality, health-related quality of life (QoL), severe hypoglycemia, non-fatal myocardial infarction/stroke, severe nocturnal hypoglycemia, severe adverse events (SAEs), and hemoglobin A1c (HbA1c).[1] The studies included had the following comparisons:

- NPH insulin vs. insulin degludec- 0 studies
- NPH insulin vs. insulin detemir- 9 studies
- NPH insulin vs. insulin glargine- 9 studies
- Insulin detemir vs. insulin glargine- 2 studies
- Insulin degludec vs insulin detemir- 2 studies
- Insulin degludec vs insulin glargine- 4 studies

Patients treated with insulin detemir had fewer episodes of severe hypoglycemia than those treated with NPH insulin (detemir 79/1000 vs. NPH 115/1000; RR 0.69, 95% CI 0.52 to 0.92; moderate certainty evidence).[1] This result is limited by inconsistency. There were no clear differences for severe night-time hypoglycemia (moderate certainty evidence), health-related QoL (low certainty evidence), SAEs (moderate certainty evidence), or HbA1c levels (moderate certainty evidence).[1] There were no clear difference in heart attack (low certainty evidence), stroke (insufficient evidence), or death (moderate certainty evidence), however these were limited by low event rates and stroke was not reported.[1]

Patients treated with insulin glargine had no clear differences compared to those treated with NPH insulin for main outcomes.[1] Moderate certainty evidence supported the results of no difference for all-cause mortality, severe hypoglycemia, severe nocturnal hypoglycemia, SAEs, and HbA1c.[1] Low certainty evidence supported health related QoL and non-fatal myocardial infarction/stroke.[1] Mortality and non-fatal myocardial infarction/stroke were limited by low event rates, and no reported myocardial infarction.[1]

The comparisons between the long-acting or ultra-long-acting insulin analogues did not find clear differences in main outcomes, and these were supported by low and very low certainty evidence usually due to few studies including these comparisons and concerns for indirectness, overall risk of bias, and imprecision.[1] There were no clear differences between adults and children for all insulin comparisons.[1]

<u>(Ultra-) Long-Acting Insulin Analogues For Adults With Type 2 Diabetes Mellitus[2]</u>

A 2020 Cochrane review evaluated the long-term effects of the use of long-acting or ultra-long-acting insulin analogues compared to each other or NPH insulin in adults with type 2 diabetes included literature through November 5, 2019.[2] A total of 24 RCTs (n=3419 adults) were included with 16 comparing insulin glargine vs. NPH insulin and 8 insulin detemir to NPH insulin. No trials comparing ultra-long-acting insulin glargine U300 or insulin degludec with NPH insulin were identified. The RCT duration ranged between 24 weeks and 5 years though only 1 study was longer than 12 months, and all trials had unclear or high risk of bias for several risk of bias domains.[2]

Insulin glargine had a reduced risk of severe hypoglycemia when compared to NPH insulin (glargine 25/1000 vs NPH 37/1000; RR 0.68, 95% CI 0.46 to 1.01; P = 0.06; absolute risk reduction (ARR) –1.2%, 95% CI –2.0 to 0; 14 trials, 6164 participants; very low-certainty evidence).[2] The incidence of confirmed hypoglycemia (BG < 55 mg/dL) was lower with insulin glargine compared to NPH (glargine 159/1000 vs. NPH 180/1000; RR 0.88, 95% CI 0.81 to 0.96, 8 trials, 4388 participants, moderate certainty evidence), as was confirmed nocturnal hypoglycemia (BG < 75 mg/dL) (glargine 274/1000 vs. NPH 351/1000; RR 0.78, 95% CI 0.68 to 0.89, 8 trials, 4225 participants, very low certainty evidence) and confirmed nocturnal hypoglycemia (BG < 55 mg/dL) (glargine 85/1000 vs. NPH 115/1000; RR 0.74, 95% CI 0.64 to 0.85, 8 trials, 4759 participants, moderate certainty evidence).[2]

Insulin detemir was no different when compared to NPH insulin for severe hypoglycemia (detemir 8/1000 vs. NPH 17/1000; RR 0.45, 95% CI 0.17 to 1.20; P = 0.11; ARR –0.9%, 95% CI –1.4 to 0.4; 5 trials, 1804 participants; very low-certainty evidence).[2] Serious hypoglycemia was less common with detemir (detemir 2/1000 vs. NPH 11/1000; Peto OR 0.16, 95% CI 0.04 to 0.61; 5 trials, 1777 participants; low-certainty evidence).[2] Insulin detemir had lower rates when compared to NPH insulin of confirmed hypoglycemia (BG < 75 mg/dL) (detemir 410/1000 vs. NPH 562/1000; RR 0.73, 95% CI 0.61 to 0.86; 4 trials, 1718 participants; low-certainty evidence), confirmed hypoglycemia (BG < 55 mg/dL) (detemir 237/1000 vs. NPH 493/1000; RR 0.48, 95% CI 0.32 to 0.71; 4 trials, 1718 participants; low-certainty evidence), confirmed nocturnal hypoglycemia (BG <75 mg/dL) (detemir 176/1000 vs. NPH 309/1000; RR 0.57, 95% CI 0.47 to 0.68; 4 trials, 1718 participants; low-certainty evidence), and confirmed nocturnal hypoglycemia (BG < 55 mg/dL) (detemir 13/1000 vs. NPH 40/1000; RR 0.32, 95% CI 0.16 to 0.63; 4 trials, 1718 participants; low-certainty evidence).[2]

Evidence was insufficient or lacking in almost all trials to evaluate death from any cause, diabetes-related complications, health-related QoL, and socioeconomic effects. The insulin analogues and NPH insulin showed no clear difference in weight gain.[2]

Comparative Efficacy and Safety of Ultra-Long-Acting, Long-Acting, Intermediate-Acting, and Biosimilar Insulins for Type 1 Diabetes Mellitus: a Systematic Review and Network Meta-Analysis[3]

A 2021 systematic review and NMA, commissioned by Health Canada and the CADTH and informed by the World Health Organization (WHO) insulin access initiative, evaluated RCTs, non-randomized controlled trials, quasi-randomized trials, quasi-experimental studies, and cohort studies for the primary efficacy outcomes of glycemic control (HbA1c, FPG). Sixty-five unique studies were included with 13 additional companion reports (n=14,200).[3] Sixty-four of the 65 studies were RCTs. Trial sample sized ranged from 8 to 749 individuals aged 23 to 54 years with duration of T1DM of 8 to 27 years.[3] The baseline average HbA1c was 7-10% and most studies were conducted in Europe and North America.[3] The risk of bias (RoB) assessment varied by included study, but unclear or high RoB was assigned to the the categories of allocation concealment (75%), blinding of participants and personnel (78%), blinding of outcome assessment (44%), incomplete outcome data (28%), selective reporting (63%), and "other" bias (e.g., funding bias, 92%).[3]

For the NMA of primary HbA1c outcomes with basal insulins, long-acting insulin had a greater HbA1c decrease compared to intermediate insulin (MD - 0.14%, 95% CI -0.22% to -0.06%, n=8327, 25 trials).[3] Ultra-long-acting insulin was not statistically significant for differences in HbA1c compared to intermediate-acting insulin (MD -0.08%, 95% CI:- 0.25% to 0.10%) or long-acting insulin (MD 0.06%, 95% CI -0.10% to 0.22%).[3] The reduction in FPG (n=7685, 21 trials) was statistically significant for both long-acting insulin compared to intermediate insulin (MD -1.03, 95% CI -1.33 to -0.73) and ultra-long-acting insulin compared to intermediate-acting insulin (MD -1.45, 95% CI -2.12 to -0.79).[3] Long-acting insulin was statistically superior to intermediate-acting insulin in several secondary outcomes including weight gain, major or serious hypoglycemia, and nocturnal hypoglycemia.[3] Ultra-long-acting insulin was statistically superior to intermediate-acting insulin for the secondary outcome of nocturnal hypoglycemia.[3]

After review, 307 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or applicability to this literature scan.

New Guidelines:

High Quality Guidelines:

VA/DoD Clinical Practice Guidelines for the Management of Type 2 Diabetes Mellitus[4]

The Department of Veterans Affairs and Department of Defense updated the 2017 guidelines for the management of T2DM in 2023.[4] It is intended for use in adult patients with T2DM who receive care at the VA or DoD health care delivery systems and not for pregnant or nursing persons or those with T1DM.

Recommendations relevant to the insulin class include:

- Recommendation 25 - In adults with T2DM, especially those 65 years and older, we suggest prioritizing drug classes other than insulin, sulfonylureas, or meglitinides to minimize the risk of hypoglycemia, if glycemic control can be achieved with other treatments. (Strength: Weak for; Category: Reviewed, New-added)[4]

- Recommendation 26 - In adults with T2DM who have concurrent cognitive impairment or risk of falls, there is insufficient evidence to recommend for or against specific treatment strategies for glucose lowering to reduce the risk of harms. (Strength: Neither for or against; Category: Reviewed, New-added)[4]

No recommendation related to specific insulin formulations or preferences for one formulation or biosimilar over another.

Standards of Care in Diabetes-2023[5,10]

The American Diabetes Association updates management standards for patients with diabetes mellitus on an annual basis.[5] Evidence recommendations are graded A (Clear evidence from well-conducted, generalizable RCTs that are adequately powered and supportive evidence from well-conducted RCTs that are adequately powered), B (supportive evidence from well-conducted cohort studies or case-control study), C (Supportive evidence from poorly controlled or uncontrolled studies or conflicting evidence with the weight of evidence supporting the recommendation, and E (Expert consensus or clinical experience).

Recommendations related to insulin therapy in T1DM include:

9.1 Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. Grade A[5]

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. Grade A[5]

9.3 Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. Grade B[5]

The insulin regimen of choice for T1DM patients includes a long-acting insulin analogue combined with a rapid-insulin analogue or an ultra-rapid insulin analogue.[5] These types are preferred based on the priorities of flexibility and lower glycemic risk, though at the expense of higher cost.[5] Less preferred alternative regimens include NPH insulin combined with rapid-insulin analogue, an ultra-rapid insulin analogue, a short-acting (regular) insulin, or NPH twice daily with short-acting insulin or a pre-mix.[5]

Recommendations related to insulin therapy in T2DM include:

9.8 A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. Grade E[5]

9.11 If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. Grade A[5]

Patients with T2DM would generally start on alternative oral and injectable pharmacotherapy before insulin. Insulin initiation may occur after insufficient response or contraindications/intolerance to alternative options. Therapy with a basal analogue or bedtime NPH dose would be first, and choice of basal insulin should be individualized for person-specific considerations, including cost.[5] Long-acting analogues (U-100 glargine or detemir) reduce the risk of symptomatic and nocturnal hypoglycemia compared to NPH, but these advantages are modest and may not persist.[5] Longer-acting basal analogues (U200 glargine and degludec) may have lower risk of hypoglycemia compared to U100 glargine when used in combination with oral agents.[5] Addition of prandial insulin may happen after maximization of other therapies. When added in addition to NPH, consider use of a pre-mixed version to decrease number of injections required.[5]

Additional Guidelines for Clinical Context:

Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update[11]

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a diabetes (DM) care plan in 2022. This care plan included a conflict of interest mitigation strategy, but many task force members, including the chair and vice chair, had many industry affiliations. The methods for guideline development, specifically the detailed search strategy which used only a single search database (PubMed), were not included. Due to these limitations, the guidelines will not be presented.

After review, 11 guidelines were excluded due to poor quality or applicability to research questions.

New Formulations:[12]

- **Insulin Glargine (SEMGLEE)**-On June 11, 2020 SEMGLEE was approved by the FDA to improve glycemic control in adults and pediatric patients with T1DM and adults with T2DM as a biosimilar to LANTUS.
- **Insulin Glargine-yfgn (SEMGLEE)-**On July 28, 2021 SEMGLEE was approved by the FDA to improve glycemic control in adults and pediatric patients with DM as an *interchangeable* biosimilar to LANTUS.
- **Insulin Lispro-aabc (LYUMJEV)**-On June 15, 2020, LYUMJEV was approved by the FDA to improve glycemic control in adults with DM. The indication was expanded in October 2022 to include use in pediatric patients with DM and addition of continuous subcutaneous insulin infusion (U100 product) as a condition of use in the pediatric population. This product is formulated with treprostinil and citrate for faster absorption than insulin lispro (HUMALOG) and is not interchangeable. It is available as a U100 and U200 formulation and should not be mixed in the same syringe as other insulins.
- **Insulin Glargine-aglr (REZVOGLAR)**-On December 17, 2021, REZVOGLAR was approved by the FDA to improve glycemic control in adults and pediatric patients with T1DM and adults with T2DM as a biosimilar to LANTUS. In November 2022 this approval was expanded to improve glycemia control in adults and pediatric patients with DM as an *interchangeable* biosimilar to LANTUS.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[12]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Regular human insulin/ NPH insulin	HUMULIN 70/30	June 2022	Warnings and Precautions	New Subsection: Hypoglycemia due to medication errors Accidental mix-ups between insulin products have been reported. To avoid medication errors between HUMULIN 70/30 and other insulins, instruct patients to always check the insulin label before each injection.
NPH insulin	HUMULIN N	June 2022	Warnings and Precautions	New Subsection: Hypoglycemia due to medication errors Accidental mix-ups between insulin products have been reported. To avoid medication errors between HUMULIN N

				and other insulins, instruct patients to always check the insulin label before each injection.
Insulin detemir	LEVEMIR	July 2022	Warnings and Precautions	New Subsection: Hyperglycemia or hypoglycemia with changes in insulin regimen Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia.
Insulin Lispro-aabc	LYUMJEV	August 2021	Warnings and Precautions	New Subsection: Hyperglycemia and ketoacidosis due to insulin pump device malfunction Pump or infusion set malfunctions can lead to a rapid onset of hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection of LYUMJEV may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
insulin aspart	INSULIN ASPART PENFILL	SUBCUT	CARTRIDGE	Y
insulin aspart	NOVOLOG PENFILL	SUBCUT	CARTRIDGE	Y
insulin aspart	INSULIN ASPART FLEXPEN	SUBCUT	INSULN PEN	Y
insulin aspart	NOVOLOG FLEXPEN	SUBCUT	INSULN PEN	Y
insulin aspart	INSULIN ASPART	SUBCUT	VIAL	Y
insulin aspart	NOVOLOG	SUBCUT	VIAL	Y
insulin aspart prot/insuln asp	INSULIN ASPART PROT MIX 70-30	SUBCUT	INSULN PEN	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30 FLEXPEN	SUBCUT	INSULN PEN	Y
insulin aspart prot/insuln asp	INSULIN ASPART PROT MIX 70-30	SUBCUT	VIAL	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30	SUBCUT	VIAL	Y
*insulin detemir	LEVEMIR FLEXPEN	SUBCUT	INSULN PEN	Y
*insulin detemir	LEVEMIR FLEXTOUCH	SUBCUT	INSULN PEN	Y
*insulin detemir	LEVEMIR	SUBCUT	VIAL	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	SUBCUT	INSULN PEN	Y
insulin glargine,hum.rec.anlog	LANTUS	SUBCUT	VIAL	Y
insulin glulisine	APIDRA SOLOSTAR	SUBCUT	INSULN PEN	Y
insulin glulisine	APIDRA	SUBCUT	VIAL	Y
insulin lispro	HUMALOG	SUBCUT	CARTRIDGE	Y
insulin lispro	HUMALOG JUNIOR KWIKPEN	SUBCUT	INS PEN HF	Y
insulin lispro	INSULIN LISPRO JUNIOR KWIKPEN	SUBCUT	INS PEN HF	Y
insulin lispro	HUMALOG KWIKPEN U-100	SUBCUT	INSULN PEN	Y
insulin lispro	HUMALOG KWIKPEN U-200	SUBCUT	INSULN PEN	Y
insulin lispro	HUMALOG TEMPO PEN U-100	SUBCUT	INSULN PEN	Y
insulin lispro	INSULIN LISPRO KWIKPEN U-100	SUBCUT	INSULN PEN	Y
insulin lispro	HUMALOG	SUBCUT	VIAL	Y
insulin lispro	INSULIN LISPRO	SUBCUT	VIAL	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin lispro protamin/lispro	INSULIN LISPRO PROTAMINE MIX	SUBCUT	INSULN PEN	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50	SUBCUT	VIAL	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25	SUBCUT	VIAL	Y
insulin NPH hum/reg insulin hm	HUMULIN 70/30 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30 FLEXPEN	SUBCUT	INSULN PEN	Y
insulin NPH hum/reg insulin hm	HUMULIN 70-30	SUBCUT	VIAL	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30	SUBCUT	VIAL	Y
insulin NPH human isophane	HUMULIN N	SUBCUT	VIAL	Y
insulin NPH human isophane	NOVOLIN N	SUBCUT	VIAL	Y

insulin regular, human	HUMULIN R U-500 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin regular, human	HUMULIN R	INJECTION	VIAL	Y
insulin regular, human	NOVOLIN R	INJECTION	VIAL	Y
insulin regular, human	HUMULIN R U-500	SUBCUT	VIAL	Y
insulin aspart (niacinamide)	FIASP PENFILL	SUBCUT	CARTRIDGE	N
insulin aspart (niacinamide)	FIASP FLEXTOUCH	SUBCUT	INSULN PEN	N
insulin aspart (niacinamide)	FIASP	SUBCUT	VIAL	N
insulin aspart/B3/pump cart	FIASP PUMPCART	SUBCUT	CARTRIDGE	N
insulin degludec	INSULIN DEGLUDEC PEN (U-100)	SUBCUT	INSULN PEN	N
insulin degludec	INSULIN DEGLUDEC PEN (U-200)	SUBCUT	INSULN PEN	N
insulin degludec	TRESIBA FLEXTOUCH U-100	SUBCUT	INSULN PEN	N
insulin degludec	TRESIBA FLEXTOUCH U-200	SUBCUT	INSULN PEN	N
insulin degludec	INSULIN DEGLUDEC	SUBCUT	VIAL	N
insulin degludec	TRESIBA	SUBCUT	VIAL	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	BASAGLAR TEMPO PEN U-100	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	INSULIN GLARGINE SOLOSTAR	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	INSULIN GLARGINE	SUBCUT	VIAL	N
insulin glargine/lixisenatide	SOLIQUA 100-33	SUBCUT	INSULN PEN	N
insulin glargine-aglr	REZVOGLAR KWIKPEN	SUBCUT	INSULN PEN	N
insulin glargine-yfgn	INSULIN GLARGINE-YFGN	SUBCUT	INSULN PEN	N
insulin glargine-yfgn	SEMGLEE (YFGN) PEN	SUBCUT	INSULN PEN	N
insulin glargine-yfgn	INSULIN GLARGINE-YFGN	SUBCUT	VIAL	N
insulin glargine-yfgn	SEMGLEE (YFGN)	SUBCUT	VIAL	N
insulin lispro	ADMELOG SOLOSTAR	SUBCUT	INSULN PEN	N
insulin lispro	ADMELOG	SUBCUT	VIAL	N
insulin lispro-aabc	LYUMJEV KWIKPEN U-100	SUBCUT	INSULN PEN	N
insulin lispro-aabc	LYUMJEV KWIKPEN U-200	SUBCUT	INSULN PEN	N
insulin lispro-aabc	LYUMJEV TEMPO PEN U-100	SUBCUT	INSULN PEN	N
insulin lispro-aabc	LYUMJEV	SUBCUT	VIAL	N
insulin NPH human isophane	HUMULIN N KWIKPEN	SUBCUT	INSULN PEN	N
insulin NPH human isophane	NOVOLIN N FLEXPEN	SUBCUT	INSULN PEN	N
insulin regular, human	AFREZZA	INHALATION	CART INHAL	N
insulin regular, human	NOVOLIN R FLEXPEN	SUBCUT	INSULN PEN	N
insulin regular in 0.9 % NaCl	MYXREDLIN	INTRAVEN	PLAST. BAG	

***** Discontinuation from market by manufacturer anticipated in 2024 (Not related to safety or efficacy.)[9]

Appendix 2: New Comparative Clinical Trials

A total of 1027 citations were manually reviewed from the initial literature search. After further review, 1018 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 9 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Bartal et al.[13] RCT, OL	1. detemir (n=57) 2. NPH (n=51) 1:1 Randomization	Pregnant adults with T2D or overt T2D at ≤ 21 weeks gestation	Composite adverse neonatal complications including: Shoulder dystocia, LGA, NICU admission, respiratory distress in first 24 hours of life, neonatal hypoglycemia.	1. 58% 2. 70% 1 vs. 2 Adjusted RR 0.88 95% CrI 0.61 to 1.12	-6 study centers -Bayesian analysis -62% Hispanic, 26% African American -82% BMI >30 kg/m^2
CONCLUDE[14] RCT, OL	1. degludec U200 (n=805) 2. glargine U300 (n=804) 1:1 Randomization Duration up to 94 weeks	Adults with T2D on basal insulin (≥ 18 y) Baseline HbA1c ≤ 9.5% BMI ≤ 45 kg/m^2	Symptomatic hypoglycemic events (Requiring 3rd party assistance or confirmed blood glucose <3.1 mmol/L)	1. 301 (40.6%) 2. 343 (46.3%) 1 vs. 2 RR 0.88 95% CI 0.73 to 1.09 NS	- approximately 9% attrition and 12.5% drug discontinuation in each arm -Industry funded
EDITION JUNIOR[15] Phase IIIb OL, RCT	1. GLA-300 (n=233) 2. GLA-100 (n=230) 1:1 Randomization	Children and Adolescents with T1DM (6 to <18 y) Baseline HbA1c ≥7.5 to ≤ 11.0%	HbA1C change from baseline to 26 weeks 1. -0.40% (0.06%) 2. -0.40% (0.06%)	1 vs. 2 LSM difference 0.004% 95% CI -0.17 to 0.18 for noninferiority	-Noninferiority design (margin 3.3 mmol/mol [0.3%]) -105 study centers, 24 countries -Industry funded
EXPECT[16] RCT, OL	1. degludec+IAsp (n=111) 2. detemir+IAsp (n=114)	Pregnant adults with T1DM (≥ 18 y)	Last planned HbA1c before delivery	1. 6.2% 2. 6.3% 1 vs. 2 ETD -0.11%	-Noninferiority design (margin 0.4% for degludec vs. detemir) - 56 study centers, 14 countries -Industry funded

	1:1 Randomization			95% CI -0.31 to 0.08; p<0.0001 for noninferiority	
ONSET 9[17] Phase IIIb, RCT, DB	1. faster aspart (n=546) 2. IAsp (n=545) 1:1 Randomization	Adults with T2DM (≥ 18 y) T2D for ≥10 y Baseline HbA1c 7.0-10.0%	HbA1C change from baseline to 16 weeks	1 vs. 2 ETD -0.04% 95% -0.11 to 0.03; p<0.001 for noninferiority	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -165 study centers, 17 countries -Industry funded
PRONTO-T1D[18] Phase III DB/OL, RCT	1. URLi DB mealtime (n=451) 2. Lispro DB mealtime (n=442) 3. URLi OL postmeal (n=329) 1 injected 0-2 min prior to meals 2 Injected at mealtime 3 Injected up to 20 min after start of meal 4:4:3 randomization	Adults with T1DM (≥ 18 y) Baseline HbA1c 7.0-9.5% BMI ≤ 35 kg/m^2	HbA1C change from baseline to 26 weeks (LSM) 1. -1.4 mmol/mol (-0.13%) 2. -0.9 mmol/mol (-0.05%) 3. 0.8 mmol/mol (0.08%)	1 vs. 2 ETD -0.08% 95% CI -0.16 to 0.00 P=0.06 for noninferiority 3 vs. 2 ETD 0.13% 95% CI 0.04 to 0.22 P=0.003 for noninferiority	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -8-week lead in to optimize basal insulin (glargine or degludec) -166 study centers, 18 countries -Industry funded
PRONTO-T2D[19] Phase III DB, RCT	1. URLi (n=336) 2. Lispro (n=337) Inject 0-2 min prior to meals	Adults with T2DM Baseline HbA1c 7.0-10.0% Up to 3 oral hypoglycemics at enrollment but	HbA1C mean change from baseline to 26 weeks 1. -0.38% 2. -0.43%	1 vs. 2 EDT 0.06% 95% CI -0.05 to 0.16	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -May continue metformin and/or SGLT2-I -8-week lead-in to optimize basal insulin, remained on prestudy basal (degludec, glargine) -Industry funded

		discontinued all except metformin and SGLT2-I during lead-in			
PRONTO-Peds[20] Phase III, RCT, DB/OL	1. URLi DB premeal (n=280) 2. Lispro DB premeal (n=298) 3. URLi OL postmeal (n=138) 1 & 2 injected 0-2 min prior to meals 3 injected up to 20 min after start of meal 2:2:1 randomization	Children and Adolescents with T1DM (1 to <18 y)	HbA1C change from baseline to 26 weeks (LSM) 1. 0.71 mmol/mol (0.06%) 2. 0.94 mmol/mol (0.09%) 3. 0.77 mmol/mol (0.07%)	1 vs. 2 LSM difference -0.23 mmol/mol 95% CI -1.84 to 1.39 ETD -0.02% 95% CI -0.17 to 0.13 3 vs. 2 LSM difference -0.17 mmol/mol 95% CI -2.15 to 1.81 ETD -0.02% 95% CI -0.20 to 0.17	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -4-week lead-in to optimize basal insulin, remained on prestudy basal (degludec, detemir, glargine) -Industry funded
SWITCH PRO[21] Phase IV, RCT, crossover, OL	1. degludec U100 (n=249 degludec first) 2. glargine U100 (n=249 glargine first) 41 week duration	Adults with T2DM and $\geq$1 hypoglycemia risk factor ($\geq$ 18 y) Baseline HbA1c $\leq$ 9.5% BMI $\leq$ 45 kg/m^2	TIR assessed by CGM (time spent in range of 3.9 to 10.0 mmol/L during weeks 17-18 and 35-36)	1. 72.1% 2. 70.7% ETD 1.43% (20.6 min/d) 95% CI 0.12 to 2.74; p=0.032	- 67 study sites, 5 countries -22 patients withdrew during first study period and 8 during second -20 patients excluded due to insufficient CGM data -n=488 in final analysis set -Industry funded

Abbreviations: ARR = absolute risk reduction; BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CrI = credible interval; DB = double blind; ETD = estimated treatment difference; faster aspart = fast-acting insulin aspart, FIASP; GLA-100 = insulin glargine 100 unit/mL; GLA-300 = insulin glargine 300 unit/mL; HbA1C = glycated hemoglobin; LSM = least squares mean; $iAUC_{0\text{-}2\,h}$ = Incremental area under curve from 0 to 2 h after meals; IAsp = insulin aspart; LGA = large for gestational age; NICU = neonatal intensive care unit; NS = not significant; OL = open label; OR = odds ratio; RCT = randomized clinical trial; RR = rate ratio; SGLT2-I = sodium-glucose cotransporter 2 inhibitor; SOC-BI = standard of care-basal insulin analogues; TIR = time in range; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; URLi = ultra rapid lispro, LYUMJEV; y = years.

Appendix 3: Abstracts of Comparative Clinical Trials

Detemir vs neutral protamine Hagedorn insulin for diabetes mellitus in pregnancy: a comparative effectiveness, randomized controlled trial[13]

BACKGROUND: Insulin detemir, being used increasingly during pregnancy, may have pharmacologic benefits compared with neutral protamine Hagedorn.
OBJECTIVE: We evaluated the probability that compared with treatment with neutral protamine Hagedorn, treatment with insulin detemir reduces the risk for adverse neonatal outcome among individuals with type 2 or overt type 2 diabetes mellitus (gestational diabetes mellitus diagnosed at <20 weeks' gestation).
STUDY DESIGN: We performed a multiclinic randomized controlled trial (September 2018 to January 2020), which included women with singleton gestation with type 2 or overt type 2 diabetes mellitus who sought obstetrical care at <=21 weeks' gestation. Participants were randomized to receive either insulin detemir or neutral protamine Hagedorn by a clinic-stratified scheme. The primary outcome was a composite of adverse neonatal outcomes, including shoulder dystocia, large for gestational age, neonatal intensive care unit admission, respiratory distress (defined as the need of at least 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure or ventilation at the first 24 hours of life), or hypoglycemia. The secondary neonatal outcomes included gestational age at delivery, small for gestational age, 5-minute Apgar score of <7, lowest glucose level, need for intravenous glucose, respiratory distress syndrome, need for mechanical ventilation or continuous positive airway pressure, neonatal jaundice requiring therapy, brachial plexus injury, and hospital length of stay. The secondary maternal outcomes included hypoglycemic events, hospital admission for glucose control, hypertensive disorder of pregnancy, maternal weight gain, cesarean delivery, and postpartum complications. We used the Bayesian statistics to estimate a sample size of 108 to have >75% probability of any reduction in the primary outcome, assuming 80% power and a hypothesized effect of 33% reduction with insulin detemir. All analyses were intent to treat under a Bayesian framework with neutral priors (a priori assumed a 50:50 likelihood of either intervention being better; National Clinical Trial identifier 03620890).
RESULTS: There were 108 women randomized in this trial (57 in insulin detemir and 51 in neutral protamine Hagedorn), and 103 women were available for analysis of the primary outcome (n=5 for pregnancy loss before 24 weeks' gestation). Bayesian analysis indicated an 87% posterior probability of reduced primary outcome with insulin detemir compared with neutral protamine Hagedorn (posterior adjusted relative risk, 0.88; 95% credible interval, 0.61-1.12). Bayesian analyses for secondary outcomes showed consistent findings of lower adverse maternal outcomes with the use of insulin detemir vs neutral protamine Hagedorn: for example, maternal hypoglycemic events (97% probability of benefit; posterior adjusted relative risk, 0.59; 95% credible interval, 0.29-1.08) and hypertensive disorders (88% probability of benefit; posterior adjusted relative risk, 0.81; 95% credible interval, 0.54-1.16).
CONCLUSION: In our comparative effectiveness trial involving individuals with type 2 or overt type 2 diabetes mellitus, use of insulin detemir resulted in lower rates of adverse neonatal and maternal outcomes compared with neutral protamine Hagedorn.

Risk of hypoglycaemia with insulin degludec versus insulin glargine U300 in insulin-treated patients with type 2 diabetes: the randomised, head-to-head CONCLUDE trial[14]

AIMS/HYPOTHESIS: A head-to-head randomised trial was conducted to evaluate hypoglycaemia safety with insulin degludec 200 U/ml (degludec U200) and insulin glargine 300 U/ml (glargine U300) in individuals with type 2 diabetes treated with basal insulin.
METHODS: This randomised (1:1), open-label, treat-to-target, multinational trial included individuals with type 2 diabetes, aged >=18 years with HbA_{1c} <=80 mmol/mol (9.5%) and BMI <=45 kg/m². Participants were previously treated with basal insulin with or without oral glucose-lowering drugs (excluding insulin secretagogues) and had to fulfil at least one predefined criterion for hypoglycaemia risk. Both degludec U200 and glargine U300 were similarly titrated to a fasting blood glucose target of 4.0-5.0 mmol/l. Endpoints were assessed during a 36 week maintenance period and a total treatment period up to 88 weeks. There were three hypoglycaemia endpoints: (1) overall symptomatic hypoglycaemia (either severe, an event requiring third-party assistance, or confirmed by blood glucose [<3.1 mmol/l] with symptoms); (2) nocturnal symptomatic hypoglycaemia (severe or confirmed by blood glucose with symptoms, between 00:01 and 05:59 h); and (3) severe hypoglycaemia. The primary endpoint was the number of overall symptomatic hypoglycaemic events in the maintenance period. Secondary hypoglycaemia endpoints included the number of nocturnal symptomatic events and number of severe hypoglycaemic events during the maintenance period.
RESULTS: Of the 1609 randomised participants, 733 of 805 (91.1%) in the degludec U200 arm and 734 of 804 (91.3%) in the glargine U300 arm completed the trial (87.3% and 87.8% completed on treatment, respectively). Baseline characteristics were comparable between the two treatment arms. For the primary endpoint, the rate of overall symptomatic hypoglycaemia was not significantly lower with degludec U200 vs glargine U300 (rate ratio [RR] 0.88 [95% CI 0.73, 1.06]). As there was no significant difference between treatments for the primary endpoint, the confirmatory testing procedure for superiority was stopped. The pre-specified confirmatory secondary hypoglycaemia

endpoints were analysed using pre-specified statistical models but were now considered exploratory. These endpoints showed a lower rate of nocturnal symptomatic hypoglycaemia (RR 0.63 [95% CI 0.48, 0.84]) and severe hypoglycaemia (RR 0.20 [95% CI 0.07, 0.57]) with degludec U200 vs glargine U300.
CONCLUSIONS/INTERPRETATION: There was no significant difference in the rate of overall symptomatic hypoglycaemia with degludec U200 vs glargine U300 in the maintenance period. The rates of nocturnal symptomatic and severe hypoglycaemia were nominally significantly lower with degludec U200 during the maintenance period compared with glargine U300.
TRIAL REGISTRATION: ClinicalTrials.gov NCT03078478 FUNDING: This trial was funded by Novo Nordisk (Bagsvaerd, Denmark).

Efficacy and Safety of Insulin Glargine 300 Units/mL (Gla-300) Versus Insulin Glargine 100 Units/mL (Gla-100) in Children and Adolescents (6-17 years) With Type 1 Diabetes: Results of the EDITION JUNIOR Randomized Controlled Trial[15]

OBJECTIVE: To compare efficacy and safety of insulin glargine 300 units/mL (Gla-300) and 100 units/mL (Gla-100) in children and adolescents (6-17 years old) with type 1 diabetes.
RESEARCH DESIGN AND METHODS: EDITION JUNIOR was a noninferiority, international, open-label, two-arm, parallel-group, phase 3b trial. Participants were randomized 1:1 to Gla-300 or Gla-100, titrated to achieve fasting self-monitored plasma glucose levels of 90-130 mg/dL (5.0-7.2 mmol/L), with continuation of prior prandial insulin. The primary end point was change in HbA_{1c} from baseline to week 26. Other assessments included change in fasting plasma glucose (FPG), hypoglycemia, hyperglycemia with ketosis, and adverse events.
RESULTS: In 463 randomized participants (Gla-300, n = 233; Gla-100, n = 230), comparable least squares (LS) mean (SE) reductions in HbA_{1c} were observed from baseline to week 26 (-0.40% [0.06%] for both groups), with LS mean between-group difference of 0.004% (95% CI -0.17 to 0.18), confirming noninferiority at the prespecified 0.3% (3.3 mmol/mol) margin. Mean FPG change from baseline to week 26 was also similar between groups. During the 6-month treatment period, incidence and event rates of severe or documented (<=70 mg/dL [<=3.9 mmol/L]) hypoglycemia were similar between groups. Incidence of severe hypoglycemia was 6.0% with Gla-300 and 8.8% with Gla-100 (relative risk 0.68 [95% CI 0.35-1.30]). Incidence of any hyperglycemia with ketosis was 6.4% with Gla-300 and 11.8% with Gla-100.
CONCLUSIONS: Gla-300 provided similar glycemic control and safety profiles to Gla-100 in children and adolescents with type 1 diabetes, indicating that Gla-300 is a suitable therapeutic option in this population.

Insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (EXPECT): an open-label, multinational, randomised, controlled, non-inferiority trial[16]

BACKGROUND: Insulin degludec (degludec) is a second-generation basal insulin with an improved pharmacokinetic-pharmacodynamic profile compared with first-generation basal insulins, but there are few data regarding its use during pregnancy. In this non-inferiority trial, we aimed to compare the efficacy and safety of degludec with insulin detemir (detemir), both in combination with insulin aspart (aspart), in pregnant women with type 1 diabetes.
METHODS: This open-label, multinational, randomised, controlled, non-inferiority trial (EXPECT) was conducted at 56 sites (hospitals and medical centres) in 14 countries. Women aged at least 18 years with type 1 diabetes who were between gestational age 8 weeks (+0 days) and 13 weeks (+6 days) or planned to become pregnant were randomly assigned (1:1), via an interactive web response system, to degludec (100 U/mL) once daily or detemir (100 U/mL) once or twice daily, both with mealtime insulin aspart (100 U/mL), all via subcutaneous injection. Participants who were pregnant received the trial drug at randomisation, throughout pregnancy and until 28 days post-delivery (end of treatment). Participants not pregnant at randomisation initiated the trial drug before conception. The primary endpoint was the last planned HbA_{1c} measurement before delivery (non-inferiority margin of 0.4% for degludec vs detemir). Secondary endpoints included efficacy, maternal safety, and pregnancy outcomes. The primary endpoint was assessed in all randomly assigned participants who were pregnant during the trial. Safety was assessed in all randomly assigned participants who were pregnant during the trial and exposed to at least one dose of trial drug. This study is registered with ClinicalTrials.gov, NCT03377699, and is now completed.
FINDINGS: Between Nov 22, 2017, and Nov 8, 2019, from 296 women screened, 225 women were randomly assigned to degludec (n=111) or detemir (n=114). Mean HbA_{1c} at pregnancy baseline was 6.6% (SD 0.6%; approximately 49 mmol/mol; SD 7 mmol/mol) in the degludec group and 6.5% (0.8%; approximately 48 mmol/mol; 9 mmol/mol) in the detemir group. Mean last planned HbA_{1c} measurement before delivery was 6.2% (SE 0.07%; approximately 45 mmol/mol; SE 0.8 mmol/mol) in the degludec group and 6.3% (SE 0.07%; approximately 46 mmol/mol; SE 0.8 mmol/mol) in the detemir group (estimated treatment difference -0.11% [95% CI -

0.31 to 0.08]; -1.2 mmol/mol [95% CI: -3.4 to 0.9]; p_{non-inferiority}<0.0001), confirming non-inferiority. Compared with detemir, no additional safety issues were observed with degludec.
INTERPRETATION: In pregnant women with type 1 diabetes, degludec was found to be non-inferior to detemir.
FUNDING: Novo Nordisk.

A Randomized Trial Evaluating the Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec With or Without Metformin, in Adults With Type 2 Diabetes (ONSET 9)[17]

OBJECTIVE: To evaluate the efficacy and safety of fast-acting insulin aspart (faster aspart) compared with insulin aspart (IAsp), both with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.
RESEARCH DESIGN AND METHODS: This multicenter, double-blind, treat-to-target trial randomized participants to faster aspart (n = 546) or IAsp (n = 545). All available information, regardless of treatment discontinuation or use of ancillary treatment, was used for evaluation of effect.
RESULTS: Noninferiority for the change from baseline in HbA_{1c} 16 weeks after randomization (primary end point) was confirmed for faster aspart versus IAsp (estimated treatment difference [ETD] -0.04% [95% CI -0.11; 0.03]; -0.39 mmol/mol [-1.15; 0.37]; P < 0.001). Faster aspart was superior to IAsp for change from baseline in 1-h postprandial glucose (PPG) increment using a meal test (ETD -0.40 mmol/L [-0.66; -0.14]; -7.23 mg/dL [-11.92; -2.55]; P = 0.001 for superiority). Change from baseline in self-measured 1-h PPG increment for the mean over all meals favored faster aspart (ETD -0.25 mmol/L [-0.42; -0.09]); -4.58 mg/dL [-7.59; -1.57]; P = 0.003). The overall rate of treatment-emergent severe or blood glucose (BG)-confirmed hypoglycemia was statistically significantly lower for faster aspart versus IAsp (estimated treatment ratio 0.81 [95% CI 0.68; 0.97]).
CONCLUSIONS: In combination with insulin degludec, faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia versus IAsp in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.

Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26-week PRONTO-T1D study[18]

AIMS: To evaluate the efficacy and safety of ultra rapid lispro (URLi) versus lispro in adults with type 1 diabetes in a 26-week, treat-to-target, phase 3 trial. MATERIALS AND METHODS: After an 8-week lead-in to optimize basal insulin glargine or degludec, patients were randomized to double-blind mealtime URLi (n = 451) or lispro (n = 442), or open-label post-meal URLi (n = 329). The primary endpoint was change from baseline glycated haemoglobin (HbA1c) to 26 weeks (non-inferiority margin 0.4%), with multiplicity-adjusted objectives for postprandial glucose (PPG) excursions after a meal test. RESULTS: Both mealtime and post-meal URLi demonstrated non-inferiority to lispro for HbA1c: estimated treatment difference (ETD) for mealtime URLi -0.08% [95% confidence interval (CI) -0.16, 0.00] and for post-meal URLi +0.13% (95% CI 0.04, 0.22), with a significantly higher endpoint HbA1c for post-meal URLi versus lispro (P = 0.003). Mealtime URLi was superior to lispro in reducing 1- and 2-hour PPG excursions during the meal test: ETD -1.55 mmol/L (95% CI -1.96, -1.14) at 1 hour and - 1.73 mmol/L (95% CI -2.28, -1.18) at 2 hours (both P < 0.001). The rate and incidence of severe, documented and postprandial hypoglycaemia (<3.0 mmol/L) was similar between treatments, but mealtime URLi demonstrated a 37% lower rate in the period >4 hours after meals (P = 0.013). Injection site reactions were reported by 2.9% of patients on mealtime URLi, 2.4% on post-meal URLi, and 0.2% on lispro. Overall, the incidence of treatment-emergent adverse events was similar between treatments. CONCLUSIONS: The results showed that URLi provided good glycaemic control, with non-inferiority to lispro confirmed for both mealtime and post-meal URLi, while superior PPG control was demonstrated with mealtime dosing.

Randomized Double-Blind Clinical Trial Comparing Ultra Rapid Lispro With Lispro in a Basal-Bolus Regimen in Patients With Type 2 Diabetes: PRONTO-T2D[19]

OBJECTIVE: To evaluate the efficacy and safety of ultra rapid lispro (URLi) versus lispro in patients with type 2 diabetes on a basal-bolus insulin regimen.
RESEARCH DESIGN AND METHODS: This was a phase 3, treat-to-target, double-blind 26-week study. After an 8-week lead-in to optimize basal insulin glargine or degludec in combination with prandial lispro treatment, patients were randomized to blinded URLi (n = 336) or lispro (n = 337) injected 0-2 min prior to meals. Patients could continue metformin and/or a sodium-glucose cotransporter 2 inhibitor. The primary end point was change in HbA_{1c} from baseline to 26 weeks (noninferiority margin 0.4%), with multiplicity-adjusted objectives for postprandial glucose (PPG) excursions during a standardized meal test.

RESULTS: HbA_{1c} improved for both URLi and lispro, and noninferiority was confirmed: estimated treatment difference (ETD) 0.06% (95% CI -0.05; 0.16). Mean change in HbA_{1c} was -0.38% for URLi and -0.43% for lispro, with an end-of-treatment HbA_{1c} of 6.92% and 6.86%, respectively. URLi was superior to lispro in controlling 1- and 2-h PPG excursions: 1-h ETD, -0.66 mmol/L (95% CI -1.01, -0.30); 2-h ETD, -0.96 mmol/L (-1.41, -0.52). Significantly lower PPG excursions were evident from 0.5 to 4.0 h postmeal with URLi treatment. There were no significant treatment differences in rates of severe or documented hypoglycemia (<3.0 mmol/L). Incidence of overall treatment-emergent adverse events was similar between treatments.
CONCLUSIONS: URLi compared with lispro in a basal-bolus regimen was confirmed to be noninferior for HbA_{1c} and superior to lispro for PPG control in patients with type 2 diabetes.

Efficacy and safety of ultra-rapid lispro versus lispro in children and adolescents with type 1 diabetes: The PRONTO-Peds trial[20]

AIMS: To evaluate the efficacy and safety of ultra-rapid lispro (URLi) versus lispro in a paediatric population with type 1 diabetes (T1D) in a Phase 3, treat-to-target study.
MATERIALS AND METHODS: After a 4-week lead-in to optimize basal insulin, participants were randomized to double-blind URLi (n = 280) or lispro (n = 298) injected 0 to 2 minutes prior to meals (mealtime), or open-label URLi (n = 138) injected up to 20 minutes after start of meals (postmeal). Participants remained on pre-study basal insulin (degludec, detemir or glargine). The primary endpoint was glycated haemoglobin (HbA1c) change from baseline after 26 weeks (noninferiority margin 4.4 mmol/mol [0.4%]).
RESULTS: Both mealtime and postmeal URLi demonstrated noninferiority to lispro for HbA1c: estimated treatment difference (ETD) for mealtime URLi -0.23 mmol/mol (95% confidence interval [CI] -1.84, 1.39) and postmeal URLi -0.17 mmol/mol (95% CI -2.15, 1.81). Mealtime URLi reduced 1-hour postprandial glucose (PPG) daily mean (P = 0.001) and premeal to 1 hour postmeal PPG excursion daily mean (P < 0.001) versus lispro. The rate and incidence of severe, nocturnal or documented hypoglycaemia (<3.0 mmol/L [54 mg/dL]) were similar for all treatments. With mealtime URLi versus lispro, the rate of postdose hypoglycaemia (<3.0 mmol/L) was higher at </=2 hours (P = 0.034). The incidence of treatment-emergent adverse events was similar for all treatments. More participants reported an injection site reaction with mealtime URLi (7.9%) versus postmeal URLi (2.9%) and lispro (2.7%). CONCLUSIONS: In children and adolescents with T1D, URLi demonstrated good glycaemic control, and noninferiority to lispro in HbA1c change for mealtime and postmeal URLi. When dosed at the beginning of meals, URLi reduced 1-hour PPG and PPG excursions versus lispro.

Effect of insulin degludec versus insulin glargine U100 on time in range: SWITCH PRO, a crossover study of basal insulin-treated adults with type 2 diabetes and risk factors for hypoglycaemia[21]

AIMS: To compare time in range (TIR) with use of insulin degludec U100 (degludec) versus insulin glargine U100 (glargine U100) in people with type 2 diabetes.
MATERIALS AND METHODS: We conducted a randomized, crossover, multicentre trial comparing degludec and glargine U100 in basal insulin-treated adults with type 2 diabetes and >=1 hypoglycaemia risk factor. There were two treatment periods, each with 16-week titration and 2-week maintenance phases (with evaluation of glucose using blinded professional continuous glucose monitoring). The once-weekly titration (target: 3.9-5.0 mmol/L) was based on pre-breakfast self-measured blood glucose. The primary endpoint was percentage of TIR (3.9-10.0 mmol/L). Secondary endpoints included overall and nocturnal percentage of time in tight glycaemic range (3.9-7.8 mmol/L), and mean glycated haemoglobin (HbA1c) and glucose levels.
RESULTS: At baseline, participants (n = 498) had a mean (SD) age of 62.8 (9.8) years, a diabetes duration of 15.1 (7.7) years and an HbA1c level of 59.6 (11.0) mmol/mol (7.6 [1.0]%). Noninferiority and superiority were confirmed for degludec versus glargine U100 for the primary endpoint, with a mean TIR of 72.1% for degludec versus 70.7% for glargine U100 (estimated treatment difference [ETD] 1.43% [95% confidence interval (CI): 0.12, 2.74; P = 0.03] or 20.6 min/d). Overall time in tight glycaemic range favoured degludec versus glargine U100 (ETD 1.5% [95% CI: 0.15, 2.89] or 21.9 min/d). Degludec also reduced nocturnal time below range (TBR; <3.9 mmol/L) compared with glargine U100 (ETD -0.88% [95% CI: -1.34, -0.42] or 12.7 min/night; post hoc) and significantly fewer nocturnal hypoglycaemic episodes of <3.0 mmol/L were observed.
CONCLUSIONS: Degludec, compared with glargine U100, provided more TIR and time in tight glycaemic range, and reduced nocturnal TBR in insulin-treated people with type 2 diabetes.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November 20, 2023, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 10, 2023

☐	1	Insulin Aspart/	805
☐	2	Insulin Detemir/	589
☐	3	Insulin Glargine/	2273
☐	4	insulin glulisine.mp.	265
☐	5	Insulin Lispro/	971
☐	6	Insulin/	200189
☐	7	Insulin, Isophane/	1058
☐	8	insulin degludec.mp.	808
☐	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	202404
☐	10	limit 9 to (english language and yr="2020 -Current")	15802
☐	11	limit 10 to humans	11542
☐	12	limit 11 to (adaptive clinical trial or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or "corrected and republished article" or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	2181
☐	13	Diabetes Mellitus, Type 1/ or Diabetes, Gestational/ or Diabetes Mellitus/ or Diabetes Complications/ or Diabetes Mellitus, Type 2/	417414
☐	14	12 and 13	1354

Appendix 5: Key Inclusion Criteria

Population	Patients with type 1 or 2 diabetes mellitus, or gestational diabetes
Intervention	Insulins
Comparator	Other insulin products
Outcomes	Mortality, micro or macrovascular complications, glucose lowering, hypoglycemia
Timing	New onset or established diabetes
Setting	Outpatient

Insulins

Goal:
Provide evidence-based and cost-effective insulin options to patients with diabetes mellitus.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred insulins
- Select preferred insulin pens (Novolin® 70/30 and Humulin® 70/30)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Go to #3
3. Is the request for an insulin pen or cartridge?	**Yes:** Go to #4	**No:** Approve for up to 12 months

Approval Criteria		
4. Has the patient tried and failed or have contraindications to any of the preferred pens or cartridges? Note: Documentation of trial and failure or contraindication to a long-acting or basal preferred product is required for non-preferred long-acting or basal insulin requests.	**Yes:** Go to #5	**No:** Pass to RPh; deny and recommend a trial of one of the preferred insulin products
5. Will the insulin be administered by the patient or a non-professional caregiver **AND** do any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is a child less than 18 years of age?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness

P&T / DUR Review: *2/24 (SF); 2/20(KS); 9/19; 11/18; 9/17; 3/16; 11/15; 9/10*
Implementation: *11/1/2019; 11/1/17; 10/13/16; 1/1/11*

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Drug Class Update: Inhalers for Asthma and COPD

Date of Review: February 2024

Date of Last Review: December 2022
Dates of Literature Search: 01/01/2022 – 10/25/2023

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to review new literature on effectiveness and safety of asthma and COPD inhaled therapies published since the last Pharmacy and Therapeutics (P &T) Committee review at the December 2022 meeting.

Plain Language Summary:
- Asthma and chronic obstructive pulmonary disease (COPD) are lung conditions that make it hard to breathe. Asthma is a condition in which the airways narrow and swell and may be blocked by extra mucus in the lungs. COPD is usually caused by damage to the lungs from cigarette smoke or other air pollutants. For both conditions, inhaled medicine can improve symptoms.
- Several types of inhaled medicines are available. Generally, quick relief (or short-acting inhalers) relax the airways to help people breathe easier when they are short of breath. Long-acting inhalers prevent shortness of breath, coughing and chest tightness over time. Long-acting inhalers need to be taken every day, even when people feel well and don't have trouble breathing or other symptoms.
- The 2023 Global Initiative for Asthma report recommends that people with asthma use 2 medicines called a corticosteroid and formoterol if they:
    - require medicine occasionally when they have trouble breathing or
    - require daily treatment with medicine to control more frequent symptoms.
- In many people with COPD, inhalers that combine 2 or 3 types of medicines help people breathe better than inhalers that contain only one type of medicine.
- Oregon Health Plan will pay for a corticosteroid (i.e., mometasone, budesonide, and fluticasone), short acting-beta agonist (albuterol), a long-acting beta agonist (salmeterol), and long-acting muscarinic antagonist (i.e., umeclidinium, tiotropium) inhaler without requiring prior authorization. Combination inhalers with a corticosteroid and salmeterol or formoterol (i.e., ADVAIR, DULERA, SYMBICORT) will also pay without requiring prior authorization. Providers must explain to the Oregon Health Authority why someone needs certain combination inhaler products (i.e., ANORO ELLIPTA, STILOTO RESPIMAT, TRELEGY, DUAKLIR PRESSAIR, and BEVESPI AEROSPHERE) before the Oregon Health Plan will pay for it.

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Research Questions:

- What is the comparative efficacy for asthma and COPD inhaler medications for important outcomes such as symptoms, lung function, hospitalizations and mortality?
- What is the evidence for harms associated with asthma and COPD inhaler medications?
- Are there subpopulations of patients based on demographics (e.g., age, racial groups, gender), comorbidities (drug-disease interactions), or other medications (drug-drug interactions) for which treatments for asthma or COPD are better tolerated or more effective?

Conclusions:

- Since the last P & T Committee review of inhalers for asthma and COPD in December 2022, 3 high-quality systematic reviews[1-3] and 2 high-quality guidelines[4,5] have been published.
- In December 2022, the Drug Effectiveness Review Project (DERP) published a report focused on effectiveness and safety of single-inhaler triple therapies for management of asthma and COPD compared with monotherapy, dual therapy, or multiple-inhaler triple therapies.[1] No significant differences were observed between triple and dual therapy in the annualized rate of severe asthma exacerbations.[1] Compared with monotherapy or dual therapies, triple therapy demonstrated improvements in frequency of COPD exacerbations, symptom control, and health-related quality of life in people with COPD.[1] Adverse events occurred in similar proportions across treatments in both asthma and COPD populations.[1] Death and early withdrawal from studies due to adverse events were rare.[1]
- A December 2022 Cochrane review assessed dual corticosteroid-long-acting beta-agonists (ICS-LABA) inhaler treatment and triple ICS-LABA-long-acting muscarinic antagonist (LAMA) inhaler treatment compared with each other and medium- to high-dose ICS monotherapy in adolescents and adults with uncontrolled asthma.[2] Compared to medium-dose dual ICS-LABA therapy, medium-dose and high-dose ICS triple inhaler therapies reduce asthma exacerbations, but not asthma-related hospitalizations (high-certainty evidence).[2] High-dose ICS triple therapy is likely superior to medium-dose ICS triple therapy in reducing asthma exacerbations (moderate-certainty evidence).[2] Compared to medium-dose ICS-LABA therapy, high-dose ICS triple therapy, but not medium-dose ICS triple therapy, results in a reduction in all-cause adverse effects (AEs; high-certainty evidence).[2] Compared to dual ICS-LABA therapy, triple therapy does not reduce all-cause serious adverse effects (SAEs; high-certainty evidence).[2] The evidence that any specific formulation would be better than the others within the same group in any outcomes is uncertain due to the scarcity of data and resulting imprecision of estimates.[2]
- A 2023 Cochrane review assessed the safety and efficacy of adding a LABA or LAMA to ICS therapy compared to increasing the ICS dose in adolescents and adults with asthma not well controlled on medium-dose ICS.[3] The findings from this review suggest that compared to medium-dose ICS monotherapy, medium- or high-dose ICS-LABA and medium-dose ICS-LAMA reduce moderate-to-severe asthma exacerbations (moderate-certainty evidence).[3] Medium-dose ICS-LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to medium-dose ICS (moderate-certainty evidence).[3]
- The updated Global Initiative for Asthma (GINA) guidance for management of asthma was published July 2023.[4] Key changes in this report include clarification of terminology for asthma medications and addition of as-needed ICS-SABA reliever therapy to track 2 of alternative treatment options.[4] The specific recommendations for treatment of adults and adolescents (aged 12 years and older) are summarized as Steps 1 through 4 in **Table 5.** Guidance for asthma treatment in children aged 6 to 11 years of age is presented in **Table 6**. Treatment recommendations are based upon the following evidence:
    - SABAs are highly effective for quick relief of asthma symptoms, but patients treated with SABAs alone are at risk of asthma-related death and urgent asthma-related health care use, even if there is good symptom control (high-quality evidence).[4]
    - Regular or frequent LABA use alone is not recommended without ICS due to risk of asthma exacerbations (high-quality evidence).[4]

- In step 4, in patients with persistently uncontrolled asthma despite medium- or high-dose ICS-LABA, consider adding on a LAMA as a separate inhaler (for age ≥ 6 years) or as combination triple therapy inhaler (for age ≥ 18 years).[4] Evidence shows:
  - this strategy may modestly improve lung function but not symptoms (high-quality evidence) and
  - in patients having exacerbations with low-dose ICS-LABA, ICS dose should be increased to medium or higher, or treatment switched to maintenance and reliever therapy with ICS-formoterol before adding LAMA (high-quality evidence).[4]

- The 2023 Global Initiative for COPD (GOLD) report contains several important revisions and updates including: a new definition of COPD; a revision of the COPD patient classification system; a new definition of COPD exacerbation; and updated evidence on therapeutic interventions to reduce COPD mortality.[5] Strong recommendations include:
  - The treatment of patients in Group A remains the same as previous reports: a bronchodilator (i.e., SABA, SAMA, LABA, or LAMA) with a long-acting bronchodilator preferred unless very occasional dyspnea is present (Strong Recommendation).[5]
  - For patients in Group B, a LAMA-LABA inhaler is now recommended since dual therapy is more effective than monotherapy, with similar side effects (Strong Recommendation).[5]
  - For patients in Group E (formerly categorized in groups C and D), LAMA-LABA is also the recommended initial therapy (Strong Recommendation).[5]
- A new ICS-SABA product, albuterol 90 mcg and budesonide 80 mcg (AIRSUPRA) received FDA approval in January 2023. This is the first ICS/SABA inhaler approved in the United States (US). In the MANDALA trial, albuterol-budesonide showed a statistically significant reduction in time to first severe asthma exacerbation compared with albuterol monotherapy.[6] Inhaled albuterol-budesonide is indicated for as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.[7] Details of the pivotal trials that led to FDA-approval are presented in **Table 10.**
- In April 2023, a new formulation of budesonide 160 mcg and formoterol 4.8 mcg (SYMBICORT AEROSPHERE) received FDA approval as maintenance treatment of patients with COPD.[8] It is not indicated for relief of acute bronchospasm or for treatment of asthma.[8] The original budesonide-formoterol (SYMBICORT) products contain formoterol 4.5 mcg and 80 to 160 mcg of budesonide. Compared with formoterol monotherapy, combination budesonide-formoterol improved time to first and rate of moderate- to severe-COPD exacerbations. Details of the pivotal trials that led to FDA-approval are presented in **Table 10.**
- There was insufficient evidence in subgroup populations with asthma or COPD to establish meaningful conclusions on efficacy or harms.

Recommendations:

- Based on 2023 GOLD guidance which recommends a LAMA-LABA inhaler as initial therapy for 2 patient groups (B and E), have at least one LAMA-LABA inhaler preferred without PA on the Preferred Drug List (PDL).
- Modify combination LAMA-LABA and LAMA-LABA-ICS Inhaler PA criteria to remove PA from preferred products.
- Maintain albuterol-budesonide (AIRSUPRA) and budesonide 160 mcg-formoterol 4.8 mcg (SYMBICORT AEROSPHERE) as non-preferred inhalers on the PDL.
- After evaluation of costs in executive session, fluticasone furoate (ARNUITY ELLIPTA) was made preferred on the PDL.

Summary of Prior Reviews and Current Policy:

- The inhaled therapies for asthma and COPD are comprised of 5 classes: short-acting beta-agonists (SABAs), LABAs, short-acting muscarinic antagonists (SAMAs), LAMAs, and ICS. For ease of administration, these drug classes are combined into single inhalers in the following iterations: ICS/LABA, LAMA/LABA, and LAMA/LABA/ICS.

- Previous reviews have found low- to moderate-quality evidence of no within-class differences in efficacy or harms for long-acting products (i.e., LABAs, LAMAs or ICS) for patients with asthma or COPD.
- Preferred therapies for asthma and COPD maintenance inhalers on the Oregon Health Plan (OHP) include:
    a. SAMA, SAMA/SABA combination: ipratropium (aerosol and solution) and ipratropium/albuterol (nebulized solution)
    b. LAMAs: tiotropium, umeclidinium
    c. SABA: albuterol (aerosol and nebulized solution)
    d. LABA: salmeterol
    e. ICS: budesonide, fluticasone propionate, mometasone
    f. ICS-LABA combinations: budesonide/formoterol, fluticasone/salmeterol, mometasone/formoterol
    g. LAMA-LABA combinations: tiotropium/olodaterol, umeclidinium/vilanterol
    h. LAMA-LABA-ICS combinations: no preferred options for triple therapy
- The complete list of inhaled products and their status on the Preferred Drug List (PDL) is presented in **Appendix 1**. There are specific prior authorization (PA) criteria for all non-preferred ICS and LABA inhalers. In addition, all LAMA-LABA and LAMA-LABA-ICS combination products require PA.
- After review at the December 2022 meeting, the Pharmacy and Therapeutics (P & T) Committee agreed to revise inhaler PA criteria to align with recently updated guidance from the 2022 GINA, 2022 GOLD and US Preventative Services Task Force (USPSTF) reports. The specific PA criteria for ICS-LABA inhalers were retired, which made non-preferred therapies subject to general PA for non-preferred products.
- Literature for inhaled anticholinergics was last evaluated in October 2021. At the time, the NAEPPCC Expert Panel recommended the use of LAMAs in patients with asthma and conditionally recommended adding LAMA to ICS controller therapy instead of continuing the same dose of ICS alone (conditional recommendation; moderate certainty of evidence).
- The American Rescue Plan (ARP) Act of 2021 included a provision that eliminates the statutory cap on rebates paid to Medicaid by drug manufacturers. Beginning January 1st, 2024, rebates will no longer be capped at 100% of the quarterly average manufacturer price (AMP). This cap previously reduced the amount of rebates paid, particularly for drugs with significant price increases over time. This "AMP CAP" removal has the potential to significantly affect drug rebate amounts. Significant price fluctuations are anticipated in response to this provision, particularly in certain drug classes, including inhalers, which have seen large prices increases over time.
- The inhaled therapies account for a significant cost to the Oregon Health Authority. Compliance to the PDL ranges from a low of 38% for the LABA class to 100% for SABA and LAMAs, as of the third quarter in 2023 (July 1 to September 30).

Background:

Asthma

Asthma is a heterogeneous disease, characterized by chronic, reversible, airway inflammation which results in bronchial hyper-responsiveness. It is defined in the GINA guidance by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough. Symptom severity can vary over time and be associated with changes in expiratory volume.[9] In 2019 the Centers for Disease Control and Prevention (CDC) estimated 25 million Americans, including 5 million children had asthma.[10] In the United States (U.S.), asthma is more than twice as common among Black children as among White children (13.5% and 6.4% respectively).[10] It is estimated about 5 to 10% of the total asthma population have severe asthma, but the exact prevalence is unknown due to the heterogeneous presentation of the disease.[11] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with management of asthma exacerbations.[12]

Diagnosis is confirmed by spirometry (improvement in forced expiratory volume in one second [FEV_1] > 200 mL or ≥ 12% from baseline after SABA use), which demonstrates airway obstruction that is at least partially reversible.[13] Asthma is characterized as mild, moderate or severe.[13] The underlying pathophysiology of asthma is multi-factorial and includes several phenotypes: eosinophil predominant, neutrophil predominant, and allergic asthma.[13] In particular, those patients with eosinophilic asthma Type 2-high, which indicates high levels of T-helper type 2 lymphocytes, respond well to ICS therapy and biologic therapy if asthma remains uncontrolled.[13] Patients with eosinophilic asthma also have high levels of sputum eosinophils. While correlation of blood eosinophil levels to sputum eosinophils is not well defined, guidelines typically diagnose eosinophilic asthma when blood eosinophils are greater than or equal to 150 cells/µL.[13]

The GINA guidelines based initial pharmacotherapy on assessment of the frequency and severity of asthma symptoms.[9] The long-term goals of asthma management are to achieve good symptom control, reduce exacerbations, and minimize future risk of asthma-related mortality.[9] Asthma treatment is initiated in a stepwise manner based on the severity of asthma symptoms.[13] For Step 1 and 2 therapy, the 2022 GINA guideline recommends use of a combination low-dose ICS and the fast-acting LABA (formoterol) taken as needed for symptom relief.[13] Formoterol has both a rapid onset and long duration of action (up to 12 hours of bronchodilation).[13] For moderate asthma (Step 3), the preferred controller therapy is a combination low-dose ICS and LABA as maintenance therapy. Because of the rapid onset of action of formoterol, a combination budesonide-formoterol inhaler can be used both for daily controller therapy and for quick relief of symptoms.[13] It is likely that a combination mometasone-formoterol inhaler can be used in the same way (for both maintenance therapy and for acute relief of symptoms), but fewer data are available with this combination.[13] For severe asthma, the preferred controller treatments are medium (Step 4) or high (Step 5) doses of an ICS in combination with a LABA. Medium to high doses of inhaled glucocorticoids require more careful monitoring for adverse effects. As in moderate asthma, the use of a SABA together with an ICS for acute relief of symptoms in patients with severe persistent asthma may improve asthma control and reduce the frequency of asthma exacerbations compared with SABA alone.[14,15] The different inhalers stratified by class are presented in **Table 1**.

Table 1. Classes of Inhaler Medications Presented as Generic (BRAND)

Inhaled Corticosteroids (ICS)	
Beclomethasone (QVAR REDIHALER) Budesonide (PULMICORT FLEXHALER) Ciclesonide (ALVESCO)	Fluticasone Furoate (ARNUITY ELLIPTA) Fluticasone Propionate (FLOVENT) Mometasone (ASMANEX)
Short-Acting Beta-Agonists (SABAs)	
Albuterol (PROAIR, PROVENTIL, VENTOLIN)	Levalbuterol (XOPENEX)
Long-Acting Beta-Agonists (LABAs)	
Arformoterol (BROVANA) Formoterol (FORADIL) Indacaterol (ARCAPTA)	Olodaterol (STRIVERDI) Salmeterol (SEREVENT) Vilanterol (only available in combination)
Short-Acting Muscarinic Antagonist (SAMAs)	
Ipratropium (ATROVENT)	
Long-Acting Muscarinic Antagonists (LAMAs)	
Aclidinium (TUDORZA PRESSAIR) Glycopyrrolate (only available in combination) Revefenacin (YUPELRI)	Tiotropium (SPIRIVA) Umeclidinium (INCRUSE ELLIPTA)

Combination Short-Acting Beta-Agonist/Corticosteroid (SABA/ICS)	
Albuterol/Budesonide (AIRSUPRA)	
Combination Short-Acting Beta-Agonist/Short-Acting Muscarinic Antagonist (SABA/SAMA)	
Albuterol/Ipratropium (COMBIVENT RESPIMAT)	
Combination Long-Acting Muscarinic Antagonist/Long-Acting Beta-Agonists (LAMA/LABA)	
Aclidinium/Formoterol (DUAKLIR PRESSAIR) Glycopyrrolate/Formoterol (BEVESPI AEROSPHERE)	Tiotropium/Olodaterol (STIOLTO RESPIMAT) Umeclidinium/Vilanterol (ANORO ELLIPTA)
Combination Corticosteroid/Long-Acting Beta-Agonists (ICS/LABA)	
Budesonide/Formoterol (SYMBICORT, BREYNA) Mometasone/Formoterol (DULERA)	Fluticasone Propionate/Salmeterol (ADVAIR DISKUS, WIXELA INHUB, AIRDUO) Fluticasone Furoate/Vilanterol (BREO ELLIPTA)
Triple Therapy Inhalers (ICS/LAMA/LABA)	
Budesonide/Glycopyrrolate/Formoterol (BREZTRI AEROSPHERE)	Fluticasone/Umeclidinium/Vilanterol (TRELEGY ELLIPTA)

Outcome measures used in asthma trials include FEV_1, asthma exacerbations, hospitalizations, emergency department (ED) visits, and need for oral corticosteroids. Change from baseline in FEV_1 is a common surrogate endpoint used in clinical trials and clinical practice since it is highly reproducible.[13] A decline in lung function is observed when FEV_1 is 60% or less of predicted values or peak expiratory flow shows a 30% or greater decrease from baseline.[16] The Asthma Control Questionnaire (ACQ) is a questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[17] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units documented as a minimal clinically important difference (MCID).[17] An ACQ score consistently greater than 1.5 indicates poor symptom control.[17] The Asthma Quality of Life Questionnaire (AQLQ-12) contains 32 items assessing disease-specific, health-related quality-of-life that include domains of activity limitations, symptoms, emotional function, and environmental stimuli in patients aged 12 years and older.[16] The scale ranges from 1 (severely impaired) to 7 (not impaired at all). Total and domain scores are calculated by taking the mean of all questions overall or for each domain.[16] The MCID for this tool is 0.5 points for each item.[16] The St. George's Respiratory Questionnaire (SGRQ) was developed to measure health in chronic health airflow limitation.[18] The questionnaire is a 50 or 76 item assessment (depending on version) that includes 2 domains: frequency and severity of symptoms and impact on activities, which can be used with a 1-month, 3-month, or 12-month recall.[16] The scale ranges from 0 (no symptoms/limitations) to 100 (severe symptoms/limitations).[16] Scoring varies by item and item scores are converted into a domain score and an overall score, both reported on the same scale.[16] The MCID for the SGRQ is 4 points.[16] The Asthma Control Test (ACT) contains 5 self-reported items related to symptoms and daily functioning over past 4 weeks used in patients aged 12 years and older.[16] Assessments include shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control.[16] The scale ranges from 5 (poor control) to 25 (complete control) with scores of 19 and greater indicating well-controlled asthma.[16] Each item is scored on 5-point Likert scale and the sum of scores across all items yields the total score.[16] The MCID for the ACT score is 3 points.[16] A summary of the outcomes commonly used in clinical trials for asthma treatment is presented in **Table 2.**

Table 2. Summary of Outcome Measures for Asthma Symptoms[16]

Measure	Scale	Minimal Clinically Important Difference (MCID)
Asthma Control Questionnaire (ACQ)	0 (totally controlled) to 6 (severely uncontrolled)	0.5 points
Asthma Control Test (ACT)	5 (poor control) to 25 (complete control)	3 points
Asthma Quality of Life Questionnaire (AQLQ-12)	1 (severely impaired) to 7 (not impaired at all)	0.5 points

St. George's Respiratory Questionnaire (SGRQ)	0 (no symptoms/limitations) to 100 (severe symptoms/limitations)	4 points

Chronic Obstructive Pulmonary Disease

The 2023 GOLD report updated the definition of COPD as "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction".[5] Chronic bronchitis and emphysema are often associated with COPD.[19] The most common cause of COPD is airway irritation, usually from cigarette smoking, although exposure to other environmental pollutants can contribute to the condition.[5] Approximately 10% of individuals aged 40 years or older have COPD, although the prevalence varies between countries and increases with age.[20] In the US, COPD is consistently ranked among the top causes of death, with mortality rates of more than 120,000 individuals each year.[21] As a result, COPD has high healthcare utilization with frequent clinician office visits, multiple hospitalizations due to acute exacerbations, and the need for chronic therapy.[22]

The diagnosis and management of COPD are based on spirometry post-bronchodilation results (i.e., FEV_1/forced vital capacity [FVC]) <0.70), symptom severity, risk of exacerbations and comorbidities.[5] In the GOLD 2023 report, COPD is classified into four stages (mild to very severe) based on spirometric measurements of FEV_1 of after bronchodilator administration for people with COPD (FEV_1/FVC <0.7) as presented in **Table 3**.[5]

Table 3. GOLD 2023 Assessment of Airflow Obstruction for Patients with COPD (FEV_1/FVC <0.7) [5]

Grade	Severity	Post-Bronchodilator FEV_1 (% predicted)
GOLD 1	Mild	≥ 80%
GOLD 2	Moderate	50 to 79
GOLD 3	Severe	30 to 49
GOLD 4	Very severe	< 30
Abbreviations: COPD = Chronic Obstructive Disease: FEV_1 = Forced Expiratory Volume in one second: FVC = Forced Vital Capacity; GOLD = Global Initiative for COPD		

Goals of therapy for COPD management are to improve symptoms, reduce frequency and severity of exacerbations, and improve exercise tolerance and daily activities.[19] Initial treatment options for patients with COPD are inhaled bronchodilators (i.e., SABAs, SAMAs, LABAs or LAMAs).[19] Use of SABAs on a regular basis is generally not recommended due to the risk of AEs.[19] For patients who require additional therapy, the combination of a LABA and LAMA is often used.[19] Triple inhaler therapy with a LABA, LAMA and ICS is recommended for those with COPD and sustained symptoms despite dual therapy.[19] Long-acting bronchodilators (LAMAs and LABAs) improve lung function, dyspnea, health status and reduce exacerbation rates.[19] Compared to ICS monotherapy, ICS-LABA combinations have been shown to improve health status, reduce exacerbations and improve lung function.[19] Conclusive evidence of benefit has not been demonstrated with ICS alone in patients with COPD.[19] No medications have shown a preventative effect in the decline of lung function in COPD.[19] Smoking cessation is the only intervention shown to reduce the rate of lung function decline.[19]

Important outcomes to access the effectiveness of COPD therapies include: lung function, quality of life (QoL), dyspnea, exacerbation rate and/or severity, and AEs. The most common surrogate outcome used in studies to determine therapy effectiveness is FEV_1.[13] The minimal clinically important difference (MCID) in FEV_1 values for COPD changes have not been clearly defined, but research in COPD patients suggest that minimally important FEV_1 changes range from 100-140

mL.[13] The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on QoL with scores ranging from 0 to 100 with higher scores indicative of more limitations.[18] In the GOLD guidelines, symptoms are assessed by the modified Medical Research Council (mMRC) dyspnea questionnaire.[5,23] The patient-reported questionnaire assesses extent of breathlessness on a scale of 0 (breathlessness only with exercise) to 4 (breathlessness when dressing).[5] The GOLD report also recommends using the COPD Assessment Test (CAT) to evaluate health status in patients with COPD.[5,24] The 8-item questionnaire ranges in score from 0 (best) to 40 (worst) points and correlates very closely with the SGRQ.[5]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Drug Effectiveness Review Project: Triple Inhaler Therapies for Asthma and COPD
In December 2022, DERP published a report focused on effectiveness and safety of single-inhaler triple therapies (SITT) for management of asthma and COPD compared with monotherapy, dual therapy, or multiple-inhaler triple therapies (MITT).[1] Two of the SITT products are FDA-approved (budesonide-glycopyrrolate-formoterol [BREZTRI] and fluticasone-umeclidinium-vilanterol [TRELEGY]), while the third product (beclomethasone-glycopyrronium-formoterol [TRIMBOW]) is currently being investigated in clinical trials and is not yet FDA-approved. For the purposes of this summary, only evidence for FDA-approved products will be reviewed.

Literature for the DERP report was searched through September 2022.[1] Twelve RCTs met inclusion criteria.[1] One RCT with a moderate risk of bias compared fluticasone-umeclidinium-vilanterol with fluticasone-vilanterol in adults with asthma.[1] Eleven RCTs were identified that evaluated SITT in adults with COPD (7 RCTs with moderate risk of bias and 4 RCTs with high risk of bias).[1] Two RCTs evaluated BREZTRI, 7 evaluated TRELEGY, and 2 evaluated TRIMBOW versus single, dual or triple therapies.[1] The comparators included tiotropium monotherapy, dual therapy with fluticasone-vilanterol, glycopyrrolate-budesonide, or budesonide-formoterol or MITT with tiotropium or umeclidinium monotherapy in combination with fluticasone-vilanterol or budesonide-formoterol dual inhaler therapy.[1] Most participants in the COPD RCTs were white, male and former smokers.[1]

Asthma Findings
In the moderate-quality RCT (n=2,436) conducted in patients with inadequately controlled asthma, fluticasone-umeclidinium-vilanterol (TRELEGY) was compared with fluticasone-vilanterol (BREO) over 24 weeks.[1] The majority of participants in this RCT were white and female.[1] No significant differences were observed between triple and dual therapy in the primary outcome, annualized rate of severe asthma exacerbations.[1] Significant improvements were observed with triple therapy versus dual therapy in secondary outcomes including trough FEV_1 (62.5mcg dose: mean difference [MD] 101 ml; 95% CI 70 to 132; $p<0.001$) and QoL as

measured by the ACQ-7 score (62.5 mcg dose: MD -0.9; 95% CI -0.16 to -0.02; p=0.008).[1] The number of participants experiencing any AE, SAE, or withdrawal from the study due to an AE was similar across all treatment groups.[1]

COPD Findings

One low-quality RCT (n=8,588) evaluated budesonide-glycopyrrolate-formoterol (BREZTRI) with glycopyrrolate-formoterol (LAMA-LABA) or budesonide-formoterol (ICS-LABA) in patients with COPD over 52 weeks.[1] This study had a high attrition rate (20% in the triple therapy arm and 25% in the dual therapy arms) which contributed to the high risk of bias.[1] Another moderate-quality RCT (n=1,902) compared budesonide-glycopyrrolate-formoterol with glycopyrrolate-formoterol or budesonide-formoterol over 24 weeks.[1] Significant improvements in favor of triple therapy versus dual therapy were observed in frequency of moderate to severe COPD exacerbations (see **Table 4**).[1] Secondary outcomes were also improved with triple therapy compared to dual therapy and included: trough FEV_1 ($p<0.01$); frequency and volume of rescue medication use ($p<0.04$); and quality of life as measured by the SGRQ ($p<0.03$).[1] The proportion of individuals experiencing any AE or SAE was similar between treatments for both RCTs.[1] Specific RCT results, which were presented at the December 2022 P&T Committee meeting, are summarized in **Table 4.**[25]

Table 4. Description of Randomized Comparative Clinical Trials for Triple Inhaler Therapy Versus Dual Inhaler Therapy[25]

Study	Comparison	Population	Primary Outcome	Results	Interpretation
Rabe, et al[26] ETHOS 52-week, phase 3, DB, MC, PG, RCT	1) Budesonide 320 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 2) Budesonide 160 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 3) Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 4) Budesonide 320 µg/ Formoterol fumarate 9.6 µg inhaled twice daily	Patients with moderate to very severe COPD and at least one exacerbation in the last year (n=8509)	The annual rate (estimated mean number per patient per year) of moderate or severe COPD exacerbations	1) 1.08 2) 1.07 3) 1.42 4) 1.24 1 vs. 3 RR 0.76 (95% CI, 0.69 to 0.83) P<0.001 1 vs. 4 RR 0.87 (95% CI, 0.79 to 0.95); P = 0.003 2 vs. 3 RR 0.75 (95% CI, 0.69 to 0.83) P<0.001 2 vs. 4 RR 0.86 (95% CI, 0.79 to 0.95) P=0.002	*Triple therapy with budesonide/glycopyrrolate/ formoterol (low [160 µg budesonide dose] and high [320 µg budesonide dose]) was more effective than glycopyrrolate/formoterol and budesonide/formoterol for reducing the rate of COPD exacerbations. The absolute reduction in exacerbations was less than 1 exacerbation per patient per year.*
Ferguson, et al[27] KRONOS	1) Budesonide 320 µg/ Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs.	Patients with moderate to severe COPD without a requirement for a history of exacerbations	FEV_1 area under the curve from 0-4 hours (AUC_{0-4}) for	FEV_1 AUC_{0-4}mL 1) 305 mL 2) 288 mL 3) 201 mL	*There was no difference between triple therapy (budesonide/glycopyrrolate/formoterol fumarate) and glycopyrrolate/formoterol*

24-week, phase 3, DB, MC, PG, RCT	2) Glycopyrrolate 18 µg/ Formoterol fumarate 9.6 µg inhaled twice daily Vs. 3) Budesonide 320 µg/ Formoterol fumarate 9.6 µg inhaled twice daily 4) Budesonide 400 µg/ Formoterol fumarate 12 µg inhaled twice daily (open-label)	(n = 3047)	1) versus 3) and 1) versus 4) Analysis of change from baseline in morning pre-dose trough FEV_1 for 1) versus 2) and non-inferiority analysis of 3) versus 4) (non-inferiority analysis of -50 mL from lower bound of 95% CI)	4) 214 mL 1 vs. 2 LSM 16 mL (95% CI, -6 to 38) P=0.1448 1 vs. 3 LSM 104 mL (95% CI, 77 to 131) P<0.0001 1 vs. 4 91 (95% CI, 64 to 117) P<0.0001 Change from baseline in morning pre-dose trough FEV_1 1) 147 mL 2) 125 mL 3) 73 mL 4) 88 mL 1 vs. 2 22 mL (95% CI, 4 to 39) P=0.0139 1 vs. 3 (prespecified secondary endpoint) 74 mL (95% CI, 52 to 95) P<0.0001 1 vs. 4 59 mL (95% CI, 38 to 80) P<0.0001	*fumarate in changes in FEV_1 AUC_{0-4} mL. Triple therapy was more effective in increasing FEV_1 AUC_{0-4}mL compared to budesonide/formoterol fumarate.* *Increases in baseline morning pre-dose trough FEV_1 were larger for budesonide/glycopyrrolate/formoterol fumarate compared to glycopyrrolate/formoterol fumarate and budesonide/formoterol fumarate.* *Differences between groups in lung function for both groups were small and unlikely to be clinically significant.*
Abbreviations: COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting Beta 2 agonist; LSM = least squares mean; MCID = minimal clinically important difference; MD = mean difference; PC = placebo-controlled; PG = parallel group; RCT = randomized controlled trial; RR = rate ratio					

Seven RCTs compared fluticasone-umeclidinium-vilanterol (TRELEGY) with monotherapy (tiotropium), dual therapy of ICS-LAMA, or MITT (risk of bias was moderate for 4 RCTS and high for 3 RCTs).[1] No statistically significant difference for any outcomes of interest were observed when SITT (fluticasone-umeclidinium-vilanterol) was compared to MITT (budesonide-formoterol plus tiotropium or fluticasone-vilanterol plus umeclidinium) over 24 weeks.[1] When triple therapy was compared to dual therapy (budesonide-formoterol, fluticasone-vilanterol, or umeclidinium-vilanterol), significant improvements in favor of triple therapy were observed in the following outcomes: trough FEV_1 ($p<0.001$), frequency and volume of rescue medication use ($p<0.02$), and quality of life

($p<0.001$).[1] When triple therapy was compared with tiotropium monotherapy, trough FEV_1 was significantly improved with triple therapy.[1] The number of participants experiencing any AE, SAE, or withdrawal from the study due to an AE was similar across all treatment groups.[1]

In summary, compared with monotherapy or dual therapies, triple therapy demonstrated improvements in frequency of COPD exacerbations, lung function (trough FEV_1), symptom control, and health-related QoL.[1] Adverse events occurred in similar proportions across treatments in both asthma and COPD populations.[1] Early withdrawal from studies due to AEs were rare, as were deaths.[1]

Cochrane: Effectiveness And Tolerability Of Dual And Triple Combination Inhaler Therapies In People With Asthma

A December 2022 Cochrane review assessed the evidence for the safety and effectiveness of dual ICS-LABA and triple ICS-LABA-LAMA inhaler treatment compared with each other and with medium- to high-dose ICS monotherapy in adolescents (12 years and older) and adults with uncontrolled asthma using pair-wise meta-analysis and network meta-analysis (NMA).[2] Authors conducted a literature search through February 2022 to identify RCTs that included patients treated with combination medium- or high-dose ICS plus LABA therapy compared to triple inhaler therapy for at least 12 weeks.[2] It is not clear if high-dose ICS increases AEs compared with medium-dose ICS. Most studies comparing dual and triple combination therapies did not consider ICS doses (i.e. low- medium- and high-doses) in their combinations.[2] Therefore, this review also analyzed the impact of high-dose versus medium-dose ICS within the dual and triple combination therapies.[2]

Seventeen RCTs (n=17,161) met inclusion criteria with a median duration of 26 weeks, in people with a mean age of 49.1 years, 81% were white, and 40% were male.[2] Current smokers were excluded in all RCTs.[2] All RCTs were multi-center and industry-funded.[2] Most RCTs had a low risk of bias; some outcomes were limited by high attrition rates.[2] The 17 studies evaluated the following ICS-LABA combinations: beclomethasone-formoterol, budesonide-formoterol, ciclesonide-formoterol, fluticasone-formoterol, mometasone-formoterol, mometasone-indacaterol, fluticasone-salmeterol, and fluticasone-vilanterol.[2] Triple therapy included ICS-LABA-LAMA combination inhalers (i.e., fluticasone furoate-vilanterol-umeclidinium and mometasone-glycopyrronium-indacaterol) or an ICS-LABA fixed combination plus a LAMA as a single inhaler (i.e., aclidinium, glycopyrronium, tiotropium, and umeclidinium).[2] RCTs for triple combination therapies included only adults.[2] The primary outcome of interest was number of moderate asthma exacerbations (defined as requiring a short course of oral corticosteroids) and number of severe exacerbations (defined as resulting in hospitalization, mechanical ventilation, or death).[2] Secondary outcome measures included asthma control using the ACQ, QoL using the AQLQ, and AEs.[2]

The pairwise meta-analysis of 6 RCTs (n=5542) suggests:

- There is little or no difference in moderate to severe asthma exacerbations between high-dose ICS-LABA and medium-dose ICS-LABA inhalers over 3 to 12 months (RR 0.93, 95% CI, 0.82 to 1.05; I^2=0; high certainty of evidence).[2]
- Compared with dual therapy, triple therapy reduces moderate to severe exacerbations (RR 0.85; 95% CI, 0.78 to 0.92; 5 RCTs; n=8173; high-certainty evidence).[2]
- High-dose ICS triple inhaler therapy likely results in a slight reduction in moderate to severe exacerbations compared to medium-dose ICS triple therapy (RR 0.85; 95% CI 0.72 to 1.01; 3 RCTs, n=3470; I^2 = 0%; moderate certainty of evidence).[2]

In the NMA, each pair of treatments was compared by estimating a hazard ratio (HR) for time-to-event outcomes (e.g., asthma exacerbations), a mean difference for continuous outcomes, and an odds ratio (OR) for dichotomous outcomes, along with their 95% credible intervals (CrIs).[2] Results from the NMA suggest:

- High-dose ICS triple therapy reduces the hazards of moderate-severe exacerbations compared to medium-dose and high-dose ICS/LABA therapy (HR 0.69; 95% CrI 0.58 to 0.82 and HR 0.93; 95% CrI 0.79 to 0.88, respectively; high-certainty evidence), but not asthma-related hospitalizations compared to medium-dose ICS-LABA therapy.[2]
- There is marginal evidence to suggest that medium-dose ICS triple inhaler therapy reduces the hazards of moderate to severe asthma exacerbations compared to medium-dose ICS-LABA therapy (HR 0.84; 95% CrI 0.71 to 0.99; moderate-certainty evidence).[2]
- High-dose ICS triple inhaler therapy reduces the hazards of moderate to severe exacerbations compared to medium-dose ICS triple inhaler therapy (HR 0.83; 95% CrI 0.69 to 0.96; moderate-certainty evidence).[2]

There is insufficient evidence to suggest that there is a clinically meaningful change in ACQ or AQLQ scores at 6 and 12 months for any of the treatment comparisons.[2] The certainty of evidence ranges from low to moderate.[2] There was no difference in the results between fixed-effect and random-effects meta-analysis models.[2] These results are qualitatively similar to those of the NMA.[2]

For all-cause AEs, 12 trials (n=12,915) comparing 4 treatment groups were included in the NMA.[2] The NMA results suggested treatment with high-dose ICS triple therapy reduces the odds of all-cause AEs compared to medium-dose ICS dual therapy and high-dose ICS dual therapy (OR 0.79; 95% CrI 0.69 to 0.90 and OR 0.79; 95% CrI 0.70 to 0.88, respectively).[2] Evidence from the pairwise analysis suggests triple therapy results in a reduction in all-cause AEs compared to dual therapy (RR 0.93; 95% CI 0.90 to 0.96; 6 RCTs; high-certainty evidence).[2] The evidence from both the pairwise meta-analysis and NMA suggests there is no or little difference in all-cause SAEs for any of the treatment comparisons (moderate- to high-certainty evidence).[2]

In summary, medium-dose and high-dose ICS triple inhaler therapies reduce asthma exacerbations, but not asthma-related hospitalizations, compared to medium-dose ICS-LABA therapy (high-certainty evidence).[2] High-dose ICS triple therapy is likely superior to medium-dose ICS triple therapy in reducing asthma exacerbations (moderate-certainty evidence).[2] High-dose ICS triple therapy, but not medium-dose ICS triple therapy, results in a reduction in all-cause AEs (high-certainty evidence) compared with ICS dual therapy.[2] Triple therapy results in little to no difference in all-cause SAEs compared to ICS-LABA therapy (high-certainty evidence).[2] The evidence that any specific formulation would be better than the others within the same group in any outcomes is uncertain due to the scarcity of data and resulting imprecision of estimates.[2]

Cochrane: Adding LABA or LAMA to ICS Therapy Versus Increasing ICS Doses For Asthma Exacerbations

A 2023 Cochrane review assessed the safety and efficacy of adding a LABA to ICS therapy or LAMA to ICS therapy, compared with increasing the ICS dose in adolescents 12 years and older and adults with asthma not well controlled on medium-dose ICS.[3] The literature search was conducted through December 2022.[3] Studies comparing 2 of the following treatments, medium- or high-dose ICS monotherapy, LABA-ICS or LAMA-ICS met inclusion criteria. Thirty-five RCTs (n=38,276) with a median duration of 24 weeks met inclusion criteria.[3] The mean age of participants was 44.1 years, 38% were white, and 69% were male.[3] A pair-wise meta-analysis and NMA were conducted to synthesize data from the 35 RCTs. All studies were industry-funded and conducted in multiple centers.[3] All except 6 studies excluded current smokers.[3] Most studies were double-blinded, reducing the risk of performance and detection bias.[3] Two open-label studies had increased risk of bias, which decreased confidence in the ACQ score outcomes.[3] Missing outcome data in several outcomes due to high or uneven attrition rates led to a high risk of bias in those RCTs.[3] There was more data identified for LABAs than for LAMAs.[3]

The primary outcome of interest was frequency of moderate to severe asthma exacerbations, using similar definitions as the previous 2022 Cochrane review.[3] For moderate to severe exacerbations, specific conclusions from the pairwise meta-analysis include:

- In the meta-analysis of 16 RCTs (n=11,141), ICS-LABA reduces moderate to severe exacerbations compared with ICS monotherapy (RR 0.69; 95% CI 0.60 to 0.79; moderate-certainty evidence).[3]
- The pairwise evidence is very uncertain for the effect of high-dose ICS monotherapy on moderate to severe exacerbations compared to medium-dose ICS monotherapy due to imprecision, a lack of robustness, and missing data.[3]

Evidence from 25 RCTs (n=25,583) which compared 6 treatment groups in the NMA regarding asthma exacerbations suggested:

- Medium-dose ICS-LAMA, medium-dose ICS-LABA, and high-dose ICS-LABA reduce moderate to severe asthma exacerbations compared to medium-dose ICS monotherapy (HR 0.56; 95% CrI 0.38 to 0.82; low-certainty evidence; HR 0.70; 95% CrI 0.59 to 0.82; moderate-certainty evidence; and HR 0.59; 95% CrI 0.46 to 0.76; moderate-certainty evidence, respectively).[3]
- High-dose ICS-LABA reduces the hazard of moderate to severe exacerbations compared to high-dose ICS monotherapy (HR 0.63, 95% CrI 0.47 to 0.84; moderate-certainty evidence). [3]
- Compared with medium-dose ICS monotherapy, high-dose ICS monotherapy does not reduce asthma exacerbations (HR 0.94; 95% CrI 0.70 to 1.24; moderate-certainty evidence).[3]

Most comparisons between the meta-analysis and NMA aligned except for the NMA evidence which suggests high-dose ICS-LABA reduces moderate to severe exacerbations compared to medium-dose ICS monotherapy (HR 0.59; 95% CrI 0.46 to 0.76; moderate-certainty).[3] The pairwise analysis suggested no difference between these 2 therapies in reducing asthma moderate to severe exacerbations (RR 0.71, 95% CI 0.33 to 1.56; 2 studies, n=1759; low-certainty evidence).[3]
A secondary outcome measure was asthma control as assessed by the change from baseline in ACQ and AQLQ scores at 6 and 12 months. Evidence from the fixed-effect meta-analysis suggests:

- Medium-dose ICS-LABA reduces the ACQ score at 12 months compared to medium-dose ICS and high-dose ICS (mean difference -0.18, 95% CrI -0.26 to -0.09; moderate-certainty evidence and mean difference -0.13, 95% CrI -0.23 to -0.03; moderate certainty, respectively).[3]
- High-dose ICS-LABA reduces the ACQ score at 12 months compared to medium-dose ICS and high-dose ICS (mean difference -0.20, 95% CrI -0.26 to -0.14; high-certainty evidence and mean difference -0.15, 95% CrI -0.24 to -0.06; high-certainty evidence, respectively).[3]
- However, these differences do not reach the MCID of 0.5 units.[3] There is insufficient evidence to suggest that there is a clinically meaningful difference in the ACQ scores at 6 or 12 months for any of the treatment comparisons based upon low- to high-certainty evidence.[3] The NMA produced similar results.[3] For AQLQ scores, both the pairwise meta-analysis and NMA failed to identify clinically important differences between groups (MCID of 0.5 units).

An ACQ responder was defined as someone who experiences a clinically meaningful improvement int their ACQ score as defined as a reduction in the ACQ score by 0.5 or more points on the 7-point ACQ scale.[3]For the outcome of ACQ responder at 6 and 12 months the pairwise meta-analysis showed:

- Medium-dose and high-dose ICS-LABA and medium-dose ICS-LAMA increase ACQ responders at 6 months compared to medium-dose ICS monotherapy (RR 1.15, 95% CI 1.07 to 1.22; 2 studies, n=1853 participants, high-certainty evidence; RR 1.14, 95% CI 1.05 to 1.23; 1 study, n=1210, high-certainty evidence and RR 1.10, 95% CI 1.03 to 1.18; 3 studies, n=2219; moderate-certainty evidence, respectively).[3]
- Little or no difference in ACQ responders at 6 and 12 months was observed in other comparisons.[3]
- High-dose ICS-LABA increases ACQ responders at 12 months compared to medium-dose ICS monotherapy (RR 1.12, 95% CI 1.04 to 1.21; 1 study, n=1167; high- certainty evidence).[3]
- Medium-dose ICS/LABA likely increases ACQ responders at 12 months compared to medium-dose and high-dose ICS monotherapy (RR 1.19, 95% CI 1.09 to 1.29; 1 study, n=774 participants and RR 1.12, 95% CI 1.03 to 1.20; 1 study, n=784 participants; moderate-certainty evidence, respectively).[3]

- The above results are in accordance with those of the NMA except for high-dose ICS-LABA versus high-dose ICS monotherapy for which the NMA evidence suggests that high-dose ICS-LABA increases the odds of ACQ responders at 12 months compared to high-dose ICS (OR 1.42, 95% CrI 1.10 to 1.84; moderate-certainty evidence), while the pairwise evidence does not (OR 1.23, 95% CI 0.93 to 1.63; 1 study, n=1177 participants; moderate-certainty).[3]

For outcomes related to AEs, the pairwise meta-analysis showed:

- Medium-dose ICS-LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to medium-dose ICS monotherapy (RR 0.86; 95% CI 0.77 to 0.96; 4 RCTs, n=2,238; moderate-certainty evidence; and RR 0.51, 95% CI 0.26 to 0.99; 4 RCTs, n=2,239; moderate-certainty evidence, respectively).[3]
- ICS-LABA or ICS-LAMA does not reduce asthma-related or all-cause SAEs compared to medium-dose-ICS monotherapy (very low-to high-certainty evidence) based on data from the NMA.[3]
- High-dose ICS and medium dose ICS monotherapy likely have little or no difference for the included safety outcomes as well as high-dose ICS/LABA compared to medium-dose ICS/LABA.[3] Evidence from the NMA is in agreement with the pairwise evidence on treatment discontinuation due to AEs, but very uncertain on all-cause AEs, due to imprecision and heterogeneity.[3]

The findings from this review suggest medium- or high-dose ICS-LABA and medium-dose ICS-LAMA reduce moderate to severe asthma exacerbations and increase the odds of ACQ responders compared to medium-dose ICS whereas high-dose ICS probably does not.[3] The evidence is generally stronger for medium-dose and high-dose ICS-LABA than for medium-dose ICS-LAMA primarily due to a larger evidence base.[3] Medium-dose ICS-LAMA likely reduces all-cause AEs and results in a slight reduction in treatment discontinuation due to AEs compared to medium-dose ICS.[3]

After review, 22 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[28-40] wrong study design of included trials (e.g., observational),[41-47] comparator (e.g., no control or placebo-controlled),[48,49] or outcome studied (e.g., non-clinical).[50]

New Guidelines:

Global Initiative for Asthma - 2023 Update

The updated GINA guidance was published in July 2023.[4] Key changes in this report include: clarification of terminology for asthma medications, addition of as-needed ICS/SABA reliever therapy to GINA track 2, and additional tables describing low, medium, and high daily ICS dosing were added based on provider requests.[4]

Asthma Medication Terminology

In the past, "controller medication" was used to described ICS-containing medications prescribed for regular daily treatment.[4] This became confusing after combination ICS-LABAs were introduced as relievers for as-needed use. To avoid confusion, the term "controller medication" has been replaced with maintenance treatment or ICS-containing treatment.[4] The term "maintenance" describes the prescribed frequency of administration, not the particular class of medication.[4] The term anti-inflammatory reliever (AIR) has been introduced and includes as-needed ICS-formoterol or ICS-SABA in steps 1 and 2 for adults and adolescents.[4] Use of as-needed ICS-formoterol is considered off-label in the US, as these products are not FDA-approved for relief of bronchospasm. Non-formoterol LABAs in combination with ICS should not be used as relievers, due to insufficient evidence for their safety and efficacy.[4] In steps 3 through 5 for

adults and adolescents, ICS-formoterol is used as maintenance and reliever therapy (MART).[4] MART is also called SMART (single-inhaler maintenance and reliever therapy). Evidence for MART therapy is only published for combination ICS-formoterol inhalers.[4]

Treatment Recommendations

Adult and adolescent treatment options are separated into 2 tracks, based on the choice of reliever inhaler (see **Table 1**). In Track 1, the preferred reliever is low-dose ICS-formoterol because it reduces the risk of severe exacerbations compared with using a SABA reliever, and because of the simplicity of the regimen.[4] In Track 2, the reliever is as-needed SABA or as-needed ICS-SABA. Track 2 is an option if Track 1 is not possible or if a patient stable, with good adherence and no exacerbations in the past year on their current therapy.[4] Starting treatment with SABA alone trains the patient to regard SABA as their primary asthma treatment.[4] Due to safety concerns, GINA does not recommend treatment of asthma in adults or adolescents with SABA alone due to the increased risk of exacerbations and asthma-related death.[4] However, as needed SABA or ICS-SABA may be an option if as needed ICS-formoterol is not available or affordable.[4] Patients should be assessed for adherence to ICS-containing therapy before starting SABA monotherapy as a part of the reliever regimen.[4]

For Step 1 therapy, the preferred maintenance treatment is low-dose ICS-formoterol taken as-needed for symptom relief.[4] This strategy is supported by evidence from 2 studies comparing as-needed low-dose budesonide-formoterol with SABA-only treatment in patients taking SABA alone, low-dose ICS, or leukotriene receptor antagonists (LTRAs).[4] Compared with as-needed SABA alone, as-needed low dose ICS-formoterol reduced severe exacerbations and ED/ hospital visits by about two-thirds.[4] Compared with daily low-dose ICS plus as-needed SABA, as-needed low-dose ICS-formoterol reduces severe exacerbations to a similar extent and reduces ED/hospital visits by approximately one-third, with a very small difference in symptom control favoring ICS-formoterol.[4]

The preferred Step 3 option is low-dose ICS-formoterol as both maintenance and reliever treatment.[4] Compared with maintenance ICS-LABA or higher dose ICS with an as-needed SABA, low-dose ICS-formoterol reduces the risk of severe asthma exacerbations with a similar level of symptom control.[4] A new step 4 option in the 2023 GINA report is higher maintenance dose ICS-LABA plus as-needed ICS-SABA in adults over 18 years of age.[4] This is based on evidence that showed use of an ICS-SABA reliever reduced severe exacerbations compared with using SABA monotherapy (albuterol) as a reliever.[4] **Table 5** provides a summary of 2023 GINA approaches for asthma treatment in adolescents and adults. For patients whose asthma is not well controlled on a particular treatment, the provider should assess adherence, inhaler technique, risk factors and comorbidities before considering a different medication in the same step or increasing the ICS dose.[4]

Table 5. GINA 2023 Recommendations for Asthma Therapy In Adolescents And Adults.[4]

GINA Step	Track 1 (Preferred) Reliever: As-needed low dose ICS-formoterol	Track 2 (Alternative) Reliever: As needed SABA or as needed ICS-SABA)
Steps 1 and 2: Symptoms less than 4-5 days/week	• Maintenance: As-needed-only low dose ICS-formoterol	• Step 1 Maintenance: Take ICS taken whenever SABA is taken • Step 2 Maintenance: Low dose ICS
Step 3: Symptoms most days, or waking with asthma once a week or more	• Maintenance: Low dose ICS-formoterol	• Maintenance: Low dose ICS-LABA

Step 4: Daily symptoms, or waking with asthma once a week or more, and low lung function	• Maintenance: Medium dose ICS-formoterol	• Maintenance: Medium/high-dose ICS-LABA
Step 5: Daily symptoms, or waking with asthma once a week or more, and low lung function	• Maintenance: ○ Add on LAMA ○ Refer for phenotypic assessment with or without biologic therapy ○ Consider high dose ICS-formoterol	• Maintenance: ○ Add-on LAMA ○ Refer for phenotypic assessment with or without biologic therapy ○ Consider high dose ICS-LABA
Abbreviations: GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; ICS-LABA = inhaled corticosteroid-long-acting beta agonist combination; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short acting beta agonist		

Approaches for asthma treatment in children aged 6 to 11 years of age are different from adult and adolescent recommendations (see **Table 6**). There is only one recommendation for a reliever medication: as-needed SABA in Steps 1 through 4 or ICS-formoterol in Steps 3 and 4.[4] A preferred maintenance medication is suggested for each step, with other maintenance medications suggested as an alternative. For children aged 6 to 11 years with mild asthma, taking an ICS whenever SABA is taken is safer than using SABA alone and is the preferred maintenance medication.[4] The preferred Step 2 maintenance treatment in children is daily low-dose ICS.[4] There are 3 preferred maintenance options for children in Step 3: low-dose ICS-LABA, medium-dose ICS, or very dose low budesonide-formoterol inhaler as MART.[4] Very low-dose budesonide-formoterol (i.e. 100/6 mcg once daily) showed a large reduction in severe asthma exacerbations for children, compared with the same dose of an ICS-formoterol or higher dose of ICS.[4] For step 4, the preferred maintenance medications are medium-dose ICS/LABA or low-dose ICS-formoterol MART.

Table 6. GINA 2023 Approaches To Initial Asthma Therapy In Children Aged 6 to 11 years.[4]

GINA Step	Preferred Maintenance Medication	Other Maintenance Medication Options
Step 1	• Reliever: As needed SABA • Maintenance: Low-dose ICS taken whenever SABA taken	• Reliever: As needed SABA • Maintenance: Consider daily low dose ICS
Step 2	• Reliever: As needed SABA • Maintenance: Low-dose daily ICS	• Reliever: As needed SABA • Maintenance: Daily LTRA or low dose ICS taken whenever SABA taken
Step 3	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Low dose ICS/LABA or medium dose ICS or very low dose ICS-formoterol MART	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Low dose ICS plus LTRA
Step 4	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Medium dose ICS/LABA, or low dose ICS-formoterol MART	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Add tiotropium or add LTRA
Step 5	• Reliever: As needed SABA or ICS-formoterol • Maintenance: Refer for phenotypic assessment with or without higher dose ICS/LABA or add-on therapy (e.g., anti-IgE, anti-IL4, or anti-IL5)	• Reliever: As needed SABA or ICS-formoterol • Maintenance: As last resort, consider add-on low dose OCS, but consider side effects

Abbreviations: ICS = inhaled corticosteroid; ICS-LABA = inhaled corticosteroid-long-acting beta-agonist combination; IgE = immunoglobulin E; IL = interleukin; LABA = long-acting beta agonist; LTRA = leukotriene receptor antagonist; MART = maintenance and reliever therapy; OCS = oral corticosteroids; SABA = short acting beta-2 agonist

Summary of GINA 2023 Medication Recommendations and Strength of Evidence

- SABAs are highly effective for quick relief of asthma symptoms, but patients treated with SABAs alone are at risk of asthma-related death and urgent asthma-related health care use, even if good symptom control (high-quality evidence).[4]
- Regular or frequent LABA use alone is not recommended without ICS due to risk of asthma exacerbations (high-quality evidence).[4]
- Combination low-dose ICS-formoterol as both reliever and maintenance therapy is effective in improving asthma symptom control, and reduces exacerbations requiring oral corticosteroids and hospitalizations compared to same or higher dose of controller with as-needed SABA reliever (high-quality evidence).[4]
- In step 4, in patients with persistently uncontrolled asthma despite medium- or high-dose ICS-LABA, consider adding on a LAMA as a separate inhaler (age ≥ 6 years) or combination triple therapy inhaler (age ≥ 18 years).[4] Evidence shows this strategy may modestly improve lung function but not symptoms (high-quality evidence).[4]
- In patients having exacerbations with low-dose ICS-LABA, ICS dose should be increased to medium or higher, or treatment switched to maintenance and reliever therapy with ICS-formoterol before adding LAMA (high-quality evidence).[4]

Global Initiative for Chronic Obstructive Lung Disease – 2023 Update

The 2023 GOLD report contains several important revisions and updates including: a new definition of COPD; a revision of the patient classification system; a new definition of COPD exacerbation; and updated evidence on therapeutic interventions to reduce COPD mortality.[5] Based on the different causes that can contribute to COPD, the GOLD 2023 report outlines an updated taxonomic classification of COPD using etiotypes to reflect recent evidence supporting an updated definition of COPD (see **Table 7**).[5,51] The goal is to raise awareness about non–smoking-related COPD and to stimulate research on the mechanisms and corresponding diagnostic, preventive, or therapeutic approaches for other types of COPD which are highly prevalent around the globe.[5]

Table 7. GOLD 2023 COPD Etiotypes[5,51]

Classification	Description
COPD-G: Genetically determined COPD	• Alpha-1 antitrypsin deficiency (AATD) • Other genetic variants with smaller effects acting in combination
COPD-D: COPD due to abnormal lung development	• Early life events, including premature birth and low birthweight, among others
COPD-C: Cigarette smoking	• Exposure tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
COPD-P: Pollution exposure	• Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD-I: COPD due to infections	• Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD-A: COPD and Asthma	• Particularly childhood asthma
COPD-U: COPD of unknown cause	• Unknown causes

The GOLD 2023 report includes a modification of the ABCD assessment tool used in previous reports to recognize the clinical impact of exacerbations independently of the level of symptoms of the patient.[5] Exacerbations of COPD (ECOPD) negatively affect health status, disease progression, and prognosis.[52] The previous GOLD definition of ECOPD was highly non-specific and defined exacerbations as "acute worsening of respiratory symptoms that results in additional therapy".[19] To address these limitations, the GOLD 2023 guidance now defines ECOPD as: "an event characterized by dyspnea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways."[5] The thresholds proposed for symptoms and history of exacerbations in the previous year are unchanged from previous GOLD documents, so the A and B groups remain unchanged, while the former C and D groups are now merged into a single group termed "E" (for "Exacerbations").[5] **Table 8** provides details of the new ABE assessment tool.

Table 8. 2023 GOLD Symptom Assessment/Exacerbation Risk for Patients with COPD[5]

Classification	Assessment Test	Exacerbations
GOLD Category A	mMRC 0-1 or CAT <10	History of 0-1 moderate to severe exacerbations (not leading to hospitalization) per year
GOLD Category B	mMRC ≥2 or CAT ≥10	History of 0-1 moderate to severe exacerbations (not leading to hospitalization) per year
GOLD Category E	mMRC ≥2 or CAT ≥10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospitalization) per year
Abbreviations: CAT = COPD Assessment Test; COPD = Chronic Obstructive Lung Disease; GOLD = Global Initiative for COPD; mMRC = modified Medical Research Council questionnaire		

The ABE assessment tool is the foundation for initiation of COPD inhaler treatment.[5] The treatment of patients in Group A remains the same as previous reports: a bronchodilator (i.e., SABA, SAMA, LABA, or LAMA) with a long-acting bronchodilator preferred unless very occasional dyspnea is present (strong recommendation).[5] For patients in Group B, a LAMA-LABA inhaler is now recommended for initial treatment since dual therapy is more effective than monotherapy, with similar side effects (strong recommendation).[5] For patients in Group E, LAMA-LABA is the recommended initial therapy (strong recommendation).[5] In patients with blood eosinophils ≥300 cells/µL, triple inhaler therapy (LABA/LAMA/ICS) can be considered.[5] This is recommendation is based upon expert opinion as direct evidence is not available to guide therapy in naïve individuals.[52] **Table 9** summarizes the pharmacotherapy guidance for initial treatment of COPD which is simplified from the 2022 guidance.

Table 9. GOLD 2023 Initial Pharmacologic Treatment Recommendations[5]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization per year	**Group E** **LABA + LAMA*** *Consider LABA + LAMA + ICS if blood eosinophils ≥ 300*	
0 or 1 moderate exacerbations per year (not leading to hospital admission)	**Group A** **A bronchodilator**	**Group B** **LABA + LAMA***
	mMRC 0-1; CAT <10	mMRC ≥ 2; CAT ≥ 10
****Single inhaler therapy may be more convenient and effective than multiple inhalers* Abbreviations: CAT = COPD Assessment Tool; eos = eosinophils; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council Dyspnea Questionnaire		

Previous studies such as the TORCH clinical trial[53] and the SUMMIT trial[54] failed to show efficacy of a LABA-ICS combination in reducing the mortality of COPD patients compared to placebo.[5] These trials had no requirement for a history of previous exacerbations. The largest LAMA treatment trial, UPLIFT, didn't demonstrate a reduction in mortality compared to placebo.[5] The majority of patients included in this study utilized an ICS.[5] Recently, evidence has emerged from two large randomized clinical trials, IMPACT[55] and ETHOS[27] which show that LABA-LAMA-ICS combinations reduce all-cause mortality compared to ICS-LABA therapy (IMPACT: HR 0.72; 95% CI, 0.53 to 0.99 and ETHOS: HR 0.51; 95% CI, 0.33 to 0.80).[5] These trials were enriched for symptomatic patients (CAT ≥ 10) with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring a hospital admission).[5]

Summary of GOLD 2023 Recommendations:
Bronchodilators in COPD

- Inhaled bronchodilators (i.e., SABA, SAMA, LABA, or LAMA) in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms (High-Quality Evidence).[5]
- Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms (High-Quality Evidence).[5]
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms (High-Quality Evidence).[5]
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates (High-Quality Evidence).[5]
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (High-Quality Evidence) and decrease hospitalizations (Moderate-Quality Evidence).[5]
- Combination treatment with a LABA-LAMA increases FEV_1 and reduces symptoms compared to monotherapy (High-Quality Evidence).[5]
- Combination treatment with a LABA-LAMA reduces exacerbations compared to monotherapy (Moderate-Quality Evidence).[5]
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance (Moderate-Quality Evidence).[5]

Anti-inflammatory Therapy in Stable COPD

- An ICS combined with a LABA is more effective than individual components administered as monotherapy in improving lung function and health status and reducing exacerbations in patients with exacerbations and modest to very severe COPD (High-Quality Evidence).[5]
- Regular treatment with ICS increased the risk of pneumonia especially in those with severe disease (High-Quality Evidence).[5]
- Triple inhaled therapy of LABA-LAMA-ICS improves lung function, symptoms and health status and reduces exacerbations compared to LABA-ICS, LABA-LAMA or LAMA monotherapy (High-Quality Evidence).[5]

After review, one guideline was excluded due to poor quality (extensive conflict of interest).[56]

New Formulations or Indications:

- A new ICS-SABA product, albuterol 90 mcg and budesonide 80 mcg (AIRSUPRA) received FDA approval in January 2023. This is the first ICS-SABA combination inhaler approved in the U.S. The albuterol-budesonide inhaler is indicated for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.[7] In the MANDALA trial, albuterol-budesonide showed a statistically significant reduction in time to first severe asthma exacerbation compared with albuterol monotherapy.[6] The recommended dose is 2 puffs as needed for asthma symptoms; not to exceed more than 6 doses in a 24-hour period.[7] The most common adverse effects observed in clinical trials included headache, oral candidiasis, cough, and dysphonia.[7] An insufficient number of pediatric patients (aged 4 to 17 years)

were enrolled in the Phase 3 RCTs (MANDALA and DENALI), so safety and efficacy in children and adolescents has not been established.[7] A summary of the phase 3 trials which led to FDA-approval is provided in **Table 10** below.

- In April 2023, a new formulation of budesonide 160 mcg and formoterol 4.8 mcg (SYMBICORT AEROSPHERE) received FDA approval as maintenance treatment of patients with COPD.[8] The original budesonide-formoterol (SYMBICORT) products contain formoterol 4.5 mcg and 80 to 160 mcg of budesonide. The recommended dose of SYMBICORT AEROSPHERE is 2 puffs twice daily.[8] It is not indicated for relief of acute bronchospasm or for treatment of asthma.[8] The efficacy of SYMBICORT AEROSPHERE was evaluated in two randomized, double-blind, multicenter, parallel group trials (TELOS and SOPHOS) in patients with COPD who remained symptomatic despite maintenance treatment for COPD.[8] Compared with formoterol monotherapy, combination budesonide-formoterol improved time to first and rate of moderate- to severe-COPD exacerbations. A summary of the phase 3 trials is provided in **Table 10** below.

Randomized Controlled Trials:

A total of 370 citations were manually reviewed from the initial literature search. After further review, 366 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the table below. The full abstracts are included in **Appendix 2**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary and Secondary Outcome	Results	Notes/Limitations
Papi A, et al.[6] MANDALA DB, PG. MC, Phase 3 RCT N=3132 Duration: 24 weeks 296 Centers in 11 countries	1. High dose albuterol 90 mcg and budesonide 80 mcg, 2 puffs as needed, maximum 6 doses per day (n=1016) vs 2. Low dose albuterol 90 mcg and budesonide 40 mcg, 2 puffs as needed, maximum 6 doses per day (n=1057) vs 3.Albuterol 90 mcg, 2 puffs as needed,	Adults and children aged 4 years and older with uncontrolled (i.e., 1 exacerbation within previous 12 months) moderate-to-severe asthma receiving medium to high dose ICS or low to high dose ICS/LABA maintenance therapy. Children less than 12 years of age were not randomized to high-dose albuterol/budesonide treatment arm. 97% of participants were 12 years of age and older.	Primary: Time to first severe asthma exacerbation. Severe exacerbation defined as: -Use of systemic corticosteroids for at least 3 consecutive days -An emergency department or urgent care visit for asthma requiring corticosteroids -An inpatient hospitalization for asthma Secondary: Annualized rate of severe asthma exacerbation	A. <u>Time to first asthma exacerbation (ITT analysis)</u> 1 vs 3 HR 0.74 95% CI 0.62 to 0.89 P=0.001 2 vs 3 HR 0.84 95% CI 0.71 to 1.00 P=0.052 B. <u>Annualized rate of severe asthma exacerbation (ITT analysis)</u> 1. 0.43 2. 0.48 3. 0.58 1 vs 3	• Most patients were white (90%) and female (64%) with a mean age of 50 years old. • Small proportion of children were enrolled (3%) and they did not receive the high-dose combination product due to risk of adverse effects. • Moderate exacerbations were not assessed. Only severe exacerbations were included as an outcome. • Trial was funded by the manufacturer.

	maximum 6 doses per day (n=1059)			RR 0.75 95% CI 0.61 to 0.91 2 vs 3 RR 0.81 95% CI 0.66 to 0.98	• Only the high dose albuterol-budesonide showed a statistically significant reduction in time to first severe asthma exacerbation in the ITT analysis. ITT results with low-dose formulation were not statistically significant.
Chipps B, et al.[57] DENALI DB, PG, MC Phase 3 RCT N=1,001 126 sites across 3 continents (North America, Europe, and South America) 12 weeks	1. High dose albuterol 90 mcg and budesonide 80 mcg, 2 puffs 4 times a day (n=197) vs 2. Low dose albuterol 90 mcg and budesonide 40 mcg, 2 puffs 4 times a day (n=204) vs 3.Albuterol 90 mcg, 2 puffs 4 times a day (n=201) vs. 4. Budesonide 80 mcg, 2 puffs 4 times a day (n=200) vs 5. Placebo, 2 puffs 4 times a day (n=199)	Patients aged ≥ 12 years with mild-to-moderate asthma receiving as-needed SABA or low-dose maintenance ICS plus as-needed SABA therapy at a stable dose for ≥ 30 days prior to enrollment. 10 children aged 4 to 11 years were enrolled, but not assigned to high-dose albuterol-budesonide treatment arm.	Co-primary endpoints: A. Change from baseline in FEV_1 AUC from 0 to 6 hours over 12 weeks B. Change from baseline in trough FEV_1 at week 12	A. LSM change from baseline in FEV_1 AUC from 0 to 6 hours over 12 weeks (mLs) 1. 258.6 2. 242.2 3. 157.2 4. 178 5. 96.7 High dose combo vs. PBO Difference: 161.9 95% CI 109.4 to 214.5 P<0.001 Low dose combo vs. PBO Difference: 145.5 95% CI 93 to 197.9 P<0.001 High dose combo vs. albuterol Difference: 101.4 95% CI 48.8 to 154.1 P<0.001 Low dose combo vs. albuterol Difference: 84.9 95% CI 32.3 to 137.5 P=0.002 High dose combo vs. ICS	• Most patients were white (90%) and female (61%) with a mean age of 50 years old. • Small proportion of children were enrolled and they did not receive the high-dose combination product due to risk of adverse effects. • Short term study (12 weeks). • Four times a day dosing used in this study exceeds recommended budesonide dosing recommendations. • Manufacturer contributed to trial funding, trial design, data collection, data analysis, data interpretations, and writing of the report. • Investigators reported several conflicts of interest. • Time to onset and duration of bronchodilation with albuterol-budesonide were

				Difference: 80.7 95% CI 28.4 to 132.9 P=0.003 Low dose combo vs. ICS Difference: 64.2 95% CI 12.1 to 116.4 P=0.016 <u>B. LSM change in trough FEV_1 at week 12 (mLs)</u> 1. 135.5 2. 123.5 3. 2.7 4. 73.3 5. 35.6 High dose combo vs. PBO Difference: 99.9 95% CI 30.9 to 168.8 P=0.005 Low dose combo vs. PBO Difference: 87.9 95% CI 18.8 to 156.9 P=0.013 High dose combo vs. albuterol Difference: 99.9 95% CI 30.9 to 168.8 P=0.005 Low dose combo vs. albuterol Difference: 120.8 95% CI 51.5 to 190.1 P<0.001 High dose combo vs. ICS Difference: 26.6 95% CI -41. 6 to 94.7 P=0.444	similar to those with albuterol.

				Low dose combo vs. ICS Difference: 14.6 95% CI -53.6 to 82.8 P=0.675	
Ferguson GT, et al.[58] TELOS DB, PG, MC, Phase 3 RCT Duration: 24 weeks N=2389 Conducted at 253 sites across 7 countries	1. High dose budesonide 320 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=664) vs 2. Low dose budesonide 160 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=649) vs 3 .Formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=648) vs 4. Budesonide 320 mcg, 2 puffs twice daily (n=209) vs 5. Budesonide 400 mcg/formoterol 12 mcg 2 puffs twice daily (n=219): open-label arm, NI assessment *Formoterol fumarate dihydrate 10 mcg =	Adults 40 to 80 years of age with symptomatic COPD despite treatment with 1 or more bronchodilators (CAT score ≥ 10). Patients did not have to have a history of COPD exacerbation.	Co-primary endpoints: A.Change from baseline in pre-dose trough FEV_1 and B. Change from baseline in pre-dose FEV_1 AUC from 0 to 4 hours at 24 weeks	<u>A.LSM change from baseline in pre-dose trough FEV_1 (mLs) at 24 weeks</u> High dose combo vs. formoterol Difference 39 95% CI 8 to 59 P=0.0018 High dose combo vs. ICS Difference 65 95% CI 29 to 101 P=0.0004 Low dose combo vs. formoterol Difference 20 95% CI -13 to 44 P=0.1132 Low dose combo vs. ICS Difference 45 95% CI 10 to 81 P<0.0131 <u>B. Change from baseline in pre-dose FEV_1 AUC from 0 to 4 hours (mLs) at 24 weeks)</u> High dose combo vs. formoterol Difference 34 95% CI 8 to 59 P=0.0092 High dose combo vs. ICS Difference 173	• Most patients were white (97%) and male (61%) with a mean age of 64 years old with a smoking history of 44 pack-years. • 70% of enrolled subjects did not have a COPD exacerbation in the previous 12 months prior to enrollment. • 2 efficacy and statistical analysis approaches, US and EU, were used in the study based on regional regulatory requirements. • Short term study (24 weeks), was not long enough to investigate exacerbation rates. • Study was funded by manufacturer. Several investigators reported conflict of interest due to grant support from the manufacturer or employment by the manufacturer. • Budesonide/formoterol 320/10 mcg and 160/10 mcg effectively improved lung function relative to budesonide monotherapy

	formoterol fumarate 9.6 mcg			95% CI 136 to 210 Low dose combo vs. formoterol Difference 18 95% CI -7 to 44 P=0.1621 Low dose combo vs. ICS Difference 157 95% CI 120 to 194 P<0.0001	(which is not a recommended COPD therapy).
Hanania NA, et al.[59] SOPHOS DB, PG, MC, Phase 3 RCT Duration: 12 to 52 weeks N=1,843 292 centers in 18 countries	1. High dose budesonide 320 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=624) vs 2. Low dose budesonide 160 mcg/formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=627) vs 3. Formoterol fumarate dihydrate 10 mcg, 2 puffs twice daily (n=613)	Adults 40 to 80 years of age with symptomatic COPD despite treatment with 1 or more bronchodilators (CAT score ≥ 10). Documented history of at least 1 moderate-to-severe COPD exacerbation in the previous 12 months.	Primary Outcome: Change from baseline in pre-dose trough FEV_1 at 12 weeks Secondary Outcome: Rate of moderate/severe COPD exacerbation	<u>A.Change from baseline in pre-dose trough FEV_1 at 12 weeks (mLs) – US approach</u> 1. 72 2. 69 3. 37 1 vs 3 Difference 34 95% CI 9 to 60 P=0.0081 2 vs 3 Difference 32 95% CI 7 to 57 P=0.0134 <u>B. Rate of moderate/severe COPD exacerbations over 52 weeks</u> 1.0.93 2.0.98 3.1.39 1 vs 3 RR 0.67 95% CI 0.54 to 0.82 P=0.0001 2 vs 3 RR 0.71	• Most patients were white (83%) and male (57%) with a mean age of 65 years old with a smoking history of 45 pack-years • 2 efficacy and statistical analysis approaches, US and EU, were used in the study based on regional regulatory requirements. • Only 10% of participants completed treatment at 52 weeks. • Study was funded by manufacturer. Several investigators reported conflict of interest due to grant support from the manufacturer or employment by the manufacturer. • Both doses of budesonide/formoterol resulted in statistically significant improvements in lung function compared with formoterol MDI.

				95% CI 0.58 to 0.87 P=0.001	

Abbreviations: AUC = area under the curve; CAT = COPD assessment tool; CI = confidence interval; DB = double-blind; COPD = Chronic Pulmonary Obstructive Disease; EU = European Union; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio; ICS = inhaled corticosteroid; ITT = intention-to- treat; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; LSM =least squares mean; MC= multi-center; mcg = micrograms; MDI = multi-dose inhaler; mLs = milliliters; NI = noninferiority; PG = parallel group; RCT = randomized clinical trial; RR = rate ratio; US = United States

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Appendix 1: Current Preferred Drug List

Long-Acting Muscarinic Antagonists (LAMA)

Generic	Brand	Route	Form	PDL
umeclidinium bromide	INCRUSE ELLIPTA	INHALATION	BLST W/DEV	Y
tiotropium bromide	SPIRIVA HANDIHALER	INHALATION	CAP W/DEV	Y
tiotropium bromide	TIOTROPIUM BROMIDE	INHALATION	CAP W/DEV	Y
ipratropium bromide	ATROVENT HFA	INHALATION	HFA AER AD	Y
tiotropium bromide	SPIRIVA RESPIMAT	INHALATION	MIST INHAL	Y
ipratropium bromide	IPRATROPIUM BROMIDE	INHALATION	SOLUTION	Y
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	INHALATION	AMPUL-NEB	Y
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	INHALATION	MIST INHAL	Y
aclidinium bromide	TUDORZA PRESSAIR	INHALATION	AER POW BA	N
revefenacin	YUPELRI	INHALATION	VIAL-NEB	N

Beta-Agonists, Inhaled Long Acting (LABA)

Generic	Brand	Route	Form	PDL
salmeterol xinafoate	SEREVENT DISKUS	INHALATION	BLST W/DEV	Y
olodaterol HCl	STRIVERDI RESPIMAT	INHALATION	MIST INHAL	N
arformoterol tartrate	ARFORMOTEROL TARTRATE	INHALATION	VIAL-NEB	N
arformoterol tartrate	BROVANA	INHALATION	VIAL-NEB	N
formoterol fumarate	FORMOTEROL FUMARATE	INHALATION	VIAL-NEB	N
formoterol fumarate	PERFOROMIST	INHALATION	VIAL-NEB	N

Beta-Agonists, Inhaled Short-Acting (SABA)

Generic	Brand	Route	Form	PDL
albuterol sulfate	ALBUTEROL SULFATE HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	PROAIR HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	PROVENTIL HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	VENTOLIN HFA	INHALATION	HFA AER AD	Y
albuterol sulfate	ALBUTEROL SULFATE	INHALATION	VIAL-NEB	Y
albuterol sulfate	PROAIR RESPICLICK	INHALATION	AER POW BA	N
albuterol sulfate	PROAIR DIGIHALER	INHALATION	AER PW BAS	N
albuterol	ALBUTEROL	INHALATION	AER REFILL	N
levalbuterol tartrate	LEVALBUTEROL TARTRATE HFA	INHALATION	HFA AER AD	N
levalbuterol tartrate	XOPENEX HFA	INHALATION	HFA AER AD	N
levalbuterol HCl	LEVALBUTEROL CONCENTRATE	INHALATION	VIAL-NEB	N
levalbuterol HCl	LEVALBUTEROL HCL	INHALATION	VIAL-NEB	N

Corticosteroids, Inhaled (ICS)

Generic	Brand	Route	Form	PDL
mometasone furoate	ASMANEX	INHALATION	AER POW BA	Y
budesonide	PULMICORT FLEXHALER	INHALATION	AER POW BA	Y
fluticasone propionate*	FLOVENT HFA	INHALATION	AER W/ADAP	Y
fluticasone propionate	FLUTICASONE PROPIONATE HFA	INHALATION	AER W/ADAP	Y
fluticasone propionate	FLOVENT DISKUS	INHALATION	BLST W/DEV	Y
fluticasone propionate	ARMONAIR DIGIHALER	INHALATION	AER PW BAS	N
budesonide	BUDESONIDE	INHALATION	AMPUL-NEB	N
budesonide	PULMICORT	INHALATION	AMPUL-NEB	N
fluticasone furoate	ARNUITY ELLIPTA	INHALATION	BLST W/DEV	N
ciclesonide	ALVESCO	INHALATION	HFA AER AD	N
mometasone furoate	ASMANEX HFA	INHALATION	HFA AER AD	N
beclomethasone dipropionate	QVAR REDIHALER	INHALATION	HFA AEROBA	N

*Anticipate discontinuation of branded product in January 2024 as generic product will be manufactured by Glaxo

Corticosteroids/SABA & LABA Combinations, Inhaled

Generic	Brand	Route	Form	PDL
fluticasone propion/salmeterol	AIRDUO RESPICLICK	INHALATION	AER POW BA	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	INHALATION	AER POW BA	Y
fluticasone propion/salmeterol	ADVAIR DISKUS	INHALATION	BLST W/DEV	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	INHALATION	BLST W/DEV	Y
fluticasone propion/salmeterol	WIXELA INHUB	INHALATION	BLST W/DEV	Y
fluticasone propion/salmeterol	ADVAIR HFA	INHALATION	HFA AER AD	Y
budesonide/formoterol fumarate	BREYNA	INHALATION	HFA AER AD	Y
budesonide/formoterol fumarate	BUDESONIDE-FORMOTEROL FUMARATE	INHALATION	HFA AER AD	Y
mometasone/formoterol	DULERA	INHALATION	HFA AER AD	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL HFA	INHALATION	HFA AER AD	Y
budesonide/formoterol fumarate	SYMBICORT	INHALATION	HFA AER AD	Y
fluticasone propion/salmeterol	AIRDUO DIGIHALER	INHALATION	AER PW BAS	N
fluticasone/vilanterol	BREO ELLIPTA	INHALATION	BLST W/DEV	N
fluticasone/vilanterol	FLUTICASONE-VILANTEROL	INHALATION	BLST W/DEV	N
albuterol sulfate/budesonide	AIRSUPRA	INHALATION	HFA AER AD	N

LAMA/LABA Combination, Inhalers

Generic	Brand	Route	Form	PDL
umeclidinium brm/vilanterol tr	ANORO ELLIPTA	INHALATION	BLST W/DEV	Y
tiotropium Br/olodaterol HCl	STIOLTO RESPIMAT	INHALATION	MIST INHAL	Y
aclidinium brom/formoterol fum	DUAKLIR PRESSAIR	INHALATION	AER POW BA	N
fluticasone/umeclidin/vilanter	TRELEGY ELLIPTA	INHALATION	BLST W/DEV	N
glycopyrrolate/formoterol fum	BEVESPI AEROSPHERE	INHALATION	HFA AER AD	N
budesonide/glycopyr/formoterol	BREZTRI AEROSPHERE	INHALATION	HFA AER AD	N

Appendix 2: Abstracts of Comparative Clinical Trials

Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma[6]

BACKGROUND: As asthma symptoms worsen, patients typically rely on short-acting beta-agonist (SABA) rescue therapy, but SABAs do not address worsening inflammation, which leaves patients at risk for severe asthma exacerbations. The use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, as rescue medication might reduce the risk of severe asthma exacerbation.

METHODS: We conducted a multinational, phase 3, double-blind, randomized, event-driven trial to evaluate the efficacy and safety of albuterol-budesonide, as compared with albuterol alone, as rescue medication in patients with uncontrolled moderate-to-severe asthma who were receiving inhaled glucocorticoid-containing maintenance therapies, which were continued throughout the trial. Adults and adolescents (>=12 years of age) were randomly assigned in a 1:1:1 ratio to one of three trial groups: a fixed-dose combination of 180 mug of albuterol and 160 mug of budesonide (with each dose consisting of two actuations of 90 mug and 80 mug, respectively [the higher-dose combination group]), a fixed-dose combination of 180 mug of albuterol and 80 mug of budesonide (with each dose consisting of two actuations of 90 mug and 40 mug, respectively [the lower-dose combination group]), or 180 mug of albuterol (with each dose consisting of two actuations of 90 mug [the albuterol-alone group]). Children 4 to 11 years of age were randomly assigned to only the lower-dose combination group or the albuterol-alone group. The primary efficacy end point was the first event of severe asthma exacerbation in a time-to-event analysis, which was performed in the intention-to-treat population.

RESULTS: A total of 3132 patients underwent randomization, among whom 97% were 12 years of age or older. The risk of severe asthma exacerbation was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P = 0.001). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P = 0.052). The incidence of adverse events was similar in the three trial groups.

CONCLUSIONS: The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 mug of albuterol and 160 mug of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies. (Funded by Avillion; MANDALA ClinicalTrials.gov number, NCT03769090.).

Albuterol-Budesonide Pressurized Metered Dose Inhaler in Patients With Mild-to-Moderate Asthma: Results of the DENALI Double-Blind Randomized Controlled Trial[57]

Background: In the phase 3 MANDALA trial, as-needed albuterol-budesonide pressurized metered-dose inhaler significantly reduced severe exacerbation risk vs as-needed albuterol in patients with moderate-to-severe asthma receiving inhaled corticosteroid-containing maintenance therapy. This study (DENALI) was conducted to address the US Food and Drug Administration combination rule, which requires a combination product to demonstrate that each component contributes to its efficacy.

Research question: Do both albuterol and budesonide contribute to the efficacy of the albuterol-budesonide combination pressurized metered-dose inhaler in patients with asthma?

Study design and methods: This phase 3 double-blind trial randomized patients aged ≥ 12 years with mild-to-moderate asthma 1:1:1:1:1 to four-times-daily albuterol-budesonide 180/160 μg or 180/80 μg, albuterol 180 μg, budesonide 160 μg, or placebo for 12 weeks. Dual-primary efficacy end points included change from baseline in FEV1 area under the curve from 0 to 6 h (FEV1 AUC0-6h) over 12 weeks (assessing albuterol effect) and trough FEV1 at week 12 (assessing budesonide effect).

Results: Of 1,001 patients randomized, 989 were ≥ 12 years old and evaluable for efficacy. Change from baseline in FEV1 AUC0-6h over 12 weeks was greater with albuterol-budesonide 180/160 μg vs budesonide 160 μg (least-squares mean [LSM] difference, 80.7 [95% CI, 28.4-132.9] mL; P = .003). Change in trough FEV1 at week 12 was greater with albuterol-budesonide 180/160 and 180/80 μg vs albuterol 180 μg (LSM difference, 132.8 [95% CI, 63.6-201.9] mL and 120.8

[95% CI, 51.5-190.1] mL, respectively; both P < .001). Day 1 time to onset and duration of bronchodilation with albuterol-budesonide were similar to those with albuterol. The albuterol-budesonide adverse event profile was similar to that of the monocomponents.
Interpretation: Both monocomponents contributed to albuterol-budesonide lung function efficacy. Albuterol-budesonide was well tolerated, even at regular, relatively high daily doses for 12 weeks, with no new safety findings, supporting its use as a novel rescue therapy.
Clinical trial registration: ClinicalTrials.gov; No.: NCT03847896

Budesonide/Formoterol MDI With Co-Suspension Delivery Technology In COPD: The TELOS Study[58]
Background: TELOS compared budesonide (BD)/formoterol fumarate dihydrate (FF) metered dose inhaler (BFF MDI), formulated using innovative co-suspension delivery technology that enables consistent aerosol performance, with its monocomponents and budesonide/formoterol fumarate dihydrate dry powder inhaler (DPI) in patients with moderate to very severe chronic obstructive pulmonary disease (COPD), without a requirement for an exacerbation history.
Study Methods: In this phase III, double-blind, parallel-group, 24-week study (NCT02766608), patients were randomised to BFF MDI 320/10 µg (n=664), BFF MDI 160/10 µg (n=649), FF MDI 10 µg (n=648), BD MDI 320 µg (n=209) or open-label budesonide/formoterol DPI 400/12 µg (n=219). Primary end-points were change from baseline in morning pre-dose trough forced expiratory volume in 1 s (FEV_1) and FEV_1 area under the curve from 0-4 h (AUC_{0-4}). Time to first and rate of moderate/severe exacerbations were assessed.
Results: BFF MDI 320/10 µg improved pre-dose trough FEV_1*versus* FF MDI (least squares mean (LSM) 39 mL; p=0.0018), and BFF MDI 320/10 µg and 160/10 µg improved FEV_1 AUC_{0-4}*versus* BD MDI (LSM 173 mL and 157 mL, respectively; both p<0.0001) at week 24. BFF MDI 320/10 µg and 160/10 µg improved time to first and rate of moderate/severe exacerbations *versus* FF MDI. Treatments were well tolerated, with pneumonia incidence ranging from 0.5-1.4%.BFF MDI improved lung function *versus* monocomponents and exacerbations *versus* FF MDI in patients with moderate to very severe COPD.

Efficacy And Safety Of Two Doses Of Budesonide/Formoterol Fumarate Metered Dose Inhaler In COPD[59]
Background: Inhaled corticosteroid/long-acting β_2-agonist combination therapy is a recommended treatment option for patients with chronic obstructive pulmonary disease (COPD) and increased exacerbation risk, particularly those with elevated blood eosinophil levels. SOPHOS (NCT02727660) evaluated the efficacy and safety of two doses of budesonide/formoterol fumarate dihydrate metered dose inhaler (BFF MDI) *versus* formoterol fumarate dihydrate (FF) MDI, each delivered using co-suspension delivery technology, in patients with moderate-to-very severe COPD and a history of exacerbations.
Study Methods: In this phase 3, randomised, double-blind, parallel-group, 12–52-week, variable length study, patients received twice-daily BFF MDI 320/10 µg or 160/10 µg, or FF MDI 10 µg. The primary endpoint was change from baseline in morning pre-dose trough forced expiratory volume in 1 s (FEV_1) at week 12. Secondary and other endpoints included assessments of moderate/severe COPD exacerbations and safety.
Results: The primary analysis (modified intent-to-treat) population included 1843 patients (BFF MDI 320/10 µg, n=619; BFF MDI 160/10 µg, n=617; and FF MDI, n=607). BFF MDI 320/10 µg and 160/10 µg improved morning pre-dose trough FEV_1 at week 12 *versus* FF MDI (least squares mean differences 34 mL [p=0.0081] and 32 mL [p=0.0134], respectively), increased time to first exacerbation (hazard ratios 0.827 [p=0.0441] and 0.803 [p=0.0198], respectively) and reduced exacerbation rate (rate ratios 0.67 [p=0.0001] and 0.71 [p=0.0010], respectively). Lung function and exacerbation benefits were driven by patients with blood eosinophil counts ≥150 cells·mm^{-3}. The incidence of adverse events was similar, and pneumonia rates were low (≤2.4%) across treatments.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1996 to October Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 25, 2023

1	Cholinergic Antagonists/ or Anti-Asthmatic Agents/ or Bronchodilator Agents/	31447
2	Ipratropium/ or Albuterol, Ipratropium Drug Combination/	912
3	Tiotropium Bromide/	1291
4	Muscarinic Antagonists/ or aclidinium.mp.	8748
5	umeclidinium.mp.	290
6	Glycopyrrolate/	844
7	Salmeterol/	1633
8	formeterol.mp.	6
9	indacterol.mp.	2
10	olodaterol.mp.	228
11	arformoterol.mp.	46
12	Budesonide, Formoterol Fumarate Drug Combination/ or Budesonide/	4464
13	Fluticasone-Salmeterol Drug Combination/ or Fluticasone/	3332
14	Beclomethasone/	1726
15	Mometasone Furoate/	878
16	flunisolide.mp. or Anti-Asthmatic Agents/	13131
17	ciclesonide.mp.	408
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	45667
19	limit 18 to (english language and humans)	33938
20	limit 19 to yr="2022 -Current"	1833
21	limit 20 to (clinical trial, all or controlled clinical trial or guideline or meta-analysis or "systematic review")	370

Appendix 4: Key Inclusion Criteria

Population	Children and Adults with Asthma; Adults with Chronic Obstructive Pulmonary Disease
Intervention	SABA, LABA, SAMA, LAMA, and ICS monotherapy or in combination
Comparator	SABA, LABA, SAMA, LAMA, and ICS monotherapy or in combination
Outcomes	Asthma and COPD exacerbations, Quality of Life, Adverse Effects
Setting	Outpatient

Inhaled Corticosteroids (ICS)

Goals:
- To optimize the safe and effective use of ICS therapy in patients with asthma and COPD.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred ICS products

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for treatment of asthma or reactive airway disease?	**Yes:** Go to #6	**No:** Go to #4

Approval Criteria		
4. Is the request for treatment of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *2/24 (DM); 10/23 (SF); 10/22 (KS), 10/20 (KS), 5/19 (KS), 1/18; 9/16; 9/15*
Implementation: *3/1/18; 10/13/16; 10/9/15*

Long-acting Beta-agonists (LABA)

Goals:
- To optimize the safe and effective use of LABA therapy in patients with asthma and COPD.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred LABA products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease?	**Yes:** Go to #5	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded
5. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *2/24 (DM); 10/23 (SF); 10/22 (KS), 10/20 (KS), 5/19 (KS); 1/18; 9/16; 9/15); 5/12; 9/09; 5/09*
Implementation: *3/1/18; 10/9/15; 8/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist (LAMA/LABA) and LAMA/LABA/Inhaled Corticosteroid (LAMA/LABA/ICS) Combinations

Goals:
- To optimize the safe and effective use of LAMA/LABA/ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage:
  - Asthma and COPD: short-acting bronchodilator and previous trial of two drug combination therapy (ICS/LABA, LABA/LAMA or ICS/LAMA). Preferred monotherapy inhaler LAMA and LABA products do NOT require prior authorization.

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred LAMA/LABA and LAMA/LABA/ICS products

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Go to #8	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Is the request for a LAMA/LABA combination product?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Go to #6
6. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is there documentation that the prescriber is willing to stop coverage of all other LAMA, LABA, and ICS inhaler combination products?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
8. Does the patient have an active prescription for an on-demand short-acting acting beta-agonist (SABA) and/or for ICS-formoterol?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the request for Trelegy Ellipta (ICS/LAMA/LABA) combination product and is there a documented trial of an ICS/LABA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers (with the exception of ICS-formoterol which may be continued)	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *2/24 (DM); 10/23 (SF); 10/22 (KS), 10/21 (SF); 12/20 (KS), 10/20, 5/19; 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *4/1/24; 1/1/21; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

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Prior Authorization Criteria Update: Oncology

Purpose of the Update:
This update identifies antineoplastic drugs recently approved by the FDA to add to the oncology policy (see **Table 1**).

Table 1. New oncology drugs

Generic Name	Brand Name
eflornithine	IWILFIN
lifileucel	AMTAGVI

Recommendation:

- Update prior authorization criteria to include new, recently approved antineoplastic drugs.

Oncology Agents

Goal(s):

- To ensure appropriate use for oncology medications based on FDA-approved and compendia-recommended (i.e., National Comprehensive Cancer Network® [NCCN]) indications.

Length of Authorization:

- Up to 1 year

Requires PA:

- Initiation of therapy for drugs listed in **Table 1** (applies to both pharmacy and physician administered claims). This does not apply to oncologic emergencies administered in an emergency department or during inpatient admission to a hospital.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #5.
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
6. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #8
8. Is there documentation based on chart notes that the patient is enrolled in a clinical trial to evaluate efficacy or safety of the requested drug?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	**No:** Go to #9
9. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria
10. All other diagnoses must be evaluated for evidence of clinical benefit. The prescriber must provide the following documentation: • medical literature or guidelines supporting use for the condition, • clinical chart notes documenting medical necessity, and • documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Table 1. Oncology agents which apply to this policy (Updated 3~~12~~/4~~29~~/2024~~3~~)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
abiraterone acetate/niraparib tosylate	AKEEGA
acalabrutinib	CALQUENCE
adagrasib	KRAZATI
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVANT
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capivasertib	TRUQAP
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI

Generic Name	Brand Name
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
eflornithine	IWILFIN
elacestrant	ORSERDU
elotuzumab	EMPLICITI
elranatamab-bcmm	ELREXFIO
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
epcoritamab-bysp	EPKINLY
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
fruquintinib	FRUZAQLA
futibatinib	LYTGOBI
gilteritinib	XOSPATA
glasdegib	DAURISMO
glofitamab-gxbm	COLUMVI
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
isatuximab	SARCLISA

Generic Name	Brand Name
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lifileucel	AMTAGVI
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
melphalan hcl/hepatic delivery kit (HDS)	HEPZATO KIT
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mobecertinib	EXKIVITY
momelotinib	OJJAARA
mosunetuzumab-axgb	LUNSUMIO
motixafortide	APHEXDA
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib and abiraterone acetate	AKEEGA
niraparib tosylate	ZEJULA
nirogacestat hydrobromide	OGSIVEO
nivolumab	OPDIVO
nivolumab; relatlimab-rmbw	OPDUALAG
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
omidubicel-onlv	OMISIRGE
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA

Generic Name	Brand Name
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
quizartinib	VANFLYTA
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
repotrectinib	AUGTYRO
retifanlimab-dlwr	ZYNYZ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
talquetamab-tgvs	TALVEY
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA

Generic Name	Brand Name
toripalimab-tpzi	LOQTORZI
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

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Prior Authorization Criteria Update: Orphan Drugs

Plain Language Summary:

- Since 2020, the Medicaid fee-for-service (FFS) program has added 24 medicines to the orphan drug policy. Medicines are designated as "orphan" when they are approved by the Food and Drug Administration (FDA) for very rare conditions. This policy requires that providers follow prescribing recommendations from the Food and Drug Administration before the Oregon Health Plan will pay for the medicine.
- Because these conditions are so rare, this policy has only been used once for the Medicaid fee-for-service (FFS) population. Thus, this policy continues to improve bandwidth for topics at the Pharmacy and Therapeutics (P&T) meetings.
- We recommend minor updates to simplify this policy.

Purpose of Update:

The purpose of this update is evaluate utilization of the orphan drug policy. Orphan drugs are defined by the FDA as drugs and biologics intended for the safe and effective treatment, diagnosis or prevention of rare diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people but are not expected to recover the costs of developing and marketing a treatment. Due to the rare incidence of these conditions, there are few FFS patients prescribed these medications, and estimated savings as a result of orphan drug policies is limited. In 2020, the Pharmacy and Therapeutics (P&T) Committee, approved implementation of prior authorization criteria for select orphan drugs to improve bandwidth for topics at P&T meetings and support medically appropriate use of these therapies based on information in the FDA label (**Appendix 1**). Since 2020, 24 orphan drugs have been added to this policy (**Table 1**). However, despite the increasing number of additions to this policy, a review of FFS claims and prior authorization requests identified only one circumstance in which this criteria was utilized reflecting the rare prevalence of these conditions. Because this criteria is utilized infrequently, we recommend simplifying criteria to reference FDA labeling instead of including information from the FDA label in the criteria. FDA labeling related to dosing, monitoring, and indication is occasionally updated after the initial approval, and including links to the FDA label will allow alignment between the policy and FDA label when changes are made.

Table 1. Unique molecular entities included in the policy by year

Year	Cumulative Number of Drugs Included on the Policy
2020	5
2021	13
2022	17
2023	24

Table 2. Recommended new orphan drugs to add to the policy

Generic Name	Brand Name
ADAMTS13, recombinant-krhn	ADZYNMA
Allogeneic processed thymus tissue-agdc	RETHYMIC
Beremagene geperpavec-svdt	VYJUVEK
Birch triterpenes	FILSUVEZ
Elivaldogene autotemcel	SKYSONA
Levoketoconazole	RECORLEV

Recommendation:

- Simplify PA criteria by linking to FDA labeling instead of including details of the labeling in the PA.
- Include new, recently approved orphan drugs in the policy.

Appendix 1. Proposed Prior Authorization Criteria

Orphan Drugs

Goal(s):

- To support medically appropriate use of orphan drugs (as designated by the FDA) which are indicated for rare conditions
- To limit off-label use of orphan drugs

Length of Authorization:

- Up to 6 months

Requires PA:

- See Table 1 (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Included orphan drugs

ADAMTS13, recombinant-krhn (ADZYNMA)
Allogeneic processed thymus tissue-agdc (RETHYMIC)
Alpelisib (VIJOICE)
Avacopan (TAVNEOS)

Belumosudil (REZUROCK)
Beremagene geperpavec-svdt (VYJUVEK)
Birch triterpenes (FILSUVEZ)
Burosumab-twza (CRYSVITA)
Cerliponase alfa (BRINEURA)
Elapegademase-lvlr (REVCOVI)
Elivaldogene autotemcel (SKYSONA)
Fosdenopterin (NULIBRY)
Givosiran (GIVLAARI)
Leniolisib (JOENJA)
Levoketoconazole (RECORLEV)
Lonafarnib (ZOKINVY)
Lumasiran (OXLUMO)
Luspatercept (REBLOZYL)
Maralixibat (LIVMARLI)
Mitapivat (PYRUKYND)
Nedosiran (RIVFLOZA)
Odevixibat (BYLVAY)
Olipudase alfa-rpcp (XENPOZYME)
Palovarotene (SOHONOS)
Plasminogen, human-tvmh (RYPLAZIM)
pozelimab-bbfg (VEOPOZ)
Sodium thiosulfate (PEDMARK)
Sutimlimab-jome (ENJAYMO)
Trientine tetrahydrochloride (CUVRIOR)
Velmanase alfa-tycv (LAMZEDE)

~~Table 1. Indications for orphan drugs based on FDA labeling~~

~~Drug~~	~~Indication~~	~~Age~~	~~Dose~~	~~Recommended Monitoring~~
~~Alpelisib (VIJOICE)~~	~~PIK3CA-Related Overgrowth Spectrum (PROS) in those who require systemic therapy~~	~~≥ 2 yrs~~	~~Pediatric 2 to <18 yrs:~~ ~~• 50 mg once daily~~ ~~• May consider increase to 125 mg once daily if ≥6 years after 24 weeks of treatment~~ ~~• May gradually increase to 250 mg once daily once patient turns 18~~ ~~Adult:~~ ~~• 250 mg once daily~~	~~Baseline Monitoring~~ ~~• Fasting BG, HbA1c~~ ~~Ongoing Monitoring~~ ~~• Fasting BG weekly x 2 weeks, then at least once every 4 weeks, then as clinically indicated~~ ~~• HbA1c every 3 months and as clinically indicated~~
~~Avacopan (TAVNEOS)~~	~~Severe active anti-neutrophil cytoplasmic autoantibody~~	~~≥18 yrs~~	~~30 mg (three 10 mg capsules) twice daily, with food~~	~~Baseline Monitoring~~

	(ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with glucocorticoids.			• Liver function tests ALT, AST, ALP, and total bilirubin • Hepatitis B (HBsAg and anti-HBc) Ongoing Monitoring • Liver function tests every 4 wks for 6 months, then as clinically indicated
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH) FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	XLH ≥ 6 mo TIO ≥ 2 yrs	Pediatric <18 yrs: Initial (administered SC every 2 wks): XLH • <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 mg for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max dose 2 mg/kg or 180mg every 2 wks)	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated • Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only: • Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels • Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Belumosudil (REZUROCK)	Treatment of chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy	≥ 12 yrs	200 mg orally once daily with food 200 mg twice daily when coadministered with strong CYP3A inducers or proton pump inhibitors	Baseline & Ongoing Monitoring • Total bilirubin, AST, ALT at least monthly • Pregnancy test (if childbearing potential)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 yrs	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history

Elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2 mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 wks) Initial: 0.4mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 wks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥1 yr: 0.9 mg/kg	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 yrs	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests • Blood homocysteine levels-If homocysteine elevated, assess folate, vitamin B12, and vitamin B6
Leniolisib (JOENJA)	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)	≥ 12 years AND ≥ 45kg	70 mg administered orally twice daily approximately 12 hours apart	Baseline and ongoing monitoring • Pregnancy test (if childbearing potential)
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 mo AND ≥0.39 m^2 BSA	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower	N/A	**<10 kg**	N/A

	urinary and plasma oxalate levels		Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months **≥ 20 kg** Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 yr	Initial: 1 mg/kg SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 3 mo	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 380 mcg/kg once daily after 1 week on initial dose, as tolerated	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Mitapivat (PYRUKYND)	Hemolytic anemia in adults with pyruvate kinase (PK) deficiency.	≥ 18 yr	Initial: 5 mg twice daily Titration: If Hb less than normal range or patient required	Baseline/Ongoing Monitoring • Hgb, transfusion requirement

			transfusion in previous 8 weeks, then after 4 weeks increase to 20 mg twice daily, and after another 4 weeks increase to 50 mg twice daily. Max dose: 50 mg twice daily Discontinuation should include down-titration.	
Nedosiran RIVFLOZA	Lower urinary oxalate levels in those with primary hyperoxaluria type 1 (PH1) and relatively preserved renal function, e.g., eGFR ≥ 30 mL/min/1.73 m^2	≥ 9 yr	Weight ≥ 50 kg: 160 mg once monthly Weight <50 kg and age ≥12 yr: 128 mg once monthly Weight <50 kg and age 9 to 11 yr: 3.3 mg/kg once monthly; max 128 mg.	Baseline/Ongoing Monitoring • eGFR
Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP 3)	≥ 3 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments Max dose: 120 mcg/kg once daily; not to exceed 6 mg	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Olipudase alfa-rpcp (XENPOZYME)	Non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD)	N/A	Initial: Age based dose escalation table per Package insert Maintenance: 3 mg/kg via IV infusion every 2 weeks Weight: • If BMI ≤ 30, use actual body weight • If BMI > 30, use adjusted body weight Adjusted body weight (kg) = (actual height in $M)^2$ x 30	Baseline Monitoring • Liver function tests (ALT, AST) within 1 month • Pregnancy test (if childbearing potential) Ongoing Monitoring • Liver function tests (ALT, AST) within 72 hours of infusions during dose escalation, then during routine clinical management once at maintenance dose
Palovarotene, (SOHONOS)	Fibrodysplasia ossificans progressive (FOP)	≥ 8 yr females	≥ 14 years: Daily: 5 mg	Baseline Monitoring • Pregnancy test (if childbearing potential)

		≥ 10 yr males	Flare wk 1-4: 20 mg once daily Flare wk 5-12: 10 mg once daily <14 years weight based: Daily 10-19.9 kg: 2.5 mg 20-39.9 kg: 3 mg 40-59.9 kg: 4 mg ≥ 60 kg: 5 mg Flare week 1-4 (daily dose) 10-19.9 kg: 10 mg 20-39.9 kg: 12.5 mg 40-59.9 kg: 15 mg ≥ 60 kg: 20 mg Flare week 5-12 (daily dose) 10-19.9 kg: 5 mg 20-39.9 kg: 6 mg 40-59.9 kg: 7.5 mg ≥ 60 kg: 10 mg Week 5-12 flare dosing may be extended in 4-week intervals and continued until symptoms resolve. If marked worsening of original symptoms or another flare occurs during flare-up treatment, may restart 12 week flare-up dosing. (all ages)	• Assessment of skeletal maturity in growing pediatric patients: hand/wrist & knee x-ray, standard growth curves, pubertal staging. • Psychiatric symptoms or signs of depression Ongoing Monitoring • Pregnancy test (if childbearing potential) • Assessment of skeletal maturity in growing pediatric patients every 6-12 months until skeletal maturity or final adult height. • Spine assessment for bone density • New or worsening psychiatric symptoms or signs of depression
Plasminogen, human-tvmh (RYPLAZIM)	Treatment of patients with plasminogen deficiency type 1 (hypoplasmino-genemia)	N/A	6.6 mg/kg body weight given IV every 2 to 4 days	Baseline Monitoring • Plasminogen activity level (allow 7 day washout if receiving with fresh frozen plasma) • CBC (bleeding) Ongoing Monitoring • Trough Plasminogen activity level 72 hours after initial dose and every 12 wks with ongoing therapy • CBC (bleeding)
pozelimab-bbfg (VEOPOZ)	CD55-deficient protein-losing enteropathy (PLE or CHAPLE disease)	≥ 1 yr	Day 1 loading dose: 30 mg/kg single IV infusion Day 8 and after maintenance dose): 10 mg/kg SC weekly	Baseline Monitoring • Meningococcal vaccination at least 2 wk prior to first drug dose unless risks of delayed therapy outweigh risk of meningococcal infection. Ongoing Monitoring • Signs of meningococcal infection

			May increase to 12 mg/kg if inadequate response after at least 3 weekly doses Max maintenance dose: 800 mg once weekly	
Sodium thiosulfate (PEDMARK)	Decrease ototoxicity associated with cisplatin infusions lasting ≤ 6 hours. Not approved for use with longer infusions.	≥ 1 mo to ≤18 yr	< 5 kg: 10 g/m^2 5-10 kg: 15 g/m^2 >10 kg: 20 g/m^2	Baseline Monitoring • Serum potassium and sodium
Sutimlimab-jome (ENJAYMO)	Decrease need for RBC transfusion due to hemolysis in cold agglutinin disease (CAD)	≥ 18 yr	Dosed IV infusion weekly for two weeks, then every two weeks thereafter. **39 to <75 kg:** 6500 mg **≥75 kg:** 7500 mg	Baseline Monitoring • Vaccination against encapsulated bacteria (*Neisseria meningitidides* (any serogroup), *Streptococcus pneumonia*, and *Haemophilus influenza*) at least prior to treatment or as soon as possible if urgent therapy needed
Trientine tetrahydrochloride (CUVRIOR)	Stable Wilson's disease who are de-coppered and tolerant to penicillamine	≥ 18 yr	Total daily dose in transition from penicillamine per table in package insert.	Baseline/Ongoing Monitoring • Serum NCC levels at baseline, 3 months, then roughly every 6 months serum levels or 6 to 12 months with urinary copper excretion
Velmanase alfa-tycv (LAMZEDE)	Treatment of non-central nervous system manifestations of alpha-mannosidosis	N/A	1 mg/kg (actual body weight) once weekly by IV infusion	Baseline and ongoing monitoring • Pregnancy test (if childbearing potential)
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase, AST = aspartate aminotransferase; BG = blood glucose; BSA = body surface area; CBC = complete blood count; CrCL = creatinine clearance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycalated hemoglobin; Hgb = hemoglobin; INR = international normalized ratio; IV = intravenous; mo = months; NCC = non-ceruloplasmin copper; RBC = red blood cells; SC = subcutaneously; wks = weeks; yrs = years				

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3

Approval Criteria		
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in ~~**Table 1**~~the FDA label (see links in **Table 1)**? Note: This includes all information required in the FDA-approved indication, including but not limited to, the following as applicable: diagnosis, disease severity, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended baseline and ongoing monitoring parameters described in the FDA label?* *FDA pages for drugs and biologics: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	**Yes:** Approve for up to 6 months Document benefit	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	**Yes**: Approve for up to 6 months Document benefit and provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/23; 10/23; 6/23; 2/23; 12/22; 6/22; 4/22; 12/21; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: 1/1/24; 11/1/23; 7/1/23; 4/1/23; 1/1/23; 7/1/22; 5/1/22; 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20

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Prior Authorization Criteria Update: Teprotumumab-trbw (Tepezza®)

Purpose of Update:
Evaluate the evidence for efficacy and safety of teprotumumab since the previous Pharmacy and Therapeutics (P & T) committee review in December 2020 and to align prior authorization criteria with an expansion of the Food and Drug Administration (FDA) approved indication.

Plain Language Summary:

- Thyroid eye disease, sometime also called Graves' Orbitopathy, is a disease that can result in sore, gritty, or red eyes, double vision, reduced sight, and blindness. Thyroid eye disease can range from mild, moderate, severe, or sight threatening. Thyroid eye disease is also either "active" where symptoms usually get worse, or "inactive", where symptoms stay stable but may still be severe.
- Teprotumumab is a medicine that has been approved to treat active thyroid eye disease for several years. In 2023, the Food and Drug Administration approved teprotumumab to also be used in inactive thyroid eye disease.
- When studied in patients with inactive thyroid eye disease, teprotumumab reduced eye bulging more than placebo (a look-alike that has no active medicine). Treating three patients with teprotumumab could reduce eye bulging by at least 2 mm for one patient. A change of 2 mm is likely enough to improve the quality of life for a person with thyroid eye disease.
- Mild muscle spasms occur more often in patients taking teprotumumab than placebo. High blood sugar and hearing impairment have also occurred in patients taking teprotumumab. Hearing impairment is sometimes permanent.
- Guidelines recommend using a medicine called glucocorticoids, or "steroids", first for most patients who have moderate to severe, active thyroid disease before teprotumumab.
- For people with fee-for-service Medicaid, the Oregon Health Plan will currently pay for teprotumumab for people with active thyroid eye disease. DURM recommends updating this policy to include patients with inactive thyroid eye disease.

Conclusions:

- Two clinical trials[1,2], one high quality guideline[3], one label expansion[4,5], and 2 Food and Drug Administration (FDA) safety labeling edits[6] have been published since teprotumumab was last reviewed.
- Teprotumumab was compared to placebo in a single, double-blind, randomized controlled trial (RCT) in patients with inactive thyroid eye disease (TED). Teprotumumab reduced proptosis more than placebo from baseline to week 24 (teprotumumab -2.41 mm vs. placebo -0.92; difference -1.48 mm; 95% confidence interval [CI] -2.28 to -0.69; P=0.0004, low quality evidence). Proptosis response (≥2 mm reduction from baseline) was achieved in 61.9% of teprotumumab patients compared to 25.0% of placebo patients (absolute risk reduction [ARR] 36.9%; 95% CI 5.4 to 59.2%; P=0.0134, number needed to treat [NNT] 3, low quality evidence).[1]

- Muscle spasms occurred in 41.5% of teprotumumab patients versus 10% of placebo patients. Hearing impairment occurred in more teprotumumab patients (22%) compared to placebo (10%).[1] One teprotumumab patient experienced hearing loss and discontinued treatment.[1] Hyperglycemia occurred in 14.6% teprotumumab treated patients and 10% of placebo patients, however 1 of the 2 placebo categorized patients experienced diabetic ketoacidosis after receiving teprotumumab in error.[1]
- The FDA has strengthened the package labeling for hyperglycemia and added a new subsection for severe hearing loss, sometimes permanent, to warnings and precautions of the medication package insert.[6]
- A consensus statement American Thyroid Association (ATA) and European Thyroid Association (ETA) recommended intravenous glucocorticoids (IVGC) as first-line therapy for active, moderate-to-severe TED when disease activity is the prominent feature in the absence of either significant proptosis or diplopia.[3] Teprotumumab is a preferred therapy, if available, in patients with active moderate-to-severe TED with significant proptosis and/or diplopia.[3]
- Data on retreatment with teprotumumab in patients who have not had an adequate response after initial therapy, or have a disease flare after treatment, is insufficient.[2]

Recommendation:

- Update prior authorization (PA) criteria as amended in **Appendix 1**.

Background and Current Policy:

Teprotumumab was reviewed by the P & T committee in December 2020 for the treatment of active TED (also referred to as Graves' Orbitopathy [GO]) where it was designated as non-preferred with specific PA criteria on the Preferred Drug List (PDL) to ensure safe and appropriate use. Detailed background information related to the acute and chronic phases of this disease and various measurement scales are included in that document.[7]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted during the search period of 7/29/2020 to 1/16/24. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 6 systematic reviews[8-13] were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

The American Thyroid Association (ATA) and European Thyroid Association (ETA) jointly published a consensus statement on the Management of TED in 2022.[3] The consensus statement scope was to address clinical assessment and develop criteria for referral to specialty care and treatment, as well as to focus on medical and surgical treatment in nonpregnant adults (18 years and older) with TED. The primary audience for the guideline was endocrinologists. Two patient-led organizations were invited to review the draft and feedback was also received from the American Academy of Ophthalmology and the American Society of Ophthalmic Plastic and Reconstructive Surgery.[3]

Recommendations were presented as "Key Points" and therapies were prioritized as (1) preferable, (2) acceptable, or (3) may be considered. Preferred therapies are supported by evidence from 2 or more RCTs that have shown efficacy against standard of care or placebo with concordant results. Acceptable therapies were defined as at least 2 RCTS with discordant results where the discordance is likely the results of different inclusion criteria or based on a single RCT showing efficacy.[3] Therapies were categorized as "may be considered" when benefit is not clear, and are typically used in clinical practice when preferred and acceptable therapies are unavailable, contraindicated, or not tolerated.

Proptosis was discussed in the consensus statement recommendations as a disease manifestation of TED which might affect preference for one treatment modality over another. "Significant proptosis" is usually defined in the literature as ≥3 mm above the upper limit for race and sex. The authors felt patients with moderate-to severe TED and a degree of proptosis of <3 mm above the upper limit for race and sex could also be defined as "significant proptosis" if it sufficiently impacted daily life and would justify the risks of treatment, in addition to using the standard numeric threshold.[3]

Key points delineating place in therapy for teprotumumab relative to other pharmacotherapy or surgical options are included below.

- Key Point 6.1.1: A single course of selenium selenite 100 µg twice daily for 6 months may be considered for patients with mild, active TED, particularly in regions of selenium insufficiency.[3]
- Key Point 7.1.1.1: Intravenous glucocorticoid (IVGC) therapy is a preferred treatment for active moderate-to-severe TED when disease activity is the prominent feature in the absence of either significant proptosis or diplopia.[3]
- Key Point 7.1.1.2: Standard dosing with IVGC consists of IV methylprednisolone (IVMP) at cumulative doses of 4.5 g over ~3 months (0.5 g weekly × 6 weeks followed by 0.25 g weekly for an additional 6 weeks).[3]
- Key Point 7.1.1.3: Poor response to IVMP at 6 weeks should prompt consideration for treatment withdrawal and evaluation of other therapies. Clinicians should be alert for worsening diplopia or onset of dysthyroid optic neuropathy that have occurred even while on IVMP therapy.[3]
- Key Point 7.1.2.1: Rituximab and tocilizumab may be considered for TED inactivation in GC-resistant patients with active moderate-to-severe TED. Teprotumumab has not been evaluated in this setting.[3]
- Key Point 7.1.3.1: Teprotumumab is a preferred therapy, if available, in patients with active moderate-to-severe TED with significant proptosis and/or diplopia.[3]
- Key Point 7.1.4.1: Evidence from RCTs is limited and divergent but suggests efficacy of rituximab for inactivation of TED and prevention of relapses at >1 year, particularly in patients with TED of <9 months duration.[3]
- Key Point 7.1.4.2: Rituximab therapy is acceptable in patients with active moderate-to-severe TED and prominent soft tissue involvement.[3]
- Key Point 7.1.6.1: Tocilizumab is an acceptable treatment for TED inactivation in GC-resistant patients with active moderate-to-severe disease.[3]

- Key Point 8.1.1: Patients with dysthyroid optic neuropathy require urgent treatment with IVGC therapy, with close monitoring of response and early (after 2 weeks) consideration for decompression surgery if baseline visual function is not restored and maintained with medical therapy.[3]

Additionally, clinical comorbidities should be considered and may affect treatment preference. In patients with a chronic infection, teprotumumab is rated as a "favored choice" or "may be favored choice" along with radiotherapy (rated "may be favored choice"). In patients with liver disease, teprotumumab is a "favored choice" or "may be favored choice" along with radiotherapy or rituximab (both rated "may be favored choice").[3]

Additional Guidelines for Clinical Context:
The European Group on Graves' Orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy were updated in 2021.[14] The methods relating to PubMed search strategies are not well described and several members of this *ad hoc* task force had significant conflicts of interest. This guideline will be presented for clinical context only.

Mild GO should be treated with local treatments and general measures to control risk factors and a 6-month selenium supplementation should be given to patients with mild and active GO of recent onset (moderate quality evidence).[14] If the impact on quality of life outweighs risks, then low-dose immunomodulatory therapy (in active GO) or rehabilitative surgery (in inactive GO) is proposed after to extensive counseling and shared decision making (low quality evidence).[14]

An intermediate dose of IVGC should be used in most cases of moderate-to-severe and active GO (high quality evidence), and high dose IVGC should be reserved for more severe cases (constant/inconstant diplopia, severe proptosis, severe soft-tissue pathology or involvement) (moderate quality evidence).[14] The cumulative dose of IVGC should not exceed 8.0 g each cycle, and patients with certain comorbidities including recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, uncontrolled hypertension, and uncontrolled diabetes mellitus should not receive IVGC (moderate quality evidence).[14] Teprotumumab is listed as a "very promising drug with strong reduction of exophthalmos, diplopia, and improvement of quality of life. Currently, [teprotumumab is a] second-line option as longer-term data, availability, affordability, costs, and need for subsequent rehabilitative surgery are pending" (moderate quality evidence).[14]

The first-line treatment recommendation for moderate to severe and active GO are IVMP in combination with mycophenolate sodium (or mofetil) based on moderate quality evidence.[14] In moderate-to-severe disease that is on the more severe end of the severity range and active GO, such as patients with constant/inconstant diplopia, severe inflammatory signs, and exophthalmos > 25 mm, high dose IVMP monotherapy is recommended as an additional first-line treatment (moderate quality evidence).[14]

Second-line treatments should be considered when response to primary treatment is poor and GO is still moderate-to-severe and active. Options include a second course of IVMP, oral prednisone/prednisolone combined with cyclosporine or azathioprine, orbital radiotherapy combined with oral or IVGC, teprotumumab, rituximab, or tocilizumab (moderate quality evidence).[14]

New FDA Approvals:
In April 2023 the Food and Drug Administration (FDA) expanded the approved indication for teprotumumab from treatment of thyroid eye disease (TED) to treatment of TED *regardless of activity or duration*.[4,5] Additional important safety edits to the package insert have been made since the initial approval (**Table 1**).

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[6]

Month / Year of Change	**Location of Change (Boxed Warning, Warnings, CI)**	**Addition or Change and Mitigation Principles** (updated underlined)
December 2022	Warning and Precautions	• Updates to "Hyperglycemia" subsection • Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or pre- existing diabetes are under appropriate glycemic control before and while receiving TEPEZZA.
July 2023	Warnings and Precautions	• New "Hearing Impairment Including Hearing Loss" subsection • May cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

Randomized controlled trials:
Evidence previously reviewed by the Pharmacy and Therapeutics Committee for teprotumumab included patients with acute TED with a duration of ≤ 9 months and Clinical Activity Score (CAS) of ≥4.

New evidence in this update includes patients with chronic or low disease activity TED in a double-masked, placebo-controlled, randomized, phase 4 trial.[1] Adult patients who had TED with a duration of 2 to 10 years and a CAS of 0 or 1, indicative of inactive disease, were eligible to participate.[1] Additional inclusion and exclusion criteria are in **Table 3**. Patient were randomized 2:1 for 8 doses given once every 3 weeks of teprotumumab (n= 42) or placebo (n=20).[1] Mean age was 48.7 years (standard deviation [SD] 14.9 years).[1] Baseline characteristics were similar with a few exceptions. Fewer female patients were assigned to the teprotumumab group (76.2%) than placebo (90.0%), more Asian participants were assigned to teprotumumab (16.7%) than placebo (5.0%), and slightly more patients randomized to teprotumumab (33.3%) had diplopia (intermittent, inconstant, or constant) than placebo (20.0%).[1] Historical use of other therapeutic modalities for TED were not reported.[1] The primary endpoint of reduction in proptosis in study eye from baseline to week 24 was higher for teprotumumab than placebo (teprotumumab -2.41 mm vs. placebo -0.92 mm, difference -1.48 mm; 95% CI -2.28 to -0.69, p=0.0004).[1] Additionally, more patients receiving teprotumumab were proptosis responders (at least 2 mm improvement in proptosis from baseline) than placebo (teprotumumab 61.9% mm vs. placebo 25.0%, difference 36.9% mm; 95% CI 5.4 to 59.2%, P=0.0134, number needed to treat [NNT] 3).[1] Improvements in the Graves' Ophthalmopathy Quality of Life (GO-QOL) visual function subscale were statistically significant in favor of teprotumumab (LSM difference 6.31, 95% CI 0.57 to 12.06, p=0.0318), but not for the GO-QOL appearance related subscale (LSM difference 2.85, 95% CI -9.62 to 15.32, p=0.649).[1] A minimum change of 6 points on either subscale is generally considered to be meaningful.[15]

Adverse events of special interest (AESI) included infusion reactions, hyperglycemia, hearing impairment, new onset inflammatory bowel disease (IBD) and exacerbation of IBD. No patients developed new onset or exacerbation of IBD; other results are presented in **Table 3**.[1] Muscle spasms were the most frequently reported adverse event, generally of the lower extremities and all were mild.[1] The most common AEs are summarized in **Table 2**. Two patients discontinued due to serious adverse events related to conductive deafness in a teprotumumab patient with a congenital abnormality and diabetic ketoacidosis in a placebo

categorized patient who received teprotumumab in error for the first treatment dose and was reported to have had undiagnosed diabetes mellitus and uncontrolled glucose levels. Trial methods specify exclusion for Hemoglobin A1C of more than 8% at enrollment.[1] Nine patients receiving teprotumumab reported hearing impairment and 3 of 9 were reporting improvement or recovery at the time of data collection.[1]

Table 2. Common adverse events[1]

Adverse Event	Teprotumumab	Placebo
Muscle Spasm	41.5%	10%
Fatigue	22.0%	10.0%
Headache	17.1%	10.0%
Dry skin	12.2%	0%
Eye pain	12.2%	5%
Eye pruritus	7.3%	0%
Hemoglobin A1C increase	7.3%	0%
Hypertension	7.3%	0%

The OPTIC-X study is an open-label, single-arm, extension study of OPTIC (which evaluated patients with acute TED) and was published in 2021.[2] Given the open-label trial design and high risk of bias with lack of placebo group this study will not be reviewed extensively. However, minimal information is available regarding durability of response and retreatment with teprotumumab. Non-responders in the original study were eligible for re-treatment (teprotumumab group) or first treatment (placebo group) at the end of the OPTIC protocol.[2] Patients who initially had responded during OPTIC (proptosis reduction of at least 2 mm from baseline) who experienced a disease flare were also eligible for treatment/re-treatment.[2] Flare was defined as increase in proptosis of 2 mm or more in the study eye and/or increase in CAS score of at least 2 points with total of 4 points or more.[2] This trial was conducted during the COVID-19 pandemic, and patients who were not present for the 24-week assessment were not included in the 24-week analysis for categorical variables.[2] The number of visits missed due to COVID-19 was not reported. There was an active treatment period of 24 weeks in OPTIC-X, followed by at 24-week follow-up period.

In the OPTIC trial, 39 of 41 patients randomized to teprotumumab completed the treatment period, and 5 of those were non-responders.[2] During OPTIC-X, 2 of those 5 patients who began retreatment discontinued early (1 lack of efficacy, 1 intracerebral hemorrhage), 2 patients had a proptosis reduction of 2 mm or more from the OPTIC-X baseline (in addition to the 1-1.5 mm reductions from the OPTIC baseline to start of OPTIC-X), and 1 patient had a 0.5 mm proptosis reduction from the OPTIC-X baseline.[2]

Thirty-three of the 34 teprotumumab responders from OPTIC continued in OPTIC-X, plus one patient who did not complete the double-blind treatment period of OPTIC. A disease flare was experienced by 10/34 of those patients (29.4%), 7 of them by week 48.[2] One of the 10 patients was ineligible for retreatment due to dysthyroid optic neuropathy and the remaining 9 were retreated in OPTIC-X . One of those was excluded from week 24 summaries due to missing that appointment secondary to COVID-19.[2] Proptosis response was achieved in 5 of 8 patients who were retreated after flare and had a week 24 assessment.[2]

In patients receiving retreatment with teprotumumab, one serious adverse event (cerebral hemorrhage) was reported.[2] It is unclear if this was related to the study medication as the patient had other risk factors for hemorrhage. No other serious adverse events or drug discontinuations due to adverse events were

reported.[2] Muscle spasm (28.6%), arthralgia (14.3%), back pain (14.3%), alopecia (14.3%), dry skin (14.3%), nasal dryness (14.3%), hearing impairment (14.3%), diarrhea (7.1%), and potential infusion-related reaction (7.1%) were reported.[2] No patients reported hyperglycemia during retreatment.[2]

A total of 3 citations[16-18] were manually reviewed from the initial literature search and were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Table 3. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Douglas, et al.[1] DB, PC, RCT	1. Teprotumumab 10 mg/kg first infusion then 20 mg/kg every 3 wk x 7 infusions 2. Placebo every 3 weeks x 8 infusion 2:1 randomization	Demographics: - Mean age 48.7 y (SD 14.9) - Female 1. 76.2% 2. 90.0% - Ethnicity -White 54.8% -Black 24.2% -Asian 1. 16.7% 2. 5.0% - Mean time since dx: 5.1-5.4 y - Current tobacco use: 12.9% - Mean proptosis study eye: 24.0-24.6 mm - Patients with diplopia 1. 14 (33.3%) 2. 4 (20.0%) - Mean CAS study eye: 0.3-0.5 - Mean GO-QOL visual functioning subscore 1. 86.4 2. 81.4 - Mean GO-QOL appearance subscore 1. 46.4 2. 40.0 Key Inclusion Criteria: - Age ≥ 18 years - TED duration 2 to <10 y - Stable/inactive disease defined as: CAS ≤ 1 in both eyes for at least 1 year OR no proptosis	ITT: 1. 42 2. 20 Attrition: 1. 3 (7%)* 2. 1 (5%) (d/c AE) *1 randomized, with d/c before drug receipt, 2 lost to follow-up	Primary Endpoint: Change in proptosis in study eye from baseline to Week 24; LSM (SE) 1. -2.41 (0.23) mm 2. -0.92 (0.32) mm Difference -1.48 mm 95% CI -2.28 to -0.69 P=0.0004 Secondary Endpoint: Proptosis responders (≥ 2mm reduction from baseline in proptosis in study eye) 1. 26/42 (61.9%) 2. 5/20 (25.0%) Difference 36.9% 95% CI 5.4 to 59.2% P =0.0134 Change from baseline in GO-QOL Visual Function Subscale LSM (SE) 1. 8.73 (1.661) 2. 2.41 (2.329) Difference 6.31 95% CI 0.57 to 12.06 P=0.0318	NA ARR 36.9%/ NNT 3 NA	Any AE 1. 33/42 (80.5%) 2. 16/20 (80%) Muscle Spasms 1. 17 (41.5%) 2. 2 (10%) Serious AE 1. 1 (2.5%) - conductive deafness 2. 1 (5%) – DKA† D/c due to AE 1. 1 (2.5%) - hearing loss 2. 1 (5%) - infusion related AESI Hearing Impairment 1. 9 (22%) 2. 2 (10%) Hyperglycemia 1. 6 (14.6%) 2. 2 (10%)† Infusion-related reactions 1. 2 (4.9%) 2. 3 (15%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization 2:1 without stratification by contract research organization using electronic data capture system. Some imbalances in baseline characteristics, and it is unclear if these differences would impact results. Performance Bias: (Unclear) Patients, investigators, trial site personnel (except pharmacists compounding trial medication) and data assessors blinded until study end. Method not described. Certain side effects more common with active drug (i.e., Muscle spasms). At least one placebo patient received active drug in error. Detection Bias: (Low) Patients, investigators, trial site personnel (except pharmacists compounding trial medication) and data assessors blinded until study end. Method not described. Primary endpoint was an objective measurement. Attrition Bias: (Low) Overall attrition was low. Missing data not imputed unless methods for handling missing data are specified per the report. Patients missing week 24 data for categorical endpoints were considered non-responders. Reporting Bias: (Low) Major endpoints reported. Protocol not found. Other Bias: (Unclear) Study sponsor was drug manufacturer and had roll in designing, collecting data, and writing the final report. **Applicability**:

		progression, no diplopia progression, & no new inflammatory TED symptoms - ≥ 3 mm increase in proptosis from before dx of TED and/or proptosis ≥ 3mm above normal for race & sex -Euthyroid (mild excursions allowed) Key Exclusion Criteria: -h/o strabismus surgery or orbital decompression -↓ visual acuity due to optic neuropathy or visual field/color defect 2° to optic nerve involvement in ≤ 6 mo - Other tx: GC use within 3 wks, rituximab within 12 mo, tocilizumab with 6 mo, non-steroid immunosuppressive within 3 mo, any monoclonal antibody within 3 mo, any h/o teprotumumab. - Pregnancy - HbA1C > 8% - h/o IBD, UC, active Crohn's disease or remission < 3 months or bowel surgery in ≤ 6 months from screening		Change from baseline in GO-QOL Appearance Subscale LSM (SE) 1. 10.03 (3.592) 2. 7.19 (5.069) Difference 2.85 95% CI -9.62 to 15.32 P=0.649	NS	†DKA experienced by undiagnosed DM patient in placebo group who received teprotumumab in error		Patient: More female than male participants is reflective of the underlying disease. Relatively good inclusion of diverse racial demographics. Population comorbidity exclusions should be noted when selecting specific TED therapies. Historical treatment experience not reported. Intervention: Dosing appropriate based on past studies and FDA label. Comparator: Placebo appropriate to establish efficacy for non-acute use. However, comparison to other therapies would be useful. Outcomes: Similar outcomes in previous trials for this medication. Proptosis response of ≥ 2 mm is expected to be clinically meaningful as it can reduce diplopia and improve corneal lid coverage.[19] Setting: 11 US centers

Abbreviations: AE = adverse event; AESI = adverse events of special interest; ARR = absolute risk reduction; CAS = clinical activity score; CI = confidence interval; CV = cardiovascular event; DB = double blind; d/c = discontinue; DKA = diabetic ketoacidosis; DM = diabetes mellitus; dx = diagnosis; dx = diagnosis; FDA = Food and Drug Administration; GC = glucocorticoid; GO-QOL = Graves' Ophthalmopathy Quality of Life; HbA1C = hemoglobin A1C; h/o = history of; HR = hazard ratio; HTN = hypertension; IBD = irritable bowel disease; ITT = intention to treat; LSM = least squares mean; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; OR = orbital radiation; PC = placebo controlled; pt = patient; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TED = thyroid eye disease, tx = treatments; UC = ulcerative colitis; w/d = withdrew; wks = weeks; y = years.

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Teprotumumab

Goal(s):

- To ensure appropriate use of teprotumumab in patients with Thyroid Eye Disease (TED)

Length of Authorization:

- 8 total lifetime doses (approve for 9 months)

Requires PA:

- Teprotumumab (pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the patient an adult (18 years or older)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being ordered by, or in consultation with, an ophthalmologist or specialized ophthalmologist (e.g. neuro-ophthalmologist or ocular facial plastic surgeon)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have **moderate**, **severe**, or **sight-threatening** TED? • Defined by the Graves' Orbitopathy Severity Assessment. Possible severity ratings are mild, moderate, severe, and sight-threatening.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4.5. Does the patient have **active** TED? • Defined as Clinical Activity Score (CAS) of 4 or higher on 7 point scale within past 3 months.	**Yes:** Go to #6 CAS score:_____ Score date:_____	**No:** ~~Pass to RPh. Deny; medical appropriateness~~ Go to # 8
~~5.6. Is the patient currently euthyroid (thyroid hormone levels no more than 50% above or below of normal range) within past 3 months?~~	~~**Yes:** Go to #7~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
6. Does the patient have any of the following: • active viral hepatitis, chronic liver disease, or a significant chronic infection or • a contraindication or severe side effect* to intermediate or high dose* corticosteroids or • failed to respond to 6 weeks of low-dose corticosteroid prophylaxis after radioactive iodine treatment or • failed to respond/relapsed after at least 3 weeks of intermediate or high dose* (IV or oral) corticosteroids *Note: • Teprotumumab is associated with hyperglycemia which may necessitate diabetic medication changes and may not be an appropriate alternative when avoiding steroids in patients with uncontrolled diabetes mellitus. • Steroid regimens may vary. Example intermediate steroid regimen: 0.5 g/week for 6 weeks then 0.25 g/week for additional 6 weeks for cumulative dose 4.5 g IV methylprednisolone over ~ 3 months. Example high-dose steroid regimen: IV methylprednisolone 0.75 g/week for 6 weeks then 0.5 g/week for 6 weeks.	**Yes:** Go to #9	**No:** ~~Pass to RPh. Deny; medical appropriateness~~ Go to #7

Approval Criteria		
7. Dose the patient have documentation of diplopia or significant proptosis*? *Note: significant proptosis is defined as ≥ 3 mm above the upper limit for race and sex or < 3 mm but of sufficient severity to impact daily quality of life.	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~8. Does the patient have **inactive** TED?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
~~7.~~9. Is the patient of childbearing potential? Not considered of childbearing potential any of the following: • Onset of menopause >2 years before current date or • Non-therapy-induced amenorrhea >12 months before current date or • Surgically sterile (absence of ovaries and/or uterus, or tubal ligation) or • Not sexually active	**Yes:** Go to #10	**No:** Go to #12
~~8.~~10. Is there documentation of negative pregnancy test within past 4 weeks?	**Yes:** Go to #11 Type of test (urine or serum): _____ Date of test:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~9.~~11. ~~Has~~ Has the provider attested that the patient has been counselled on risk of fetal harm AND agreed to use at least one reliable form of contraceptive for entire duration of drug therapy and for 180 days (6 months) after final dose? • Reliable forms of birth control have less than 1% failure rate/year with consistent and correct use • Examples include: implants, injectables, combined oral/intravaginal/transdermal contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner • Hormonal methods should be started at least one full menstrual cycle prior to initiation of teprotumumab.	**Yes:** Go to #12 ~~Date of Counselling: _____~~ Contraceptive method:_____	**No:** Pass to RPh. Deny; medical appropriateness
12. Is there documentation that there has been a risk/benefit discussion with the patient related to risk of potentially permanent hearing impairment with teprotumumab AND documentation of a plan to assess/monitor hearing before, during, and after treatment?~~.~~	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
~~10.~~13. Has the patient previously received any doses of teprotumumab?	**Yes:** Approve balance to allow 8 total lifetime doses† (8 doses – previous # doses = current approval #) Previous number of doses_____	**No:** Approve 8 doses†

† All approvals will be referred for and offered optional case management

P&T/DUR Review : 4/24 (SF); 12/20 (SF)
Implementation: TBD; 1/1/2021

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Drug Class Literature Scan: GLP-1 Receptor Agonists and Dual GLP-1/GIP Receptor Agonists

Date of Review: April 2024

Date of Last Review: October 2022
Literature Search: 08/01/22 – 02/01/24

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- The purpose of this review is to look at new research for medicines called glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dual GLP-1 RA/glucose-dependent insulinotropic polypeptides (GIP) agonists.
- There are 4 GLP-1 RAs that are available: dulaglutide, exenatide, liraglutide, and semaglutide.
- There is one FDA approved GLP-1/GIP agonist available: tirzepatide.
- These medicines lower blood sugars in people with type 2 diabetes (T2DM). Most of these medicines are injections. One of the medicines, semaglutide, can be taken by mouth or injected.
- These medicines have been shown to cause stomach upset, including nausea, vomiting and diarrhea.
- This review found that liraglutide, when added with metformin, can further lower blood sugars in children with diabetes.
- Either dulaglutide or liraglutide are recommended in children 10 years of age and older who have T2DM.
- Any of these medicines are recommended to further lower blood sugars in people with T2DM who have tried other medicines to lower blood sugars and still need additional sugar lowering. Many of them are very helpful in people with diabetes who also have heart disease or kidney disease, or if weight loss is desired.

Conclusions:

- One new high-quality systematic review, 5 high-quality clinical practice guidelines, one expanded Food and Drug Administration (FDA) indication, one updated FDA safety warning and 2 new randomized controlled trials (RCTs) were identified in this literature scan.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) evaluated the evidence for the use of liraglutide in youth (ages 10-17 years) for the treatment of type 2 diabetes mellitus (T2DM).[1] Liraglutide demonstrated more hemoglobin (HbA1c) lowering than placebo in children. The estimated treatment difference (ETD) was -0.9% to -1.06% in trials lasting 5 to 26 weeks. Adverse events (AE) were similar to trials of liraglutide in adults with gastrointestinal (GI) AE being the most common.[1]

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- In young people with T2DM over the age of 10 years who require drug therapy, the National Institute for Health and Care Excellence (NICE) recommend metformin, dulaglutide, liraglutide or empagliflozin in addition to lifestyle modifications.[2]
- The 2023 NICE guideline recommends tirzepatide in adults with T2DM who are unable to achieve target HbA1C with metformin and 2 other oral antidiabetic drugs.[3]
- Recommendations for the management of adults with T2DM was provided by a 2023 Veterans Administration/Department of Defense (VA/DoD) Guideline. The use of GLP-1 RAs are strongly recommended for those with atherosclerotic cardiovascular (CV) disease. In patients with T2DM with chronic kidney disease (CKD), who are unable to take sodium- glucose co-transporter 2 (SGLT-2) inhibitors, the use of GLP-1 RAs are strongly recommended.[4]
- The Kidney Disease Improving Global Outcomes (KDIGO) group recommend GLP-1 RAs in people with T2DM and CKD after metformin and SGLT-2 inhibitors.[5]
- The 2024 American Diabetes Association (ADA) recommend GLP-1 RAs and dual GLP-1/GIP RAs for adults with T2DM who require weight reduction.[6]
- Dulaglutide received an expanded indication for children 10 years of age and older who have T2DM.[7,8]
- An FDA safety warning was added to oral semaglutide (RYBELSUS) after post-marketing reports identified dizziness and dysgeusia with use.[9]
- A trial found that insulin glargine and liraglutide were more effective than the other therapies at maintaining glucose control over 5 years.[10]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on review of the evidence.
- Evaluate costs in the executive session.

Summary of Prior Reviews and Current Policy
- The GLP-1 and dual GLP-1/GIP RAs were last reviewed in October 2022.
- The dual GLP-1/GIP RAs were added to the GLP-1 RA prior authorization (PA) criteria (**Appendix 6**). Tirzepatide was reviewed and kept as a non-preferred on the PDL.
- Preferred GLP-1 RAs are dulaglutide, exenatide, and liraglutide. Semaglutide and tirzepatide are subject to PA approval (**Appendix 6**).
- There were over 300 hundred claims for the GLP-1 RAs and dual GLP-1/GIP RAs last quarter (October – December 2023). This class represents substantial cost to the Oregon Health Authority (OHA).

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

CADTH – Liraglutide for Pediatric Patients with Type 2 Diabetes

In a Health Technology Review conducted by CADTH in 2023, the efficacy and safety of liraglutide in pediatric patients with T2DM was evaluated.[1] The literature was searched from January 2013 through June 2023. Two parallel-group, placebo-controlled RCTs met the inclusion criteria for evaluation. Patients were 10-17 years of age with a mean age of 14.6 years in one trial and 14.8 years in the second trial. Most of the patients were White and female.[1] Both trials allowed metformin as background therapy for all treatment groups. Follow up was 5 weeks (n=19) in one trial and 26 weeks in the second trial (n=135). The target maintenance dose for liraglutide was 1.8 mg weekly. The primary outcome was HbA1c changes from baseline compared to placebo.[1]

Both trials reported statistically significant decrease in HbA1c in those treated with liraglutide compared to placebo. In the 26-week follow-up study, HbA1c was reduced more with liraglutide than with placebo (ETD -1.06%; 95% CI, -1.65 to -0.46%; p<0.001); results were similar in the 5-week study versus placebo (-0.90%; 95% CI, -1.36 to -0.45%; p=0.0007).[1] Minor reductions in body weight with liraglutide were also reported relative to placebo (-0.5 kg and -1.91 kg). Hypoglycemia and gastrointestinal adverse events were more commonly reported with liraglutide than placebo.[1] This review provided moderate quality evidence that liraglutide, when combined with metformin, further decreases HbA1c in youth with T2DM versus metformin alone.[1]

After review, 5 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[11–15]

New Guidelines:

NICE – Management of Type 1 and Type 2 Diabetes Mellitus in Children

In 2023, NICE updated guidance on the treatment of young people with T1DM and T2DM. Literature was searched through February 2023.

- Maintenance of an HbA1c of 6.5% or less minimizes long-term complications.[2]
- Metformin is recommended as a first-line agent in children who require medication, in addition to dietary support.
- Basal-bolus insulin is recommended in children who present with ketosis without diabetic ketoacidosis (DKA).
- Review glucose monitoring 4 weeks after treatment is started.
- If a change in treatment is required for individuals 10 years and older with T2DM taking metformin monotherapy, offer liraglutide or dulaglutide if the following are met:
    - HbA1c remains at 6.5% or greater,
    - Plasma glucose greater than126 mg/dL? (4 or more days a week when fasting or before meals), or
    - Plasma glucose greater than 162 mg/dL? (on 4 or more days a week, 2 hours after meals).
- Empagliflozin may be added to metformin children 10 years or older with T2DM who are not able to tolerate liraglutide or dulaglutide or have a clear preference for empagliflozin.
- Insulin can be considered in young people with T2DM who are taking metformin, with or without liraglutide, dulaglutide, or empagliflozin, if an HbA1c of 6.5% cannot be obtained on current therapy.[2]
- In children on metformin and insulin, the addition of liraglutide or dulaglutide can be considered for those who are already on insulin therapy, instead of increasing insulin, if their HbA1c or glucose levels do not meet criteria (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals] or plasma glucose >162 mg/dL [on 4 or more days a week, 2 hours after meals]).

- The addition of empagliflozin is recommended, instead of increasing insulin, in children already on insulin if their HbA1c or glucose levels do not meet recommendations for reducing or stopping insulin (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals]) and they are not able to tolerate liraglutide or dulaglutide or if they specifically request empagliflozin.[2]
- The lowest dose of medications should be used that achieves target HbA1c and blood glucose levels.

NICE – Tirzepatide for Type 2 Diabetes Mellitus

The efficacy and safety evidence for tirzepatide was evaluated by NICE in 2023.[3] The recommendation was based off of policy that recommends that injectable treatment be considered after metformin and 2 other oral antidiabetic drugs have failed to reduce blood glucose to target levels, or alternatively the oral therapy are not tolerated or are contraindicated.

Direct evidence has demonstrated that tirzepatide decreases HbA1c and body mass index (BMI) more than semaglutide, insulin or placebo.[3] No studies have directly compared tirzepatide to other GLP-1 RAs.

NICE recommends tirzepatide for treatment of T2DM in adult patients in conjunction with diet and exercise if blood glucoses are not controlled with metformin and two other oral antidiabetic agents (or if oral therapy is not tolerated or contraindicated). Other criteria include:
- Patient has a BMI of 35 kg/m^2 or more and psychological or medical comorbidities associated with obesity;
- Patient has a BMI less than 35 kg/m^2 but insulin would impose significant occupational implications or weight loss would improve obesity-related complications; or
- Reduced BMI thresholds (e.g., reduce by 2.5 kg/m^2) should be considered for individuals from the following backgrounds: South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean.[3]

Veteran Affairs/Department of Defense Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus

The VA/DoD published a clinical practice guideline for the treatment of T2DM in 2023.[4] Evidence was evaluated and graded from "Strong" to "Weak" based on the quality of evidence and not necessarily clinical importance. Recommendations for GLP-1 RAs are presented but recommendations for the use of GLP-1/GIP RAs (e.g., tirzepatide) were not included in the guideline.

The VA/DoD recommends:
- Targeting a HbA1c of 7.0% to 8.5% for most patients (weak recommendation).[4]
- GLP-1 RAs or SGLT-2 inhibitors that have demonstrated cardiovascular (CV) benefit in adults with T2DM and atherosclerotic CV disease (strong recommendation).
    - The evidence for the benefits of GLP-1 RAs on CV outcomes was conducted primarily in adults with CV disease, and less in those at high risk. Additionally, 71-82% of patients were also taking metformin.[4]
- GLP-1 RAs or SGLT-2 inhibitors that have demonstrated CV benefit in adults with T2DM who are at high risk for atherosclerotic CV disease (e.g., chronic kidney disease (CKD), left ventricular hypertrophy, heart failure) (weak recommendation).[4]
    - There was insufficient high quality evidence on the benefits of GLP-1 RAs on CV outcomes for those who are at low risk for CV disease.
- GLP-1 RAs with proven renal protection to improve macroalbuminuria for adults with T2DM who have CKD and are not able to take SGLT-2 inhibitors (strong recommendation).

- This recommendation was based on evidence that GLP-1 RAs benefit kidney outcomes in adults with T2DM (Hazard Ratio: 0.79 vs. placebo; 95% CI: 0.73–0.87).[4] Renal benefits of GLP-1 RAs (e.g., liraglutide, semaglutide, dulaglutide) are primarily driven by a decrease in new onset macroalbuminuria.

- GLP-1 RAs or SGLT-2 inhibitors for adults with T2DM who have CV disease or renal disease even if they have already achieved target blood glucose levels on baseline medication (weak recommendation).[4]
  - There is evidence that GLP-1 RAs may improve CV and renal outcomes independent of glucose lowering.
- Classes of antidiabetic therapies besides insulin, sulfonylureas or meglitinides in adults, especially those 65 years and older, to reduce risk of hypoglycemia (weak recommendation).

Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

The KDIGO updated guidance in 2022 for management of individuals with diabetes mellitus with CKD.[5] The strength of the recommendation was either Level 1 (strong), which are *recommendations*, and Level 2 (weak) which are *suggestions*. The quality of evidence is graded from A (high) to D (low). The evidence for the use of GLP-1 RAs and GLP-1 RA/GIPs in CKD will be presented.

- In patients with T2DM and CKD (without dialysis and estimated glomerular filtration rate [EGFR] of ≥30 ml/min/1.73 m^2), metformin with a SGLT-2 inhibitor is recommended (1A recommendation).[5]
- Long-acting GLP-1 RAs with CV benefit are recommended for patients requiring additional medications for glucose lowering or who cannot tolerate metformin and/or SGLT-2 inhibitors (1B recommendation).
  - GLP-1 RAs are also preferred for those patients desiring weight loss, have heart failure, high-risk of atherosclerotic cardiovascular disease (ASCVD), and wish to avoid hypoglycemia.[5]
  - The combined use of GLP-1 RAs and DDP-4 inhibitors should not be used.
  - If GLP-1 RAs are used with sulfonylureas or insulin, the dose of those products should be reduced to reduce the risk of hypoglycemia.

American Diabetes Association: Standards of Care in Diabetes

The ADA updates guidance for diabetes care every year. In the 2024 guidance, the use of GLP-1 RAs and GLP-1 RA/GIPs are evaluated and recommendations are graded based on the evidence.[6]

- Combination therapy upon initiation is recommended if needed to meet glucose goals (Grade A).
- GLP-1 or dual GLP-1/GIP RAs are preferred for patients with T2DM who would benefit from weight management (Grade A).
- GLP-1 RAs should be considered independent of HbA1c in adults with T2DM and established CV disease, who are at high risk of CV disease, HF, or CKD, because of evidence of benefit in these populations. (Grade A).[6]
- GLP-1 RAs are preferred in adults with T2DM and advanced CKD (eGFR <30 mL/min per 1.73 m^2). GLP-1 RAs are preferred for glucose lowering because of evidence of reduced CV risk and hypoglycemia in this population. (Grade B).[6]
- GLP-1 and dual GLP-1 /GIP RAs are recommended over insulin in people with T2DM because of the beneficial effect on weight and hypoglycemic risk (Grade A).[6]

New Formulations:

Dulaglutide (TRULICITY): In November 2022, dulaglutide received the expanded indication to improve glycemic control in pediatric patients 10 years of age or older with T2DM, as an adjunct to diet and exercise. The expanded indication was based on one placebo-controlled, RCT in 154 children (**Appendix 2**).

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Semaglutide[9]	RYBELSUS	January 2024	Adverse Drug Reactions – post-marketing reports	Nervous system disorders: dizziness and dysgeusia

References:

1. Kaulback K, Walter M. Liraglutide for Pediatric Patients With Type 2 Diabetes. *Canadian Agency for Drugs and Technology in Health.* 2023;3(7). doi:10.51731/cjht.2023.698.

2. National Institute for Health and Care Excellence. Diabetes (type 1 and type 2) in Children and Young People: Diagnosis and Management. *NICE Guideline*. May 2023. Available at: https://www.nice.org.uk/guidance/ng18. Accessed January 20, 2024.

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12. The Grade Study Group. Glycemia Reduction in Type 2 Diabetes — Microvascular and Cardiovascular Outcomes. *New England Journal of Medicine*. 2022;387(12):1075-1088. doi:10.1056/NEJMoa2200436.

13. Guo X, Sang C, Tang R, et al. Effects of glucagon-like peptide-1 receptor agonists on major coronary events in patients with type 2 diabetes. *Diabetes Obes Metab*. 2023;25 Suppl 1:53-63. doi:10.1111/dom.15043.

14. Yang XY, Yin S, Yu YF, et al. Is tirzepatide 15 mg the preferred treatment strategy for type 2 diabetes? A meta-analysis and trial-sequence-analysis. *Eur Rev Med Pharmacol Sci*. 2023;27(15):7164-7179. doi:10.26355/eurrev_202308_33290.

15. Jahagirdar D, Mahood Q. Semaglutide for Type 2 Diabetes (2 mg). *Canadian Agency for Drugs and Technology in Health*. 2023;3(10). doi:10.51731/cjht.2023.752.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL	Route
dulaglutide	TRULICITY	PEN INJCTR	Y	Subcutaneous
exenatide	BYETTA	PEN INJCTR	Y	Subcutaneous
liraglutide	VICTOZA 2-PAK	PEN INJCTR	Y	Subcutaneous
liraglutide	VICTOZA 3-PAK	PEN INJCTR	Y	Subcutaneous
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N	Subcutaneous
semaglutide	OZEMPIC	PEN INJCTR	N	Subcutaneous
semaglutide	RYBELSUS	TABLET	N	Oral
tirzepatide	MOUNJARO	PEN INJCTR	N	Subcutaneous

Appendix 2: New Comparative Clinical Trials

A total of 45 citations were manually reviewed from the initial literature search. After further review, 42 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Arslanian, et al[8] DB, PC, PG, Phase 3	1. Dulaglutide 0.75 mg once weekly 2. Dulaglutide 1.5 mg once weekly 3. Placebo 26 weeks	-Age 10 to <18 y -BMI >85th percentile - Lifestyle modification -Metformin with or without basal insulin (n=154)	Change in HbA1c at 26 weeks	1. -0.6% 2. -0.9% 3. 0.6% <u>Dulaglutide 0.75 vs. placebo:</u> -1.2% (95% CI, -1.8 to -0.6%; P<0.001) <u>Dulaglutide 1.5 vs. placebo:</u> -1.5 % (95% CI, -2.1 to -0.9%; P<0.001)	Mean age 14 years; 71% female; 55% White; Mean BMI 34; 63% on metformin monotherapy. Most common AE: GI
GRADE Study Research Group[10] DB, PG, Phase 3	1. Insulin glargine U-100 initiated at 20 units and titrated according to glucose levels while avoiding hypoglycemia 2. Glimepiride 1-2 mg, titrated up to 8 mg daily in divided doses 3. Liraglutide 0.6 mg daily titrated up to 1.8 mg daily 4. Sitagliptin 100 mg daily, adjusted to renal function	-Adults -T2DM duration <10 y (diagnosed at age 30 y or later) -Metformin 500 mg/d -HbA1c 6.8-8.5%	Failure rate (defined as HbA1c ≥7.0% (evaluated quarterly)† † Metformin was increased to ≥1000 mg/day with target dose of 2000 mg/day during run-in phase	<u>Failure rate at 5 years:</u> 1. Glargine: 67% 2. Glimepiride: 72% 3. Liraglutide: 68% 4. Sitagliptin: 77% <u>Glargine vs. sitagliptin:</u> HR 0.71 (95% CI, 0.64 to 0.78; P≤0.001) ARR 10%/NNT 10 <u>Glargine vs. glimepiride:</u> HR 0.89 (95% CI, 0.81 to 0.98; P≤0.05) <u>Liraglutide vs. sitagliptin:</u> HR 0.69 (95% CI, 0.63 to 0.76; P≤0.001) ARR 9%/NNT 11 <u>Glimepiride vs. sitagliptin:</u>	Mean age 57 y; 63.6% male; 65.7% White, 19.8% Black; Mean BMI 34.3; Mean duration of T2DM 4 y Glargine and liraglutide had less failure rates over 5 years than glimepiride and sitagliptin.

				HR 0.79 (95% CI, 0.72 to 0.88; P≤0.001) ARR 5%/NNT 20	

Abbreviations: AE = adverse events; ARR = absolute risk reduction; BMI = body mass index; DB = double-blind; CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HbA1c = hemoglobin A1c; HR = hazard ratio; MI = myocardial infarction; NI = non-inferiority; NNT = number needed-to-treat; PC = placebo-controlled; PG = parallel group; RCT = randomized clinical trial; SC = subcutaneous; T2DM = type 2 diabetes mellitus.

Appendix 3: Abstracts of Comparative Clinical Trials

Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes

Silva Arslanian, Tamara Hannon, Philip Zeitler, Lily C Chao , Claudia Boucher-Berry, Margarita Barrientos-Pérez, Elise Bismuth, Sergio Dib, Jang Ik Cho, David Cox; AWARD-PEDS Investigators

Background: The incidence of type 2 diabetes mellitus is increasing among youths. Once-weekly treatment with dulaglutide, a glucagon-like peptide-1 receptor agonist, may have efficacy with regard to glycemic control in youths with type 2 diabetes.

Methods: In a double-blind, placebo-controlled, 26-week trial, we randomly assigned participants (10 to <18 years of age; body-mass index [BMI], >85th percentile) being treated with lifestyle modifications alone or with metformin, with or without basal insulin, in a 1:1:1 ratio to receive once-weekly subcutaneous injections of placebo, dulaglutide at a dose of 0.75 mg, or dulaglutide at a dose of 1.5 mg. Participants were then included in a 26-week open-label extension study in which those who had received placebo began receiving dulaglutide at a weekly dose of 0.75 mg. The primary end point was the change from baseline in the glycated hemoglobin level at 26 weeks. Secondary end points included a glycated hemoglobin level of less than 7.0% and changes from baseline in the fasting glucose concentration and BMI. Safety was also assessed.

Results: A total of 154 participants underwent randomization. At 26 weeks, the mean glycated hemoglobin level had increased in the placebo group (0.6 percentage points) and had decreased in the dulaglutide groups (-0.6 percentage points in the 0.75-mg group and -0.9 percentage points in the 1.5-mg group, P<0.001 for both comparisons vs. placebo). At 26 weeks, a higher percentage of participants in the pooled dulaglutide groups than in the placebo group had a glycated hemoglobin level of less than 7.0% (51% vs. 14%, P<0.001). The fasting glucose concentration increased in the placebo group (17.1 mg per deciliter) and decreased in the pooled dulaglutide groups (-18.9 mg per deciliter, P<0.001), and there were no between-group differences in the change in BMI. The incidence of gastrointestinal adverse events was higher with dulaglutide therapy than with placebo. The safety profile of dulaglutide was consistent with that reported in adults.

Conclusions: Treatment with dulaglutide at a once-weekly dose of 0.75 mg or 1.5 mg was superior to placebo in improving glycemic control through 26 weeks among youths with type 2 diabetes who were being treated with or without metformin or basal insulin, without an effect on BMI. (Funded by Eli Lilly; AWARD-PEDS ClinicalTrials.gov number, NCT02963766.).

Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes

GRADE Study Research Group; David M Nathan, John M Lachin, Ashok Balasubramanyam, Henry B Burch, John B Buse, Nicole M Butera, Robert M Cohen, Jill P Crandall, Steven E Kahn, Heidi Krause-Steinrauf, Mary E Larkin, Neda Rasouli, Margaret Tiktin, Deborah J Wexler, Naji Younes

Abstract

Background: The comparative effectiveness of glucose-lowering medications for use with metformin to maintain target glycated hemoglobin levels in persons with type 2 diabetes is uncertain.

Methods: In this trial involving participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%, we compared the effectiveness of four commonly used glucose-lowering medications. We randomly assigned participants to receive insulin glargine U-100 (hereafter, glargine), the sulfonylurea glimepiride, the glucagon-like peptide-1 receptor agonist liraglutide, or sitagliptin, a dipeptidyl peptidase 4 inhibitor. The primary metabolic outcome was a glycated hemoglobin level, measured quarterly, of 7.0% or higher that was subsequently confirmed, and the secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5%.

Results: A total of 5047 participants (19.8% Black and 18.6% Hispanic or Latinx) who had received metformin for type 2 diabetes were followed for a mean of 5.0 years. The cumulative incidence of a glycated hemoglobin level of 7.0% or higher (the primary metabolic outcome) differed significantly among the four groups ($P<0.001$ for a global test of differences across groups); the rates with glargine (26.5 per 100 participant-years) and liraglutide (26.1) were similar and lower than those with glimepiride (30.4) and sitagliptin (38.1). The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. There were no material differences with respect to the primary outcome across prespecified subgroups defined according to sex, age, or race or ethnic group; however, among participants with higher baseline glycated hemoglobin levels there appeared to be an even greater benefit with glargine, liraglutide, and glimepiride than with sitagliptin. Severe hypoglycemia was rare but significantly more frequent with glimepiride (in 2.2% of the participants) than with glargine (1.3%), liraglutide (1.0%), or sitagliptin (0.7%). Participants who received liraglutide reported more frequent gastrointestinal side effects and lost more weight than those in the other treatment groups.

Conclusions**:** All four medications, when added to metformin, decreased glycated hemoglobin levels. However, glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining target glycated hemoglobin levels. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; GRADE ClinicalTrials.gov number, NCT01794143.).

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 01, 2024

Search Strategy:

#	Searches	Results
1	dulaglutide.mp.	777
2	exenatide.mp. or Exenatide/	3898
3	liraglutide.mp. or Liraglutide/	4283
4	semaglutide.mp.	1551
5	tirzepatide.mp.	390
6	limit 5 to (english language and humans and yr="2022 -Current")	231
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	45

Appendix 5: Key Inclusion Criteria

Population	Patients with type-2 diabetes mellitus (T2DM)
Intervention	GLP-1 receptor agonists (injectable and oral)
Comparator	Placebo or active treatment
Outcomes	HbA1c, cardiovascular death, myocardial infarction, stroke, chronic kidney disease, hypoglycemia
Setting	Outpatient

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred GLP-1 receptor agonists and GLP-1 receptor + GIP agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed to meet hemoglobin A1C goals with metformin or have contraindications to metformin? (document contraindication, if any)	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin. See below for metformin titration schedule.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *4/24 (KS), 10/22 (KS), 8/20 (KS), 6/20), 3/19, 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *1/1/23; 9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*

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Drug Effectiveness Review Project Summary Report – Pharmacologic Agents for Weight Management

Date of Review: April 2024 **Literature Search:** 02/01/23-01/08/24

Plain Language Summary:

- Medicines can help people lose weight. The Food and Drug Administration has approved medicines be prescribed along with increased physical activity and diets to promote healthy eating and decrease calories.
- Medicines studied for weight loss include semaglutide, liraglutide, tirzepatide, exenatide, orlistat, setmelanotide, combination phentermine and topiramate (phen/top), and combination naltrexone and bupropion. Compared to a sugar pill (placebo), medicines had 11 to 26.4 pounds of weight loss in people that were overweight or obese. Semaglutide, liraglutide and phen/top also decreased weight in children and young adults (ages 10-18 years).
- Side effects that commonly occur with weight loss drugs include nausea, diarrhea and vomiting.
- Several organizations make recommendations for weight management:
    - The National Institute for Health and Care Excellence recommends liraglutide and semaglutide for patients who are overweight with other medical conditions or are obese. Patients must also be willing to participate in healthy eating and exercise programs.
    - The Veterans Administration/Department of Defense suggests that liraglutide, naltrexone/bupropion, orlistat, and the combination product phentermine and topiramate can be considered as options for people that need to lose weight because these medicines caused more weight loss compared to placebo.
    - The American Diabetes Association recommends that people with type 2 diabetes be treated with medicines such as semaglutide and tirzepatide because they lower blood sugar levels and also cause weight loss.
    - The American Academy of Pediatrics recommends diet and exercise for children and adolescents that are overweight. Medicines to lower weight may be an option in children 12 years and older.
- Semaglutide studies show that cardiovascular deaths, such as heart attacks and strokes, are reduced by 1.5% in some people that have heart disease and are overweight.
- The Oregon Health Plan does not currently pay for weight loss medicines for most members. The Drug Research and Management Group recommends that the Oregon Health Authority (OHA) evaluate the costs of medicines used for weight loss and secure funds before paying for these medicines.

Purpose of the Review:

Drugs for weight management are currently an optional benefit for Medicaid programs and are not covered for most members. Coverage under the Early Periodic Screening and Treatment (EPSDT) program can be considered with individual review for members who are less than 21 years of age. The purpose of this review is to evaluate effectiveness, safety, and comparative evidence for weight management agents to assist evaluation of coverage by the Oregon Health

Author: Kathy Sentena, PharmD

Authority. This review will describe populations for which weight management agents have been studied, available comparative evidence of clinical efficacy and safety between agents, and coverage recommendations from various guidelines.

Current Status of PDL Class:
Drugs used for weight loss are currently not covered by Oregon Medicaid and are exempt from the requirement for coverage under Federal Law. Coverage under the Early Periodic Screening and Treatment (EPSDT) program can be considered with individual review for members who are less than 21 years of age. See **Appendix** 1 for drugs with indications for weight management.

Research Questions:
1. What is the evidence for efficacy and harms for the use of weight loss therapies in adults, children and adolescents for important outcomes such as weight loss, weight-related comorbidity benefits (e.g., HbA1c, cardiovascular benefits), and durability of weight loss?
2. Are there subgroups of people that would specifically benefit or be harmed by weight management therapies (e.g. BMI, comorbidities)?

Conclusions:
- The 2023 report on weight management by the Drug Effectiveness Review Project (DERP) was the primary evidence source for this review. The DERP Reports are not clinical guidelines but provide comparative clinical effectiveness between efficacy and harms of medications used for weight management. Evidence presented in the DERP Reports serve as a high-quality evidence. Primary literature included in the DERP Report are summarized below. The DERP Report considered youth participants as those 10 to 18 years. Eight high-quality guidelines, one new drug approval, and 5 randomized controlled trial (RCTs) were identified with a supplemental literature search through January 8, 2024.
- Drugs approved by the Food and Drug Administration (FDA) for weight loss include liraglutide, semaglutide, tirzepatide, bupropion/naltrexone and phentermine/topiramate. Background therapy with diet and exercise or intensive behavioral therapy is recommended for all agents.[1]
- Outcomes evaluated by the Drug Effectiveness Review Project (DERP) included weight loss, CV risk factors (e.g., systolic blood pressure, low density lipoprotein [LDL] levels and hemoglobin A1c [HbA1c]).
- Weight loss
    - Clinically meaningful weight loss (e.g., ≥5% decrease in BMI compared to placebo) in adults was demonstrated with tirzepatide (ARR 53%/NNT 2; moderate quality of evidence), semaglutide (ARR 49%/NNT 2; low quality of evidence), liraglutide (ARR 33%/NNT 3; low quality evidence) and phentermine-topiramate (ARR 47%/NNT 2) low quality of evidence) when compared to placebo.[1]
    - There was moderate quality of evidence that exenatide caused more weight loss compared to glyburide in adults with T2DM who are overweight.[1]
    - Liraglutide and naltrexone-bupropion, compared to placebo, demonstrated statistically significant reductions in body weight in adults; however, changes were not considered clinically meaningful.[1]
    - Tirzepatide, at 5 mg, 10 mg or 15 mg SC weekly, resulted in a greater reduction in BMI compared to placebo at 72 weeks (-15% to -20.9% vs. -3.1% for placebo; moderate quality evidence).[2]
    - In people with T2DM and obesity, tirzepatide 10 mg and 15 mg weekly reduced weight by -12.8% to -14.7% compared to -3.2% with placebo over 18 months (moderate strength evidence).[3]
    - In adult patients who had lost 5% or more of body weight with lifestyle modifications, tirzepatide 10 mg or 15 mg SQ weekly, was more effective than placebo at reducing weight and the percentage of patients achieving 5% or more weight loss at 72 weeks, based on moderate quality evidence.[4]

- Evidence for weight loss drugs studied by DERP in youth (ages 10-18) were identified for liraglutide, semaglutide, exenatide, phentermine-topiramate and setmelanotide.[1] All therapies studied demonstrated clinically significant weight loss in youth with the exception of exenatide. The evidence for semaglutide demonstrated the most weight loss with a reduction of -16.7% in BMI based on moderate evidence.[1]

- CV risk factors
  - Beneficial effect of weight management therapies on CV risk factors (e.g., blood pressure, LDL levels and HbA1c) was not consistently demonstrated.[1]
  - Changes in indirect outcomes (e.g., LDL levels and systolic blood pressure [SBP]) were decreased statistically, but not clinically, more than placebo in adult patients treated with liraglutide, semaglutide and phen/top.[1] There were statistically and clinically significant decreases in HbA1c in adult patients that were overweight or obese treated with semaglutide, liraglutide, and naltrexone-bupropion. Studies demonstrating HbA1c reductions enrolled patients with T2DM.[1]
  - In youth 10 to 18 years of age, only semaglutide produced clinically significant changes for reduction in HbA1c levels compared to placebo.[1]
- Morbidity and mortality
  - Conclusive benefit on reduction in morbidity (e.g., prevention or improvement in weight related co-morbidities) and mortality has not been established due to lack of long-term evidence.
  - There is moderate strength of evidence that semaglutide reduces the composite endpoint of risk of death from CV causes, nonfatal myocardial infarction (MI) or nonfatal stroke, compared to placebo, in adults with CV disease and who are overweight or obese (e.g., a BMI of 27 kg/m^2 or greater).[5] Sixty-seven people would need to be treated for 3.3 years to prevent one CV event (absolute risk reduction [ARR] 1.5%/number needed to treat [NNT] 67).[5] Seventeen percent of patients discontinued semaglutide due to adverse events compared to 8% of patients taking placebo ($p<0.001$) (mean duration of follow-up was 39.8 months).
- Safety
  - Withdrawals due to adverse events (AE) were higher than placebo in patients treated with liraglutide (RR 2.20), semaglutide (RR 1.81) , phen/top (1.88) and bupropion/naltrexone (1.92).[1] Common AE experienced with liraglutide, semaglutide, tirzepatide, and exenatide were gastrointestinal (e.g., nausea, diarrhea). Phen/top is associated with dizziness, insomnia, dry mouth and increased heart rate. Adverse reactions experienced with naltrexone/bupropion are nausea, constipation, insomnia and vomiting. Naltrexone/bupropion should not be used in those with uncontrolled hypertension (HTN) or chronic opioid use.
  - There is moderate strength of evidence that patients who continued on treatment, after a 36 week open-label lead-in period followed by a 52-week, double-blind, placebo-controlled trial, maintained larger weight loss reductions compared to placebo.[6] Two-percent of patients discontinued treatment due to adverse reactions related to tirzepatide compared to 1% of placebo treated patients. The lead-in period likely contributed to the low rates of discontinuations.[6] In an 18 month study of tirzepatide in people with T2DM and obesity, discontinuation rates were 9% to 14% in patients treated with tirzepatide compared to 15% for placebo.[3]
- Guideline recommendations
  - The National Institute for Health and Care Excellence (NICE) recommend semaglutide and liraglutide for weight management in adults who meet specific criteria based on BMI and comorbidities (e.g., based on recommendations from 2023 and 2020, respectively.[7,8] Pharmacotherapy should be taken in conjunction with a weight management behavioral lifestyle program. Naltrexone/bupropion is not recommended for weight management by NICE.[7–9]
  - A 2020 Veterans Administration (VA)/Department of Defense (DOD) guideline found moderate quality evidence that liraglutide, naltrexone/bupropion, orlistat, and phen/top caused more weight reduction than placebo. The VA/DOD suggests pharmacotherapy, with lifestyle

modifications, for adults who are overweight or obese and meet clinical criteria (e.g., BMI specifications and weight related comorbidities) (weak recommendation).[10]
    - The Canadian Agency for Drugs and Technologies in Health (CADTH) reviewed semaglutide for weight management in 2022, prior to the release of evidence demonstrating CV benefits of semaglutide in select populations.[11] They recommended against use of semaglutide for weight management.
    - The Institute for Clinical and Economic Review (ICER) evaluated drugs approved for weight management (e.g., semaglutide, liraglutide, phen/top, and bupropion/naltrexone) compared to lifestyle interventions in 2022.[12] The evidence is graded by assessing the certainty and magnitude of benefit. Recommendations are rated from "A" (superior – high certainty of a substantial net health benefit) to "I" (insufficient – level of certainty in the evidence is low).[13] Semaglutide and liraglutide were given a B+ and B rating for evidence of comparative effectiveness to lifestyle modifications, respectively. Phen/top and bupropion/naltrexone received a C++ and C+ rating, respectively.[12]
    - In guidance from 2024, The American Diabetes Association (ADA) strongly recommends that adults who are overweight or obese with type 2 diabetes mellitus (T2DM) be treated with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or glucose-dependent insulinotropic polypeptide receptor agonist (GIP RA). Recommendations were to use drugs with evidence of the largest weight reduction, such as semaglutide and tirzepatide.[14]
    - The American Academy of Pediatrics (AAP) recommends intensive health and behavior modifications for children and adolescents who are overweight (BMI $\geq 85^{th}$ to $<95^{th}$ percentile for age and sex), obese (BMI $\geq 95^{th}$ percentile) and severely obese (BMI $\geq$120% of the 95^{th} percentile) in guidance released in 2023.[15] APA recommends offering pharmacotherapy to those children who are obese, in addition to lifestyle changes, in those 12 and older based on level B evidence.[15]
- Tirzepatide received FDA approval in November of 2023 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) with at least one weight-related condition (e.g., hypertension, dyslipidemia, T2DM, obstructive sleep apnea or CV disease).[16]
- There is a lack of evidence on weight changes upon discontinuation of therapy, optimal duration of use and conclusive benefit on weight related comorbidities (e.g., SBP changes, LDL changes and reduction in adverse CV outcomes). All medications were studied in conjunction with lifestyle modification programs. Studies are limited by a higher number of female participants and high attrition rates in most medication management trials.

Recommendations:
- Recommend the Oregon Health Authority (OHA) perform a budgetary analysis and identify a funding plan before opening up coverage for weight management drugs. Draft prior authorization (PA) criteria for adults will be presented to the committee to inform future steps.
- Recommend implementation of PA criteria for members who qualify for coverage under the Early Periodic Screening Diagnostic and Treatment (EPSDT) Program.
- Weight management pharmacotherapy should be used in conjunction with diet and lifestyle modifications (e.g., reduction in daily calorie of approximately 500 kcals, and physical activity of at least 150 minutes weekly).
- Recommend the OHA evaluate and establish clinically appropriate minimum standards for required lifestyle modification.

Methods:
The October 2023 drug class report on Pharmacological Agents for Weight Management: Clinical Evidence and Management Strategies by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

DERP Summary Findings:

A recent report from DERP evaluated the risks and benefits of the use of pharmacotherapy to assist in weight management.[1] Lifestyle modifications are recommended first line for weight loss, but often individuals who are overweight require assistance in obtaining and maintaining long term weight loss. Six drugs are FDA approved for chronic weight loss management. The DERP report focuses on drugs used for management of weight loss for adults and children who are overweight (BMI of 25 to up to 30 kg/m^2) or obese (BMI of 30 kg/m^2 or greater). FDA approved drugs for weight management were included in the review.[1] Studies had to be at least 12 months in duration to be included, with the exception of studies enrolling pediatrics and people with type 1 diabetes mellitus (T1DM), which needed to be 6 months or longer. There were no restrictions on study length for setmelanotide. Forty-four studies were identified from a literature search through February 2023, 36 of which were used to evaluate effectiveness and harms (**Table 1**).[1] All studies had conflicts of interest with funding provided by industry. Comparators included lifestyle modifications, active treatment comparisons, surgery or other interventional procedure or devices. Studies that met inclusion criteria included comparators to placebo, liraglutide, glyburide and usual care.[1]

Table 1. Therapies for Weight Loss Included in the DERP Review[1]

Drugs	Dose	Studies Included in the DERP Report	FDA Approved Indication in Adults	FDA Approved for Weight Loss in Youth
GLP-1 RAs				
Liraglutide (SAXENDA)	0.6, 1.2, 1.8, 2.4 or 3.0 mg SC daily	14	Weight Loss	Ages 12 and older
Semaglutide (WEGOVY)	0.25, 0.5, 1.0, 1.7 or 2.4 mg SC weekly	8	Weight Loss	Ages 12 and older
Dulaglutide (TRULICITY)	0.75, 1.5, 3.0 or 4.5 mg SC weekly†	0	T2DM	Not studied; approved for youth for T2DM who are 10 years of age and older
Exenatide (BYETTA AND BYDUREON BCISE)	BYETTA: 5 or 10 mcg SC twice daily BYDUREON BECISE: 2 mg SC weekly	3	T2DM	Off-label; approved for youth for T2DM who are 10 years of age and older
Liraglutide (VICTOZA)	0.6, 1.2 or 1.8 mg SC daily	0	T2DM	Off-label; approved for youth for T2DM who are 10 years of age and older
Lixisenatide (ADLYXIN)	10 or 20 mcg SC daily	0	T2DM	Not studied; not approved for use in youth for T2DM
Semaglutide (OZEMPIC AND RYBELSUS)	OZEMPIC: 0.25, 0.5, 1.0 or 2.0 mg SC weekly RYBELSUS: 3, 7 or 14 mg orally daily	0	T2DM	Off-label; not approved for use in youth for T2DM
GLP-1 RAs and GIP RA				

Tirzepatide (ZEPBOUND)*	2.5, 5.0, 7.5, 10.0, 12.5 or 15 mg SC weekly	0	Weight Loss	Not studied; not approved for use in youth for T2DM
Tirzepatide (MOUNJARO)	2.5, 5.0, 7.5, 10.0, 12.5 or 15 mg SC weekly	1	T2DM	Not studied; not approved for use in youth for T2DM
Misc. Agents				
Naltrexone-bupropion (CONTRAVE)	4 tablets (32 mg + 360 mg) orally daily (available as 8 mg/90 mg tablets)	5	Weight Loss	Not studied
Phentermine-topiramate (QSYMIA)	4 capsules (15 mg + 92 mg) orally daily (available as 3.75 mg/23 mg, 7.5/ 46 mg, 11.25 mg/69 mg, 15 mg/92 mg)	3	Weight Loss	Ages 12 and older
Setmelanotide (IMCIVREE)	3.0 mg SC daily	1	Weight Loss – for obesity caused by genetic conditions	Ages 6 and older
Orlistat (XENICAL, ALLI)	XENICAL: 120 mg orally three times daily ALLI: 60 mg orally up to 3 times daily	0	Weight Loss	Not studied
Key: * Not included in DERP due to approval on 11/8/23 for weight loss. Included in table for completeness. † Not commonly used clinically due to undesirable adverse effects leading to high discontinuation rates.				
Abbreviations: GIP RA = glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SC = subcutaneous; T2DM = type 2 diabetes mellitus.				

Outcomes of interest evaluated in the report include body weight changes, proportion with a 5% or more weight loss, CV outcomes (e.g., stroke and MI), changes in related comorbidities (e.g., blood pressure, T2D), health related quality of life, mortality and adverse events.[1] In children and adolescents the conversion of BMI percentiles to z-scores are used for assessing longitudinal change in adiposity in youth with obesity.[15] The z-score is a statistical measure that describes a value to a population mean derived from the CDC Growth charts. The BMI expressed as a percentage (e.g., BMI percentile above the 95th percentile for the age and sex) is also another option for categorizing adiposity in youth. Minimal clinically important differences (MCID) for important outcomes are presented in **Table 2**.[1] Clinically meaningful changes related to therapy help to interpret efficacy findings; however, they should be interpreted in the context of patient population and other study variables.

Table 2. Weight Loss Outcomes and Associated Minimal Clinically Important Differences[1]

Outcome	MCID
Percent change in body weight	5% or more weight loss
Body Mass Index (BMI) z or standard deviation score (SD)* (BMI z/SD score) - Measure of relative weight adjusted according to references standards for the age of the child (2 to 20 years) and sex - Scores quantify a measurement's distance from the mean; often converted to percentiles	0.15 to 0.25 or more units
Percent change in BMI	5% or more loss of BMI

Systolic blood pressure	5 mmHg or more reduction has been shown to reduce major CV events by 10%
Low-density lipoprotein (LDL) cholesterol	1 mmol/L (40 mg/dL) decrease associated with 23% to 25% reduction in major CV events. Goal of statin therapy is 50% or more reduction in LDL cholesterol
Hemoglobin A1c (HbA1c)	0.3% to 0.4%
Impact of Weight on Quality of Life-Lite survey (IWQoL-Lite) • 20-item self-report survey of 20 items to assess obesity-specific QoL I adults • Scores range from 0-100 with higher scores indicating better quality of life	Increases of 7.7 to 12 points of total score
SF-36 Physical Function Score • Scores range from 0-100 with higher scores indicating better quality of life	3.8 points or more for obesity health-related QoL
Pediatric quality of life inventory (PedsQL)	4.4 points or more for health-related QoL
Key: * Measurement of relative weight adjusted according to reference standards for child age (2 to 20 years) adjusted for sex; scores correspond to growth chart percentiles.	
Abbreviations: CV = cardiovascular; MCID = minimal clinically important difference; QoL = quality of life	

All drugs studied were compared to placebo except for 2 trials evaluating semaglutide versus liraglutide and exenatide versus glyburide. Liraglutide, semaglutide, exenatide and phentermine-topiramate were studied in youth.[1]

LIRAGLUTIDE

Adults

Liraglutide was studied in 11 RCTs versus placebo and 1 RCT versus semaglutide in adult patients.[1] Trials included patients with and without diabetes. Three RCTs included patients with T2DM and 3 trials were studied in patients with T1DM. Two RCTs studied weight loss maintenance in those individuals who had lost at least 5% body weight during a run-in period using diet and exercise.[1] Doses of liraglutide studied for weight loss were 3.0 mg daily and 1.8 mg daily. Most of the studies also offered diet and exercise or intensive behavioral therapy as background treatment. Study duration were from 24 to 68 weeks. Three trials enrolled participants with a BMI of 25 kg/m^2 or greater, 4 studies evaluated a BMI of 27 kg/m^2 or greater, 4 enrolled people with a BMI of 30 kg/m^2 (3 studies also allowed participants with a BMI of 27 kg/m^2 if comorbidities) and one trial included participants with a BMI of 32 kg/m^2 to 43 kg/m^2. Participants had a mean age of mid to late 40's and baseline BMI of 35-40 kg/m^2. Twelve of the studies had moderate risk of bias and the remaining 2 had high risk of bias.[1]

Liraglutide use was associated with more weight loss than placebo (**Table 3**). There was heterogeneity across the trials, so variations in results were probably not due to chance alone. Enrollment of differing population, such as diabetes, could influence heterogeneity levels. One trial, not included in the assessment of evidence, followed participants for 160 weeks. Weight loss was maintained out to 3 years, -5.4% at 56 weeks and -4.2% at 160 weeks.[1]

Liraglutide use demonstrated favorable findings on comorbidity outcomes. There is moderate strength of evidence that liraglutide reduced systolic blood pressure (SBP) (mean difference [MD] -2.89 mmHg; 95% confidence interval [CI], -3.54 to -2.24; p<0.001); however, this difference did not a achieve thresholds for a clinically meaningful change.[1] Changes in LDL cholesterol were greater for liraglutide compared to placebo but were not clinically meaningful (standardized mean difference [SMD] -0.12 mmol/L; 95% CI, -0.17 to -0.06; p<0.001) (moderate quality of evidence). There was low quality evidence that changes in hemoglobin A1c (HbA1c) were reduced more with liraglutide compared to placebo (MD -0.33%; 95% CI, -0.44 to -0.21; p<0.001) by a clinically meaningful amount (in people with and without diabetes).[1] No difference in HbA1c was demonstrated between liraglutide and placebo in those with T1DM. There was low quality of evidence that quality of life may have slightly improved with liraglutide compared to placebo. Liraglutide use caused more withdrawals due to AEs compared to placebo that was not dose dependent (relative risk [RR] 2.20; 95% CI, 1.75 to 2.76; p<0.001) (moderate strength of evidence).[1] The most common AEs were nausea, constipation, diarrhea and vomiting in those taking liraglutide. Gallbladder issues (e.g., cholecystitis, cholelithiasis) occurred more often in those treated with liraglutide compared to placebo.

Table 3. Weight Outcomes for Liraglutide in Adults[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI ≥25 kg/m^2 (3 studies) - BMI ≥ 27 kg/m^2 (4 studies) - BMI of 30 kg/m^2 (4 studies; 3 studies also allowed participants with a BMI of 27 kg/m^2 if comorbidities) - BMI of 32 kg/m^2 to 43 kg/m^2 (1 study) - Diabetes excluded (2), T1DM included (3), T2DM (3) - liraglutide 1.8 mg daily (0.6 mg weekly to until target), liraglutide 3.0 mg daily - Trials lasted 56-172 weeks			
Change in BMI % (7 RCTs; n=5,864)	MD -4.61% (95% CI, -5.44 to -3.78; p<0.001)	Low	Percent change in body weight were not clinically meaningful with liraglutide treatment but are statistically significant (5% or more reduction is considered clinically meaningful).
Change in Body Weight (8 RCTs; n=4,777)	MD -5.58 kg (95% CI, -7.63 to -2.41; p<0.001)	Moderate	Patients taking liraglutide lost more weight compared to placebo.
Change in BMI (5 RCTs; n=5,129)	MD -1.82 kg/m^2 (95% CI, -1.95 to -1.68; p<0.001)	Low	BMI was reduced with liraglutide compared to placebo.
Proportion with ≥ 5% weight loss (7 RCTs; n=5,817)	RR 2.04 (95% CI, 1.61 to 2.57; p<0.001)	Low	Liraglutide treated patients were more likely to lose more body weight compared to placebo.
Proportion with ≥ 10% weight loss (8 RCTs; n=6,012)	RR 2.66 (95% CI, 2.00 to 3.53; p<0.001)	Moderate	Liraglutide treated patients were more likely to lose more body weight compared to placebo.
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; RR = relative risk			

Youth

Liraglutide was studied in 2 RCTs for weight loss use in youth (**Table 4**).[1] One study enrolled youth with HbA1c levels over 7% (all had T2DM and were on metformin) and the other study included youth with an average normal HbA1c (5.3%) and approximately 30% had prediabetes or T2DM. Youth had to have a BMI of at least the 85th percentile in one study and 95th percentile or more in the second study.[1] The study durations lasted from 52-56 weeks and doses were 1.8 mg weekly in one study and 3.0 mg weekly in the second study. Compared to placebo, liraglutide resulted in a potentially clinically meaningful change in BMI z/SD score, according to some estimates.[1] Other weight outcomes were not clinically meaningful. There was moderate evidence of no difference in LDL cholesterol measurements between liraglutide and placebo. There was a small, statistically significant, but not clinically meaningful change, at 52 weeks in in systolic blood pressure (MD -2.06; 95% CI, -4.06 to -0.05; P=0.04) between liraglutide and placebo (moderate evidence).[1] There was no difference in change in HbA1c between liraglutide and placebo (very low evidence; p=0.29). Moderate quality of evidence found no difference between liraglutide and placebo in quality of life. Withdrawals due to adverse events were not different between groups based on very low evidence. In both studies, liraglutide was associated with an increased risk of AEs and severe adverse events (SAEs) when compared to placebo; however the differences were not considered statistically significant (strength of evidence was not provided).[1] In the 5 studies that evaluated medication use, people randomized to liraglutide were less likely to require of medications for hypertension, lipids and diabetes (when applicable) compared to placebo.

Table 4. Weight Outcomes for Liraglutide in Youth[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI of 85th percentile or more in one study and 95th percentile in the second study - Diabetes (1 study) - Portion with prediabetes or diabetes (1 study) - Ages: 10-17, 12-18			
Changes in BMI z/SD score (2 RCTs; n=386)	MD -0.21 SDs (95% CI, -0.31 to -0.11; p<0.001)	Low	Clinically meaningful decreases with liraglutide according to some estimates. Clinically meaningful effect is cited as a change in SD of -0.15 or -0.25.
Change in BMI % (1 RCT; n=251)	MD -4.64% (95% CI, -7.12 to -2.16; p<0.001)	Low	Results of liraglutide treatment are not clinically meaningful by a small margin.
Change in Body Weight (1 RCT; n=251)	MD -5.02% (95% CI, -7.63 to -2.41; p<0.001)	Moderate	Growth and height development can influence weight changes in youth so results aren't clinically meaningful.
Change in BMI (1 RCT; n=251)	MD -1.58 kg/m^2 (95% CI, -2.47 to -0.69; p<0.001)	Moderate	Unlikely to be clinically meaningful.
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation			

SEMAGLUTIDE

Adults

Semaglutide was studied in 7 placebo-controlled trials and one active treatment trial which compared semaglutide to liraglutide in adult patients who were overweight or obese.[1] One trial enrolled diabetic patients exclusively, one allowed enrollment for people with or without T2DM, and the other trials excluded those with T2DM. All trials offered diet and exercise or behavioral counseling therapy as background therapy. Trial durations were 68 weeks for 6 trials and 104 weeks for one trial. Five trials enrolled patients with a BMI of at least 30 kg/m^2 or those with a BMI of 27 kg/m^2 and at least one comorbidity.[1] One trial required participants to have a BMI of at least 27 kg/m^2. One trial included those with a BMI of at least 27 kg/m^2 plus at least 2 comorbidities or a BMI of 35 kg/m^2 plus at least 1 comorbidity.[1] Majority of trials enrolled patients in their mid 40's to early 50's with baseline BMIs around 38 kg/m^2. Trials were considered to have a moderate risk of bias due to conflicts of interests. Enrollment of participants with differing baseline characteristics (e.g., diabetes) caused heterogeneity across the included studies.[1]

Semaglutide was associated with favorable results for all weight loss outcomes (e.g., change in BMI and body weight) in which decreases met the threshold for being clinically meaningful (**Table 5**). In the trial, enrolling people with T2DM, the treatment effect was less when compared to the trials studied in participants without diabetes (change in body weight compared to placebo, MD -6.22% for patients with diabetes versus -12.53% for those without diabetes). Reasons for the difference between study results are not entirely clear, and additional studies are needed to clarify these results. The one trial which studied patients out to 104 weeks found percent change in body weight increased slightly from week 52 to 104 in both the semaglutide and placebo group, but not back to baseline in either group.[1] There was low quality evidence that semaglutide treatment resulted in a decrease in SBP and LDL cholesterol more than placebo, but by a magnitude which did not meet established thresholds for clinically meaningful differences (low quality of evidence). Low quality evidence found semaglutide decreased HbA1c more than placebo, which was statistically and clinically meaningful (MD -0.43%; 95% CI, -0.55 to -0.30; p<0.001).[1] The evidence for the decrease in HbA1c mostly came from 2 trials which enrolled participants with T2DM (all participants had T2DM in the first trial and 25% had T2DM in the second trial). Changes in quality of life were not significantly different between semaglutide and placebo.[1] There was moderate quality evidence for more withdrawals due to AE in those treated with semaglutide compared to placebo (RR 1.81; 95% CI, 1.34 to 2.44; p<0.001). The most common AEs were nausea, constipation, diarrhea and vomiting. Evidence for changes in medication use were considered exploratory and were small subpopulations of study participants.

One study evaluated the comparison of semaglutide 2.4 mg to liraglutide 3.0 mg and placebo (n=253) enrolling participants without diabetes.[1] An open-label study design comparison was used for the semaglutide versus liraglutide comparison. For this reason, the trial was considered to be at moderate risk of bias. Semaglutide was found to be superior to liraglutide for weight outcomes based on low quality of evidence. A decrease in body weight percentage was higher with semaglutide compared to liraglutide (MD -9.40%; 95% CI, -11.82 to -6.98; p<0.001) and body weight (MD -8.50 kg; 95% CI, -11.19 to -5.81; p<0.001).[1] Those participants treated with semaglutide were more likely to lose at least 10% more body weight compared to liraglutide (RR 2.77; 95% CI, 1.99 to 3.85; p<0.001).[1] Changes between semaglutide and liraglutide were not statistically different for the outcomes of SBP and LDL cholesterol. Participants randomized to semaglutide had lower HbA1c compared to liraglutide, but differences were not clinically significant (MD -0.2%; 95% CI, -0.2 to -0.1; p-value not reported).[1] About 34-35% of people in each group had prediabetes. There was very low quality evidence that semaglutide participants withdrew from the trial due to AEs less frequently than those randomized to liragutide.[1] Gastrointestinal AEs were common in both groups.

Table 5. Weight Outcomes for Semaglutide in Adults[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI of 27 kg/m^2 and those with 2 or more comorbidities or a BMI of 35 kg/m^2 and 1 or more comorbidity (1 study) - BMI ≥ 27 kg/m^2 (1 study)			

- BMI of 30 kg/m^2 or BMI of 27 kg/m^2 if comorbidities (5 studies) - Those with and without T2DM - Doses Studied**:** Semaglutide 2.4 mg SC weekly (initiated at 0.25 mg and increased every 4 weeks to target dose) - Trials lasted 52-120 weeks			
Change in BMI % (7 RCTs; n=4,997)	MD -11.59% (95% CI, -14.09 to -9.09; p<0.001)	Low	Percent change in body weight were clinically meaningful with semaglutide treatment (5% or more reduction is considered clinically meaningful). Downgraded for significant heterogeneity between studies.
Change in Body Weight (6 RCTs; n=4,190)	MD -12.00 kg (95% CI, -13.32 to -10.68; p<0.001)	Moderate	Patients taking semaglutide lost more weight compared to placebo.
Change in BMI (5 RCTs; n=3,979)	MD -4.25 kg/m^2 (95% CI, -4.75 to -3.76; p<0.001)	Moderate	BMI was reduced with semaglutide compared to placebo.
Proportion with ≥ 5% weight loss (6 RCTs; n=4,786)	RR 2.34 (95% CI, 1.93 to 2.83; p<0.001) ARR 49% /NNT 2	Low	Patients treated with semaglutide were more likely to lose more body weight compared to placebo.
Proportion with ≥ 10% weight loss (7 RCTs; n=4,727)	RR 4.70 (95% CI, 3.53 to 6.26; p<0.001) ARR 54% / NNT 2	Low	Patients treated with semaglutide were more likely to lose more body weight compared to placebo.
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinical trial; SD = standard deviation			

Youth

The use of semaglutide 2.4 mg was compared to placebo in one trial in youth over 68 weeks (**Table 6**).[1] About 4% of participants had diabetes and participants could be taking metformin (percent not reported). Thirteen percent of patients had HTN. Diet and exercise counseling was also provided. Youth had to have a BMI of at least the 95th percentile for their sex and age or the 85th percentile plus at least one comorbidities to be included.[1] Semaglutide demonstrated significant differences in all weight outcomes, clinically and statistically. There is moderate evidence that the reductions in systolic blood pressure were not significantly different from placebo. Semaglutide caused significant reductions in LDL cholesterol compared to placebo (MD -6.08%; 95% CI, -11.90 to -1.70; p=0.009) (moderate evidence).[1] Clinically meaningful decreases (0.3% or more) in HbA1c were demonstrated with semaglutide versus placebo (MD -0.30%; 95% CI, -0.35 to -0.25; p<0.001). There was no difference in withdrawals due to AEs between semaglutide or placebo. Gastrointestinal AEs (e.g., nausea, diarrhea, vomiting, and abdominal pain) were more common with those taking semaglutide.

Table 6. Weight Outcomes for Semaglutide in Youth[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI of ≥95th percentile or ≥85th percentile plus at least one comorbidity - Diabetes (4%)			

Changes in BMI z/SD score (1 RCT; n=201)	MD -01.00 SDs (95% CI, -1.30 to -0.70; p<0.001)	Moderate	Clinically meaningful decreases in weight with semaglutide
Change in BMI % (1 RCT; n=201)	MD -16.70% (95% CI, -20.25 to -13.15; p<0.001)	Moderate	Clinically meaningful reductions in BMI % with semaglutide (5% or more reduction is considered clinically meaningful)
Change in Body Weight (1 RCT; n=201)	MD -17.40% (95% CI, -21.10 to -13.70; p<0.001)	Moderate	Growth and height development can influence weight changes in youth so results aren't clinically meaningful
Proportion with ≥ 5% weight loss (1 RCT; n=201)	RR 4.09 (95% CI, 2.37 to 7.06; p<0.001)	Moderate	Semaglutide caused more weight loss than placebo
Proportion with ≥ 10% weight loss (1 RCT; n=201)	RR 7.67 (95% CI, 3.27 to 17.96; p<0.001)	Moderate	Semaglutide caused more weight loss than placebo
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation			

EXENATIDE

Adults

Exenatide was studied in one RCT active treatment comparison to glyburide in adult patients.[1] In the active treatment trial exenatide 20 mcg daily was compared to oral 15 mg daily of glyburide. Patients (n=128) had T2DM, with HbA1c >8%, and were also taking background metformin. Lifestyle modifications of diet and exercise were used in conjunction with pharmacotherapy. To be eligible, patients had to have a BMI between 25 and 30 kg/m^2.[1] The trial lasted 52 weeks. It was considered to have high risk of bias because it was single-blind and lacked detail on methodology. Only changes in body weight and BMI were studied. There were no statistically significant differences in HbA1c levels or withdrawals due to AEs between the two groups. Cardiovascular outcomes were not reported.

Table 7. Weight Outcomes for Exenatide in Adults[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI of ≥25 to <30 kg/m^2 - Diabetes (100%) - Trial lasted 52 weeks			
Change in Body Weight (1 RCT; n=128)	MD -12.70 kg (95% CI, -15.60 to -9.80; p<0.001)	Moderate	Patients on exenatide lost more weight compared to glyburide, which could be clinically meaningful.
Change in BMI (1 RCT; n=128)	MD -4.10 kg/m^2 (95% CI, -4.59 to -3.61; p<0.001)	Moderate	BMI was reduced with exenatide compared to glyburide.
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation			

Youth

Exenatide was studied in 2 trials enrolling youth (**Table 8**).[1] Both studies enrolled individuals without diabetes and compared exenatide 2.0 mg weekly to placebo. One trial lasted 52 weeks and one trial lasted 24 weeks. One study enrolled individuals who had severe obesity (BMI 1.2, or greater, times 95th percentile or 35 kg/m^2 or greater), and the second trial enrolled those with a BMI of 30 kg/m^2 or greater.[1] There was no difference in SBP or HbA1c between exenatide and placebo (low quality of evidence). Changes in LDL cholesterol levels were mixed. One study demonstrated a small, statistically significant reduction in LDL cholesterol with exenatide compared to placebo and the other study did not (very low quality of evidence).[1] The results may be due to study design differences and differing baseline LDL cholesterol levels. No differences between exenatide and placebo were found for quality of life, based on low quality evidence. Withdrawals due to AEs occurred in only one participant taking exenatide across the 2 trials (very low quality of evidence).[1] There were more gastrointestinal AEs (e.g., nausea, diarrhea, vomiting and constipation) in those taking exenatide compared to placebo.

Table 8. Weight Outcomes for Exenatide in Youth[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI 1.2 times or greater than 95th percentile or 35 kg/m^2 or greater) (1 study) - BMI of 30 kg/m^2 or greater (1 study) - Non-diabetics			
Changes in BMI z/SD score (1 RCT; n=44)	MD -0.09 SDs (95% CI, -0.18 to -0.00; p<0.05)	Very low	Differences in weight loss with exenatide were not clinically meaningful
Change in BMI % (1 RCT; n=66)	MD -4.1% (95% CI, -8.6 to -0.5; p=0.08)	Very low	There were no statistical or clinical differences between groups
Percent of 95th BMI percentile (2 RCTs; n=110)	MD -1.84% (95% CI, -3.18 to -0.49; p=0.008)	Low	Those treated with exenatide experienced significantly more weight loss than those treated with placebo but weight loss may depend on duration of treatment (longer durations may result in more weight loss)
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation			

TIRZEPATIDE

There was one RCT (n=2,539) identified for inclusion into this review. Adult participants without diabetes were randomized to tirzepatide 5.0 mg weekly, 10 mg weekly, or 15 mg SC weekly compared to placebo for 72 weeks (doses were pooled).[1] Patients were eligible for inclusion if they had a BMI of 30 kg/m^2 or more or had a BMI of 27 kg/m^2 or more plus at least one comorbidity. There was moderate evidence of a clinically meaningful difference in percent change in body weight for tirzepatide compared to placebo (MD -15.37%; 95% CI, -16.68 to -14.06; p<0.001).[1] More patients taking tirzepatide lost 5% or more of body weight compared to placebo, (88.3% versus 34.5%; RR 2.56; 95% CI, 2.30 to 2.85; p<0.001). More participants taking tirzepatide lost 10% or more of body weight compared to placebo (76.7% versus 18.8%; RR 4.08; 95% CI, 3.47 to 4.80; p<0.001; moderate quality of evidence).[1] There was a dose-related decrease in weight

loss between the different doses of tirzepatide were -15%, -19.5%, and -20.9%. Treatment discontinuation due to adverse events occurred for 2.6% of people in the placebo group compared to 4.3%, 7.1%, and 6.2% for tirzepatide 5 mg, 10 mg and 15 mg, respectively.[2] Additional study details are presented in Table 15.

NALTREXONE-BUPROPION

Adults

Five placebo-controlled studies evaluated the combination of naltrexone-bupropion in adults. Four studies used the same dose; naltrexone 32 mg and bupropion 360 mg. One study also evaluated 16/360 mg naltrexone-bupropion[1]. One trial included patients with T2DM and the other 4 trials excluded those with T2DM. Trials lasted 52-56 weeks and enrolled 242 to 1,742 patients. Three trials enrolled patients with a BMI between 30 kg/m^2 and 45 kg/m^2 or patients with a BMI between 27 and 45 kg/m^2 plus HTN or hyperlipidemia.[1] One trial included patients with a BMI of ≥27 kg/m^2 and ≤45 kg/m^2. The last trial included patients with a BMI of ≥27 kg/m^2 and HTN or hyperlipidemia. The mean ages ranged from 44-46 years and BMI of 36 kg/m^2 to 37 kg/m^2.[1]

Small, non-significant increases in SBP were demonstrated with naltrexone-bupropion (low strength of evidence).[1] LDL cholesterol was slightly improved with the use of naltrexone-bupropion compared to placebo; however, differences were small and not considered clinically meaningful (low strength of evidence). In the one study which enrolled patients with T2DM, HbA1c levels were reduced with the use of naltrexone-bupropion compared to placebo (MD -0.5%; 95% CI, -0.78 to -0.22; p<0.001), which was considered clinically significant based on low strength of evidence.[1]

Table 9. Weight Outcomes for Naltrexone-Bupropion in Adults[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI of 30 to 45 kg/m^2 or 27 to 45 kg/m^2 or greater with HTN or hyperlipidemia (3 studies) - BMI of ≥27 kg/m^2 and ≤45 kg/m^2(1 study) - BMI of ≥27 kg/m^2 and HTN or hyperlipidemia (1 study) - T2DM (1 study), excluded those with T2DM (4 studies) - Trials lasted 26-56 weeks			
Changes in Body Weight % (4 RCTs; n=4,122)	MD -4.25% SDs (95% CI, -5.07 to -3.42; p<0.001)	Low	Statistically significant decreases in weight with naltrexone-bupropion compared to placebo but differences did not meet thresholds for clinically meaningful changes.
Change in Body Weight (2 RCTs; n=3,023)	MD -4.49 kg (95% CI, -5.28 to -3.71; p<0.001)	Low	Statistically significant decreases in weight with naltrexone-bupropion compared to placebo but differences did not meet thresholds for clinically meaningful changes.
Proportion with ≥ 5% weight loss (4 RCTs; n=3,710)	RR 2.31 (95% CI, 1.66 to 3.23; p<0.001) ARR 29%/NNT 4	Low	Patients treated with naltrexone-bupropion lost more weight than placebo.
Proportion with ≥ 10% weight loss (4 RCTs; n=3,035)	RR 3.12 (95% CI, 2.07 to 4.68; p<0.001) ARR 19.5%/NNT 5	Low	Patients treated with naltrexone-bupropion lost more weight than placebo.

Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation; T2DM = type 2 diabetes mellitus

PHENTERAMINE-TOPIRAMATE

Adults

The use of phen/top in adults was studied in 2 RCTs lasting 56 weeks.[1] The dose was phen/top 15/92 mg daily compared to placebo in both trials in conjunction with lifestyle modifications. Each trial also studied a lower dose, phen/top 3.75/23 mg daily and phen/top 7.5/46 mg daily. The trials enrolled participants with and without diabetes. One study included participants with a BMI of 27 kg/m^2 to 45 kg/m^2 and at least 2 comorbidities; the second study enrolled those with a BMI of 35 kg/m^2 or greater.[1] Change in BMI was not reported in the studies. Studies had a high risk of bias due to lack of details on methods, conflicts of interest, high attrition, and variable discontinuation rates. The mean ages for participants in the trials were 42 to 45 years old. Baseline BMI ranged from 36 kg/m^2 to 42 kg/m^2.

Evidence from 2 RCTs demonstrated that phen/top was statistically and clinically more effective at reducing weight compared to placebo based on moderate quality of evidence (**Table 10**). There was moderate quality evidence that there were not clinically meaningful reductions in SBP, LDL or HbA1c. Withdrawal rates were significantly higher in those randomized to phen/top compared to placebo in trials lasting 1 year.

Table 10. Weight Outcomes for Phentermine/Topiramate in Adults[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI of 27 kg/m^2 to 45 kg/m^2 and at least 2 comorbidities or those with a BMI of 35 kg/m^2 or greater - Included those with and without diabetes - Trials lasted 26 -108 weeks			
Change in body weight % (2 RCTs; n=3513)	MD -8.56% (95% CI, -9.93 to -7.19; p<0.001)	Low	Statistically and clinically meaningful reductions in body weight percent with phen/top compared to placebo.
Change in weight (1 RCT; n= 2487)	MD -8.10 kg (95% CI, -8.86 to -7.34; p<0.001)	Moderate	Phen/top use caused more weight loss compared to placebo
Proportion with 5% or greater weight loss (2 RCTs; n=3444)	RR 3.47 (95% CI, 2.93 to 4.11; p<0.001)	Moderate	Participants treated with phen/top were more likely to lose at least 5% body weight when compared to placebo.
Proportion with 10% or greater weight loss (2 RCTs; n=3444)	RR 6.12 (95% CI, 5.08 to 7.38; p<0.001)	Moderate	Participants treated with phen/top were more likely to lose at least 10% body weight when compared to placebo.
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; RR = relative risk			

Youth

Phen/top was studied for weight loss in adolescents in one RCT (**Table 11**).[1] Doses included phen/top 15/92 mg daily and phen/top 7.5/46 mg daily compared to placebo. Doses were pooled for outcome analysis. Eligible participants had to have a BMI of 95th percentile or greater, for sex and age. Outcomes were assessed at 56 weeks, and all participants received background diet and exercise counseling. The study was considered to have a high risk of bias due to lack of details on methods, study design, and conflicts of interest.

Phen/top resulted in statistically and clinically meaningful decreases in weight outcomes (**Table 10**).[1] There was no clinically significant differences between semaglutide and placebo based on a low quality evidence.[1] Withdrawals due to AEs were not different between phen/top and placebo (very low quality evidence).

Table 11. Weight Outcomes for Phentermine-Topiramate in Youth[1]

Outcomes	Results	Strength of Evidence	Comments
General study characteristics: - BMI of 95th percentile or greater - Diabetes not reported			
Changes in BMI z/SD score	Not reported	N/A	N/A
Change in BMI % (1 RCTs; n=223)	MD -9.70% (95% CI, -12.93 to -6.47; p<0.001)	Low	Statistically and clinically meaningful reductions in percent of BMI with phen/top (5% or more reduction is considered clinically meaningful)
Change in BMI (kg/m^2) (1 RCTs; n=223)	MD -4.83 kg/m^2 (95% CI, -5.86 to -3.79; p<0.001)	Low	Phen/top significantly reduced BMI compared to placebo
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; N/A = not applicable; RCT = randomized clinically trial; SD = standard deviation			

SETMELANOTIDE

Setmelantotide was studied in 3 trials, one was a RCT. Setmelanotide 3.0 mg daily was given to people with obesity caused by genetic variants.[1] Variants included in the studies were Bardet-Biedl syndrome, Alstrom syndrome, proopiomelanocortin (POMC) deficiency and leptin receptor (LEPR) deficiency. In the RCT, participants (n=69) were a mean age of 21 years and were treated for 14 weeks with either setmelanotide or placebo.[1] Placebo treated patients were transferred to setmelanotide after 14 weeks to an additional 52 weeks in an open-label study. Studies enrolled people with or without diabetes and the one RCT also included nutritional counseling. All studies were considered to have a high-risk of bias.

More weight loss was reported with setmelanotide compared to placebo in all 3 trials with percent body weight loss ranging from -5.5% to -25%. In the RCT the change in body weight percent between setmelanotide and placebo was -2.1% (95% CI, -4.6 to 0.4; p=0.052).[1] The pooled weight loss results were also not statistically significant and quality of evidence was graded as very low. There were no statistically significant differences between setmelanotide and placebo for comorbidity risk factors (very low quality evidence). Quality of life measures were higher in those taking setmelanotide compared to placebo; however, p-values

were not reported. Withdrawals due to adverse events were lower in those treated with setmelanotide compared to placebo but not they were not significant (RR 0.33; 95% CI, 0.04 to 2.93; p=0.32).[1]

Guidelines:

New Guidelines:

NICE- Liraglutide for Managing Overweight and Obesity

In 2023 NICE published guidance for the use liraglutide in the management of patients who are overweight or obese.[8] NICE recommends that if liraglutide is used then it should be used in conjunction with a reduced-calorie diet and increased physical activity. Recommendation are focused on adults that have a high risk of experiencing the adverse consequences of obesity. Adults who are candidates for liraglutide should have the following clinical criteria:[8]

- A BMI of at least 35 kg/m^2. Some ethnic groups are known to be at equivalent risk for consequences of obesity at a lower BMI compared to people who identify as white. These populations should have a BMI of at least 32.5 kg/m^2 and
- A diagnosis of non-diabetic hyperglycemia (an HbA1c of 6.0% to 6.4%) or a fasting plasma glucose of 99 mg/dl to 124.2 mg/dl and
- A high risk of CV disease based on risk factors such as HTN and dyslipidemia and
- Prescribed by a specialty multidisciplinary tier 3 weight management service. Tier 3 weight management services provide dietary, lifestyle and behavior modification with psychological support.

NICE – Semaglutide for Managing Overweight and Obesity

In March of 2023, NICE published guidance for the use of semaglutide.[7] Evidence showed that adults that use semaglutide with a supervised weight management support lose more weight than management support alone. Semaglutide was associated with more weight loss than liraglutide. Semaglutide use in adults with non-diabetic hyperglycemia, who also used lifestyle modifications, had more normalized blood glucose levels more often than lifestyle modifications alone.[7] Semaglutide has been shown to reduce the risk of CV disease.

The recommendations for semaglutide, in conjunction with a reduced-calorie diet and increased physical activity, in adults for weight management are as follows[7]:

- Maximum use of 2 years and in conjunction with a specialist weight management service providing management of overweight and obesity AND
- Presence of one weight related comorbidity AND
- A BMI of:
    - At least 35 kg/m^2 or
    - 30 kg/m^2 to 34.9 kg/m^2 and meet the criteria for referral to a specialist weight management services (e.g. has not been able to manage weight with education on diet, nutrition, lifestyle and behavior advice for up to 12 weeks)
    - Lower BMI thresholds are recommended for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds. Usually a reduction of 2.5 kg/m^2.

Reassessment of semaglutide efficacy should be performed at 6 months, and if there is less than a 5% weight loss from the initial weight, then consider discontinuing therapy.

NICE- Obesity: Identification, Assessment and Management Clinical Guideline

A 2023 publication from NICE offers updated guidance, from their original publication in 2014, on the pharmacotherapy recommendations for children and adults who are obese.[9] Diet, exercise and behavioral therapy is recommended before pharmacotherapy should be offered. If target weight loss had not been achieved, then drug treatment may be considered, along with continued counseling on diet, physical activity and behavior strategies.

Drug treatment recommendations include liraglutide, semaglutide and orlistat.[9] Naltrexone-bupropion is not recommended for weight management by NICE due to lack of long-term effectiveness data and unknowns regarding cost-effectiveness. Specific recommendations by NICE regarding the use of liraglutide and semaglutide are discussed above. NICE recommends that orlistat be an option for those with a BMI of at least 30 kg/m^2 or at least 28 kg/m^2 with associated risk factors (risk factors not specifically described).[9] Reassessment at 3 months is recommended with continuation of therapy if at least 5% of initial body weight has been lost since starting orlistat.

In children younger than 12 years of age, drug therapy for weight management is not routinely recommended by NICE.[9] Drug therapy in children 12 and younger should only be done by a pediatric specialist. Orlistat is recommended for children 12 and older if physical comorbidities (e.g., orthopedic problems or sleep apnea) are severe and drug therapy is recommended by a pediatric specialist.[9] A 6 to 12-month trial is recommended with follow-up for assessment of adverse reactions, effectiveness and adherence.

VA/DOD – Clinical Practice Guideline for the Management of Adult Overweight and Obesity

In a 2020 guideline the VA/DOD reviewed evidence for weight management including the use of pharmacotherapy.[10] Twenty-three studies were included, 5 had high risk of bias. Bias was commonly attributed to lack of details on allocation concealment. The VA/DOD strongly recommends comprehensive lifestyle interventions (CLI) that include behavioral, dietary, and physical activity aspects for adults that are overweight or obese. There is evidence for sustained weight loss with CLI in addition to improvements in obesity related conditions.

The recommendation for the use of long-term pharmacotherapy was considered weak; however, the recommendation was based on moderate quality evidence for the outcomes of weight loss and 5% to 10% weight loss compared to placebo. Treatments evaluated include: liraglutide, naltrexone/bupropion, orlistat, or phen/top (**Table 12**).[10] Patients are candidates for treatment if they have BMI of at least 30 kg/m^2 or have a BMI of 27 kg/m^2 with obesity-associated comorbidities. Pharmacotherapy should be used in conjunction with a CLI. There was a statistically significant increase in discontinuations due to adverse events, compared to placebo, for all medications studied.[15] The highest rate of discontinuations was found with liraglutide. The effect of weight management medications on cardiometabolic parameters were inconsistent.

Table 12. Evidence for Long-term Weight Loss Medications[10]

Medications	Mean weight loss versus placebo	5% or more weight loss (odds ratio)	10% or more weight loss (odds ratio)	Discontinuations due to Adverse Events (odds ratio)
Phentermine/topiramate	-8.8 kg	9.22	11.40	2.29
Liraglutide	-5.24 kg	5.54	4.99	2.95
Naltrexone/bupropion	-4.95 kg	3.96	4.19	2.64
Orlistat	-2.63 kg	2.70	2.42	1.84

Evidence for use of medications to maintain weight loss was also evaluated, emphasizing the importance of initial weight loss and maintenance of weight loss. Liraglutide was associated with a higher number of patients maintaining initial weight loss when compared to placebo.[15] Weight is often regained after discontinuation of weight management medications and long-term therapy is needed.[10]

There was insufficient evidence for the short-term, long-term or intermittent use of phentermine monotherapy, benzphetamine, diethylpropion, or phendimetrazine based on low quality evidence. The recommendation was neither in support or against the use of these therapies.

Limitations to the evidence include very specific inclusion and exclusion criteria for enrollment into the studies, particularly due to comorbidity requirements which exclude many in the general population. There was a higher rate of female participants enrolled across most the studies. Attrition was high (above 30%) in most studies. Long-term outcome data is lacking for efficacy and safety outcomes.

CADTH – Semaglutide Reimbursement Recommendation

A 2022 review from CADTH evaluated the evidence for the use of semaglutide in people who are overweight or obese.[11] The recommendation was made before the publication of the SELECT trial (**Table 15**), which found semaglutide reduced the risk of CV events more than placebo in adult patients with CV disease who are overweight or obese.[5] Evidence cited for the reasoning for the recommendation was the lack of data demonstrating preventing or reducing the risk of weight-related comorbidities (e.g., HTN, CV disease). There was also insufficient evidence for improvements in health-related quality of life with the use of semaglutide.

Therefore, semaglutide was not recommended as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m2 or greater or 27 kg/m2 or greater in the presence of at least 1 weight-related comorbidity (e.g., hypertension, T2DM, dyslipidemia, or obstructive sleep apnea).[11]

ICER – Medications for Obesity Management: Effectiveness and Value

The Institute for Clinical and Economic Review (ICER) released guidance on the use of pharmacotherapy for weight management.[12] Medications FDA approved for weight management (e.g., semaglutide, liraglutide, phen/top, and bupropion/naltrexone), in addition to lifestyle interventions, were compared to placebo. Types of lifestyle management programs varied for the included studies, from diet and exercise counseling to intensive behavioral therapy (IBT) and meal replacement programs. Weight loss outcomes, HRQoL, weight gain and weight-related comorbidities (e.g., HbA1c, SBP, and LDL) were evaluated. Evidence of comparative clinical effectiveness was graded from highest (A) to lowest (I).

Evidence demonstrated efficacy of weight management drugs in adults without diabetes and who had obesity or overweight (BMI of 27 kg/m2 or greater) with at least one weight-related comorbidity (**Table 13**).[12] Indirect and direct evidence found semaglutide and phen/top caused greater weight loss compared to liraglutide and bupropion/naltrexone. Long-term data is lacking. All drugs were found to have higher discontinuation rates compared to placebo. There was insufficient evidence on sustained weight loss and weight regain upon medication discontinuation.

Table 13. ICER Evidence Ratings of Weight Management Pharmacotherapy[12]

Pharmacotherapy	Comparator	Evidence Rating
Semaglutide	Lifestyle modification	B+
Liraglutide	Lifestyle modification	B

Phen/Top	Lifestyle modification	C++
Bupropion/naltrexone	Lifestyle modification	C+
Semaglutide*	Liraglutide	C+
	Phentermine/topiramate	C+
	Bupropion/naltrexone	C++
* Based on direct and indirect comparisons		

ADA – Standards of Care: Recommendations for Obesity and Weight Management

In 2024 the ADA published guidance on the use of pharmacotherapy in patients with T2DM.[14] Recommendations are graded from A to E, strongly recommended to expert consensus. Management of obesity has demonstrated evidence for delaying the progression of prediabetes to diabetes. In those with T2DM, a weight reduction of 3-7% has shown to improve glucose levels and other CV risk factors.[14] A sustained weight loss of 10% or more may potentially lead to remission of T2DM and improved CV outcomes.

ADA recommends pharmacotherapy that has beneficial weight loss effects to reduce blood glucose in patients with T2DM who are overweight or obese (Grade A). Therapies with clinical meaningful weight loss are the following: GLP-1 RAs, GLP-1 RA/GIP RAs, sodium glucose cotransporter 2 (SGLT-2) inhibitors, metformin and amylin mimetics.[14] Weight neutral options include the dipeptidyl peptidase 4 (DPP-4) inhibitors, alpha-glucosidase inhibitors, central acting dopamine agonists (e.g., bromocriptine) and bile acid sequestrants. Weight gain is associated with insulin, sulfonylureas, meglitinides, and thiazolidinedione. Structured lifestyle programs, in conjunction with pharmacotherapy, are also strongly recommended (Grade A).[14]

Providers should also review patient medications to ensure concomitant medications (e.g., antipsychotics, antidepressants, steroids) are not contributing to weight gain.[14]

All therapies are associated with potential safety concerns with long term use. Phentermine/topiramate is contradicted with use of monoamine oxidase inhibitors (MOAIs) and may cause birth defects, cognitive impairment, and acute angle glaucoma.[14] Naltrexone/bupropion should not be used in those with uncontrolled hypertension and/or seizure disorders, chronic opioid therapy, acute angle glaucoma and there is a boxed warning of an increased risk of suicidal behavior in those younger than 24 years with depression.[14] The GLP-1 RAs and dual GIP RAs/GLP-1 RAs have a boxed warning of the risk of thyroid C-cell tumors in rodents. They also have a risk of pancreatitis, precautions in those with kidney disease, may cause GI disorders, cholelithiasis and gallstone-related complications. Tirzepatide may also influence concentrations of narrow therapeutic index drugs and contraceptives.[14]

The preferred treatment option in patients with T2DM and are overweight or obese is a GLP-1 RA or GLP-RA/GIP RA as they have evidence of the largest amount weight loss potential such as semaglutide or tirzepatide (Grade A).[14]

American Academy of Pediatrics– Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity

The AAP released their first guidance on managing obesity in children and adolescents in January 2023.[15] Methodology was well described. Conflicts of interest were solicited and reported by one author. Recommendations were graded from Level A, high quality evidence, to Level D, expert opinion. An additional evidence designation of Level X was given to situations which were “validating studies cannot be performed and there is clear preponderance of benefit or harm”.

BMI is as useful evaluation measure to identify children and adolescents who are obese or overweight.3/27/2024 2:25:00 PM Evidence has demonstrated that BMI correlates well with direct measures of body fat, bioelectrical impedance, densitometry, and dual-energy x-ray absorptiometry.[15] The use of BMI may under- or over detect adiposity in specific ethnic and racial groups, as BMI does not directly measure body composition. Additionally, some children who have a high fat-free mass may be categorized as overweight or obese.[15]

Intensive health behavior and lifestyle treatment (IHBLT) is recommended for children and adolescents who are overweight or obese (**Table 14**).[15]

Drug therapy may be considered in children 8 years of age and older, in addition to IHBLT.[15] Evidence for the use of weight reduction therapies in children and adolescents included the following: metformin, exenatide, orlistat or other medications (phentermine, mixed carotenoids, topiramate, ephedrine and recombinant human growth hormone).[15] Additional therapies (e.g., setmelanotide, liraglutide, and combination phentermine/topiramate) have evidence for use that was published after the initial evidence review and are included as well. Recommendations for the use of pharmacotherapy in children and adolescents are presented below. Evidence for specific therapy recommendations were not graded.

- Metformin: can be considered as an adjunct to IHBLT in patients when other indications for metformin are present (e.g., polycystic ovary syndrome, prediabetes, prevention of weight gain when used with an atypical antipsychotic). Metformin is not FDA approved for weight loss but is approved for T2DM in patients 10 and older.[15]
- Orlistat: approved for children 12 and older for the long-term treatment of obesity.[15]
- GLP-1 RAs (semaglutide, liraglutide, dulaglutide, exenatide): exenatide is approved for use in children 10-17 years with T2DM. GLP-RAs are associated with BMI reductions of 0.9 to 1.8 U. Liraglutide was associated with a 4.5 kg weight reduction. Liraglutide and semaglutide are approved for weight loss in youth 12 and older.[15]
- Melanocortin 4 receptor (MC4R) agonist (e.g., setmelanotide): setmelanotide demonstrated weight loss of 12% to 25% in one uncontrolled study in those with rare genetic deficits.[15] Setmelanotide is approved for use in those patients 6 years and older with proopiomelanocortin (POMC) deficiency, proprotein subtilisin or kexin type 1 deficiency, and leptin receptor deficiency.[15]
- Phentermine: approved for short-course therapy, up to 3 months, in those 16 years and older.[15]
- Topiramate: approved for use in children 2 years and older for epilepsy and headache prevention. One study in children did not show benefits over placebo for weight management. Topiramate is FDA -approved in adults for binge eating disorder.[15]
- Phentermine and topiramate: evidence has demonstrated weight loss with a BMI reduction of -10.44% (phen/top 15 mg/92 mg) and -8.11% (phen/top 7.5 mg/92 mg) compared to placebo. Phen/top is approved for weight loss in adults.[15]
- Lisdexamfetamine: approved for binge eating disorder in those 18 and older. Lisdexamfetamine is approved for attention-deficit/hyperactivity disorder (ADHD) in children 6 and older. There is insufficient evidence for use in children to assist in weight management.[15]

Table 14. Recommendations from the American Academy of Pediatrics[15]

Recommendation	Grade of Recommendation
Pediatricians and other primary health care providers (PHCP) should measure height and weight, calculate BMI, and assess BMI percentile using age- and sex-specific Centers for Disease Control and Prevention growth charts or growth charts for children with severe obesity	B

(assessment interval not reported) or at least annually for all children 2 to 18 years of age to screen for overweight (BMI ≥85th percentile to <95th percentile), obesity (BMI ≥95th percentile) and severe obesity (BMI ≥120% of the 95th percentile for age and sex).	
Pediatricians and other PHCPs should provide or refer children 6 years and older (Grade B) and may provide or refer children 2 through 5 years of age (Grade C) with overweight (BMI ≥85th percentile to <95th percentile) and obesity (BMI ≥95th percentile) to intensive health behavior and lifestyle treatment. Health behavior and lifestyle treatment is more effective with greater contact hours; the most effective treatment includes 26 or more hours of face-to-face, family-based, multicomponent treatment over a 3 to 12-month period.	B and C
Pediatricians and other PHCPs should offer weight loss pharmacotherapy to adolescents 12 years and older with obesity (BMI ≥95th percentile) according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.	B

New Approvals:

Tirzepatide (ZEPBOUND):

In November 2023, tirzepatide received an FDA approved indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of:[16]

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) with the presence of at least one weight-related condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea or CV disease)

Approval was based off of 2 double-blind, placebo-controlled, RCTs (SURMOUNT-1 and SURMOUNT-2).[16] The primary endpoint, mean percent change in body weight and the percentage of patients achieving a 5% or more weight reduction compared to placebo, was assessed at 72 weeks. Tirzepatide was titrated over 20 weeks to a maintenance dose of 5 mg (one study only), 10 mg or 15mg subcutaneously once weekly. Tirzepatide was used in conjunction with a reduced calorie diet (500 kcal/day deficit approximately) and physical activity of 150 min/week. Patients in SURMOUNT-1 lost more weight taking tirzepatide compared to placebo, mean difference of -11.9% to -17.8%.[16] In SURMOUNT-2, treatment with tirzepatide resulted in a mean weight loss compared to placebo of -9.6% and -11.6%. Higher doses were associated more weight reduction.

Table 15. Randomized Clinical Trials

Study	Drug	Population	Primary Endpoint	Results	Comments
Aronne, et al[6] (SURMOUNT-4) DB, PC, Phase 3, RCT	Tirzepatide 10 or 15 mg SC weekly (maximum tolerated dose) Vs. Placebo	Adults with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 and weight-related complication, excluding diabetes (n=783, open-label) (n=660, double-blind)	Mean percent change in weight from week 36 to week 88 who maintained a least 80% of the weight-loss during the lead-in period	Mean percent weight change: Tirzepatide: -5.5% Placebo: 14.0% (MD -19.4%; 95% CI, -21.2% to -17.7%; P<0.001)	71% women, 89.5% of patients receiving tirzepatide at 88 weeks maintained at least 80% of weight loss compared to 16.6% receiving placebo (p<0.001)

	36 week open-label lead-in period followed by a 52-week, double-blind, placebo-controlled trial.				
Garvey, et al[3] (SURMOUNT-2) DB, PC, Phase 3, RCT	Tirzepatide 10 or 15 mg SC weekly (maximum tolerated dose) Vs. Placebo (72 weeks duration – including a 12 to 20 weeks of dose escalation)	Adults with a BMI of $\geq$27 kg/m^2, with T2DM and HbA1c of 7% to 10% (n=1514)	Co-primary endpoints of percent change in bodyweight from baseline and bodyweight reduction of 5% or higher	Least squares mean change in body weight: Tirzepatide 10 mg: -12.8% Tirzepatide 15 mg: -14.7% Placebo: -3.2% Tirzepatide 10 mg vs. placebo: -9.6% (95% CI, -11.1% to -8.1%); p<0.0001 Tirzepatide 15 mg vs. placebo: -11.6% (95% CI, -13.0% to -10.1%); p<0.0001 Bodyweight reduction of 5% or higher: Tirzepatide 10 mg: 79% Tirzepatide 15 mg: 83% Placebo: 32% P<0.0001 Tirzepatide 10 mg vs. placebo: OR 8.3 (95% CI, 5.6 to 12.3) P<0.0001 ARR 47% /NNT 3 Tirzepatide 15 mg vs. placebo: OR 10.5 (95% CI, 6.8 to 16.1) P<0.0001 ARR 51% /NNT 2	Mean age of 54.2 years, 76% white, 51% female with a baseline BMI of 36.1 kg/m^2.

Jastreboff, et al[2] (SURMOUNT-1) DB, PC, Phase 3, RCT	Tirzepatide 5*, 10 or 15 mg SC weekly (maximum tolerated dose) Vs. Placebo (72 weeks duration including a 20-week dose-escalation phase) * Tirzepatide 5 mg was analyzed as a secondary endpoint and was not part of the co-primary endpoint.	Adults with a BMI of $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with at least one weight related complication (excluding diabetes) (n=2539)	Co-primary endpoints of percent change in bodyweight from baseline and bodyweight reduction of 5% or higher	Mean change in body weight: Tirzepatide 5 mg: -15.0% Tirzepatide 10 mg: -19.5% Tirzepatide 15 mg: -20.9% Placebo: -3.1% Tirzepatide 5 mg vs. placebo: -11.9% (95% CI, -3.4% to -10.4%); p<0.001 Tirzepatide 10 mg vs. placebo: -16.4% (95% CI, -17.9% to -14.8%); p<0.001 Tirzepatide 15 mg vs. placebo: -17.8% (95% CI, -19.3% to -16.3%); p<0.001 Bodyweight reduction of 5% or higher: Tirzepatide 5 mg: 85% Tirzepatide 10 mg: 89%% Tirzepatide 15 mg: 91% Placebo: 35% P<0.001 Tirzepatide 5 mg vs. placebo: ARR 50% / NNT 2 Tirzepatide 10 mg vs. placebo: ARR 54% / NNT 2 Tirzepatide 15 mg vs. placebo: ARR 56% / NNT 2	Mean baseline BMI 38.0 kg/m^2, mean age of 44.9 years, 67.5% female and 70.6% white.
Knop, et al[17] (OASIS 1) DB, PC, Phase 3, RCT	Semaglutide 50 mg orally Vs. Placebo daily	Adults with a BMI of least 30 kg/m^2 or at least 27 kg/m^2 with bodyweight-related complications and comorbidities, without T2DM	Co-primary endpoints of percent change in bodyweight from baseline and bodyweight	Mean change in bodyweight: Semaglutide: -15.1% Placebo: -2.4% ETD -12.7% (95% CI, -14.2 to -11.3) P<0.0001 Bodyweight reduction of 5% or higher:	Adults enrolled with comorbidities were most likely to have hypertension (46%) or dyslipidemia (40%). Seventy-three percent of participants were female, mean BMI was

	(17 months)	(n=667)	reduction of 5% or higher	Semaglutide: 269 (85%) Placebo: 76 (26%) P<0.0001 ARR 59%/NNT 2	37.5 kg/m^2 and average age of 50 years.
Lincoff, et al[5] (SELECT Trial) DB, PC, Phase 3, RCT	Semaglutide 2.4 mg SC weekly Vs. Placebo (mean exposure of 34.2 months)	Adults with CV disease, and BMI of 27 kg/m^2 or greater and no diabetes (n=17604)	Composite of death from CV causes, nonfatal MI or nonfatal stroke	CV end-point event: Semaglutide: 569 (6.5%) Placebo: 701 (8.0%) HR 0.80 (95% CI, 0.72 to 0.90) P<0.001 ARR 1.5%/NNT 67	Mean duration of exposure was 34.2 months, mean age was 61.6 years, 73% male, and 84% White. Mean bodyweight was a BMI of 33 kg/m^2. Individual components of composite endpoint were not statistically different between semaglutide and placebo. Sixty-seven people would need to be treated for approximately 34 months to prevent one CV event.
Wadden, et al[4] (SURMOUNT-3) DB, PC, Phase 3, RCT	Tirzepatide 10 or 15 mg SC weekly (maximum tolerated dose) Vs. Placebo (72 weeks duration)	Adults with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with at least one weight related complication (excluding diabetes) who achieved ≥5.0% weight reduction in 12-week intensive lifestyle program (n=579)	Co-primary endpoints of percent change in bodyweight from baseline and bodyweight reduction of 5% or higher	Least squares mean change in body weight: Tirzepatide 10 mg and 15 mg (pooled results): -18.4% Placebo: -2.5% Tirzepatide vs. placebo: -20.8% (95% CI, -23.2% to -18.5%); p<0.001 Bodyweight reduction of 5% or higher: Tirzepatide 10 mg and 15 mg (pooled doses): 87.5% Placebo: 16.5% OR 34.6 (19.2 to 62.6) P<0.001 ARR 71% / NNT 2	Baseline BMI was 39 kg/m^2, mean age of 46 years, 63% female and 86% White.
Abbreviations: ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; CV = cardiovascular; DB = double-blind; HbA1c = hemoglobin A1c; MD = mean difference; MI = myocardial infarction; NNT = number needed to treat; OR = odds ratio; PC = placebo-controlled; RCT = randomized controlled trials; SC = subcutaneous; T2DM = type 2 diabetes mellitus					

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route
benzphetamine HCl	BENZPHETAMINE HCL	TABLET	Oral
diethylpropion HCl	DIETHYLPROPION HCL	TABLET	Oral
diethylpropion HCl	DIETHYLPROPION HCL ER	TABLET ER	Oral
liraglutide	SAXENDA	PEN INJCTR	Subcutaneous
orlistat	ORLISTAT	CAPSULE	Oral
orlistat	XENICAL	CAPSULE	Oral
phendimetrazine tartrate	PHENDIMETRAZINE TARTRATE ER	CAPSULE ER	Oral
phendimetrazine tartrate	PHENDIMETRAZINE TARTRATE	TABLET	Oral
phentermine HCl	ADIPEX-P	CAPSULE	Oral
phentermine HCl	PHENTERMINE HCL	CAPSULE	Oral
phentermine HCl	ADIPEX-P	TABLET	Oral
phentermine HCl	LOMAIRA	TABLET	Oral
phentermine HCl	PHENTERMINE HCL	TABLET	Oral
semaglutide	WEGOVY	PEN INJCTR	Subcutaneous
setmelanotide acetate	IMCIVREE	VIAL	Subcutaneous
tirzepatide	ZEPBOUND	PEN INJCTR	Subcutaneous
naltrexone/bupropion	CONTRAVE	TABLETS	Oral
Phentermine/topiramate	QSYMIA	CAPSULES	Oral

Appendix 2: Search History

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 05, 2024

Search Strategy:

#	Searches	Results
1	Benzphetamine/	326
2	diethylpropion.mp. or Diethylpropion/	399
3	liraglutide.mp. or Liraglutide/	4247
4	orlistat.mp. or Orlistat/	2408
5	phendimetrazine.mp.	110
6	phentermine.mp. or Phentermine/	1298
7	semaglutide.mp.	1482
8	setmelanotide.mp.	99
9	tirzepatide.mp.	373
10	naltrexone.mp. or Naltrexone/	11344
11	bupropion.mp. or Bupropion/	5700
12	phentermine.mp. or Phentermine/	1298
13	topiramate.mp. or Topiramate/	5834
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	31140
15	limit 14 to (english language and humans and yr="2022 -Current")	1896
16	limit 15 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	241

Weight Management Drugs for Youth

Goal(s):

- Allow case-by-case review for members covered under the EPSDT program. Recommend semaglutide as weight reduction pharmacotherapy in patients which evidence has demonstrated efficacy, including CV benefits. (e.g. patients with a BMI ≥30 kg/m^2 or with a BMI of ≥27 kg/m^2 and comorbid conditions [e.g., diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease]).

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs used for weight management.

Table 1. Drugs FDA Approved for Weight Management

Drug	Adults	Pediatrics
Liraglutide (SAXENDA)	Yes	Yes – 12 years and older
Naltrexone/bupropion (CONTRAVE)	Yes	No
Phentermine/topiramate (QSYMIA)	Yes	Yes – 12 years and older
Semaglutide (WEGOVY)	Yes	Yes – 12 years and older
Tirzepatide (ZEPBOUND)	Yes	No
Setmelanotide (IMCIVREE)	Yes	Yes – 6 years and older

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 2. BMI Cutoffs for Obesity by Sex and Age for Pediatric Patients Aged 12 Years and Older (CDC Criteria)

Age (years)	Body mass index (kg/m2) at 95% percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8

14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy after an initial approval by FFS?	**Yes**: Go to renewal criteria	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is requested medication for a patient less than 21 years of age and 12 years of age or older?	**Yes:** Go to #5	**No:** Deny; weight loss drugs are not covered by OHP for adults
5. Is the request for setmelanotide?	**Yes**: Go to #6	**No:** Go to #8
6. Does the patient have obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance OR does the patient have Bardet—Biedl syndrome (BBS)?	**Yes**: Go to #7	**No:** Deny; medical appropriateness.
7. Does the patient have a history of depression and/or suicidal ideation?	**Yes**: Deny; medical appropriateness.	**No:** Approve for up to 6 months.

Approval Criteria		
8. Does the patient have a BMI corresponding to 30 kg/m^2 or ≥27 kg/m^2 and comorbid conditions [e.g., diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease] for adults or a BMI at the 95th percentile or greater for age and sex (Table 2 above)?	**Yes:** Go to #9 Record baseline BMI	**No:** Deny; medical appropriateness
9. Does the patient have comorbidities (e.g., hypertension, dyslipidemia, diabetes, fatty liver disease, depression, or sleep apnea)?	**Yes:** Go to #11	**No:** Go to #10
10. Has the patient previously tried a weight loss treatment plan administered by a health care provider (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) for a time period of at least 3 months within the previous 6 month timeframe*? * See Clinical Notes Below	**Yes:** Go to #11	**No:** Deny; medical appropriateness. Lifestyle modifications are recommended by guidelines.
11. Will the patient be engaged in a weight management lifestyle modification program in addition to pharmacotherapy?	**Yes:** Approve for 6 months. Medication supply is subject to quantity limits.	**No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.

Renewal Criteria		
1. Is this a request for a weight loss medication previously approved under the EPSDT program?	**Yes**: Go to #2	**No:** Go to **Approval Criteria** above
2. Is the person requesting the medication less than 21 years of age?	**Yes:** Go to #3	**No:** Deny; weight loss not covered by OHP
3. Has the patient lost at least 1% of BMI from baseline or maintained at least a 1% BMI weight loss?	**Yes:** Go to #4	**No:** Deny; medical appropriateness
4. Is the patient continuing with a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet)?	**Yes:** Go to #5	**No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.
5. Has the patient been adherent to therapy based on provider attestation?	**Yes:** Approve for 6 months	**No:** Deny; medical appropriateness

P&T/DUR Review: 4/24 (KS)
Implementation: TBD

*Clinical Notes

Adapted from the following guideline on the treatment of adolescents with obesity:

- American Academy of Pediatrics. *Pediatrics*. 2023;151(2): e2022060640. Available at: https://publications.aap.org/pediatrics/article/151/2/e2022060640/190443/Clinical-Practice-Guideline-for-the-Evaluation-and?autologincheck=redirected

Recommended Behavior Strategies	
Strategy	**Description**
1. Reduction in sugar-sweetened beverages (SSBs)	Higher intake of sugar-sweetened beverages (carbonated beverages, sweetened beverages, soda, sports drinks, and fruit drinks) is associated

	with greater weight gain in adults and children. The American Heart Association (AHA) recommends not more than 25 g (6 tsp) each day of added sugar and not more than 1, 8-oz serving of SSB per week. The AAP discourages the consumption of sports drinks and energy drinks for children and adolescents. The AAP statement on fruit juice notes that it is a poor substitute for whole fruit because of its high sugar and calorie content and pediatricians should advocate for elimination of fruit juice in children with excessive weight gain.
2. Choose My Plate	MyPlate is the US Department of Agriculture's (USDA) broad set of recommendations for healthy eating for Americans. These recommendations include multiple healthy diet goals: low in added sugar, low in concentrated fat, nutrient dense but not calorie dense, within an appropriate calorie range without defined calorie restriction, and with balanced protein and carbohydrate. The principles can be adapted to different food cultures. There is a surprising dearth of literature on the impact of these guidelines on health and BMI outcomes and on the most effective education practices. **Available at: USDA choose my plate.gov**
3. 60 minutes daily of moderate to vigorous physical activity	Aerobic exercise, especially for 60 min at a time, is associated with improved body weight in youth although its effect may be small and variable. It is also associated with better glucose metabolism profiles. High-intensity interval training in youth with obesity may improve body fat, weight, and cardiometabolic risk factors, although the effect is variable. The Physical Activity Guidelines for Americans recommends 60 min per day for children and adolescents.
4. Reduction in sedentary behavior	Reduction in sedentary behavior, generally defined as reduced screen time, has consistently shown improvement in BMI measures, although impact is small. Early studies focused on reduced television, a discrete activity that is simpler than current multifunctional electronic devices. The AAP recommends no media use under age 18 month, a 1-hour limit for ages 2–5 years, and a parent- monitored plan for media use in older children, with a goal of appropriate, not- excessive use but without a defined upper limit.
The activities most commonly associated with positive behavior change are: parental involvement in goal setting, problem solving, social support, demonstrating desired behaviors, and home environment modifications to support positive change.	

Abbreviations: AAP – American Academy of Pediatrics; BMI = body mass index; oz = ounce; tsp = teaspoon; USDA = United States Department of Agriculture

Proposed Draft Prior Authorization Criteria for Adults for Modeling Purposes

Weight Management Drugs for Adults

Goal(s):

- To provide guidance for the use of weight management therapies to ensure they are used in the most appropriate patient populations in which evidence supports efficacy and safety.

Length of Authorization:

- Up to 6 months

Requires PA:

- All drugs used for weight management.

Table 1. Drugs FDA Approved for Weight Management

Drug
Liraglutide (SAXENDA)
Naltrexone/bupropion (CONTRAVE)
Phentermine/topiramate (QSYMIA)
Semaglutide (WEGOVY)
Tirzepatide (ZEPBOUND)
Setmelanotide (IMCIVREE)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy after an initial approval?	**Yes**: Go to **Renewal Criteria** below	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #5
5. Is the request for setmelanotide?	**Yes**: Go to #6	**No:** Go to #8
6. Does the patient have obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance OR the patient has Bardet-Biedl syndrome (BBS)?	**Yes**: Go to #7	**No:** Deny; medical appropriateness.
7. Does the patient have a history of depression and/or suicidal ideation?	**Yes**: Deny; medical appropriateness.	**No:** Approve for up to 6 months.

Approval Criteria		
8. Has the patient tried a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet), for at least 3 months duration, within the last 6 months and been unable to meet weight loss goals?	**Yes:** Go to #9	**No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.
9. Does the patient have a BMI $\geq$30 kg/m^2 or a BMI of $\geq$27 kg/m^2 and at least one weight-related comorbid condition (e.g., type 2 diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease)?	**Yes:** Go to #10	**No:** Deny; medical appropriateness
10. Is the patient enrolled in a Medicaid approved lifestyle modification program*?	**Yes:** Approve for up to 6 months to allow for titration. Medication supply is subject to quantity limits.	**No:** Deny; medical appropriateness
* An approved Oregon FFS Medicaid lifestyle modification program is to be determined and should document adherence to diet modifications and physical activity requirements		

Renewal Criteria		
1. Is this a request for a weight loss medication previously approved?	**Yes**: Go to #2	**No:** Go to Approval Criteria above
2. Has the patient lost at least 5% of their BMI from baseline or maintained at least a 5% BMI weight loss?	**Yes:** Go to #3	**No:** Deny; medical appropriateness
3. Is the request for continuation of therapy without a lapse in treatment?	**Yes:** Go to #5	**No:** Go to #4

Renewal Criteria		
4. Is the request for an additional trial of the same or different weight loss drug within the last 2 years AND the medication is being prescribed by a specialist?	**Yes:** Go to #5	**No:** Deny; medical appropriateness. Refer patient to a specialist to ensure appropriate weight loss management.
5. Is the patient continuing with a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) and has been adherent to drug therapy?	**Yes:** Approve for 12 months	**No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.

P&T/DUR Review: 4/24 (KS)
Implementation:

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Review: Bowel Preparations

Date of Review: April 2024 **End Date of Literature Search:** November 29, 2023

Purpose for Class Review:
Review the evidence for drugs used in cleansing the bowel prior to diagnostic or therapeutic colonoscopy. Recommend development of a Preferred Drug List (PDL) class with preferred and nonpreferred agents based on safety and efficacy.

Plain Language Summary:

- Colorectal cancer is cancer of the large intestine (colon) or rectum. The risk for having colorectal cancer is highest in people with a family history of colorectal cancer or polyps, which are small early cancer growths that form in the lining of the intestine. Other risk factors for colorectal cancer include a history of Crohn's disease, ulcerative colitis, cigarette smoking, being overweight, or eating a lot of processed meats and high fat meals. It is recommended that people begin screening for colon cancer at 45 years of age.
- The easiest way to screen for colorectal cancer is by testing the stool for blood at home. This test checks for unusual bleeding in the large intestine, but it will not find polyps. A more through physical exam called a colonoscopy can find small polyps. A colonoscopy lets a doctor look inside the large intestine using an instrument called a scope. During this exam, the doctor checks for unusual inflammation, polyps, and ulcers in the large intestine. Polyps can be removed during the colonoscopy, which decreases the odds of developing cancer.
- Before undergoing a colonoscopy, the large intestine must be completely cleaned so the doctor can get a clear view of the intestinal tract lining. Different medicines called laxatives are used to help empty the large intestine before a colonoscopy. Most doctors prescribe polyethylene glycol (PEG) because is safe and effective. This medicine causes watery diarrhea for several hours to remove stool from the large intestine.
- Polyethylene glycol is supplied as 4 liters (approximately 1 gallon) of liquid which must be taken before the procedure. Many people find it difficult to drink an entire gallon of liquid the night before colonoscopy. For this reason, split-dose dosing is now recommended. In split dosing, one-half of the laxative liquid is taken the night before the procedure and the other half is taken the morning of the colonoscopy. Adding a flavor packet, drinking through a straw, and chilling the solution help improve the taste of the medicine and can reduce side effects such as nausea or bloating.
- An alternative to taking one gallon of PEG solution is a salt-based laxative which is available as a liquid or tablet. These products do not require the patient to drink as much fluid as the PEG products and may be easier for some people to swallow. People with heart failure, kidney problems, or liver disease should not use salt-based laxatives because the large amount of salt in these products can cause serious side effects.
- We recommend at least one PEG product and one oral salt-based laxative be available to Oregon Health Plan members. For all other medicines in this class, the provider must explain to the Oregon Health Authority why their patient needs that medicine. This is process is called prior authorization.

Research Questions:

1. What is the comparative efficacy for saline-based laxatives and PEG 3350 for cleansing the bowel prior to colonoscopy and detecting polyps or adenomas?
2. What are the comparative harms of saline-based laxatives and PEG 3350 laxatives?
3. Are there specific populations (i.e., elderly patients, patients with renal or hepatic disease) in which certain laxative formulations are better tolerated or more effective?

Conclusions:

- A literature search for recently published, high-quality evidence on the safety and efficacy of bowel preparation prior to colonoscopy identified 6 systematic reviews[1-5] and 2 clinical practice guidelines.[6,7]
- Ineffective bowel cleansing prior to colonoscopy increases the risk of not detecting precancerous lesions and increases costs related to repeat procedures.[6]
- A 2019 systematic review and meta-analysis evaluated the efficacy of polyp detection of 2 pre-colonoscopy dosing regimens. Single dose administration was compared with splitting the administration of bowel preparations into 2 doses (split-dose).[1] Medications of interest included high- and low-volume PEG solutions, sodium phosphate, oral sulfate solutions, and the combination product of sodium picosulfate, magnesium oxide, and citric acid (SPMC).[1] Pooled data from 4 randomized controlled trials (RCTs) that compared split-dose versus day-before bowel preparation regimens showed an increased detection rate of adenomas in the split-dose groups (risk ratio (RR) 1.26; 95% confidence interval (CI) 1.10 to 1.44; I^2 = 0%; n=1,258).[1] In addition, when split-dose administration was compared with day-before administration, there was increased detection of advanced adenomas (RR 1.53, 95% CI 1.22 to 1.92; 3 RCTs; I^2 = 0%; n=1,155).[1] Compared with day-before bowel preparation regimens, split-dose bowel preparations regimens increased the detection of adenomas and advanced adenomas.[1]
- A 2020 systematic review and meta-analysis evaluated efficacy of bowel preparation prior to colonoscopy with high-volume PEG products (>2 L [liter]) versus low-volume laxatives (≤ 2 L) administered in split-dose regimens.[2] In the pooled analysis of 17 RCTs (n=7528), no significant differences in adequacy of bowel cleansing were identified between the low- versus high-volume split-dose regimens (86.1% vs. 87.4%; RR 1.00; 95% CI 0.98 to 1.02; I^2 = 17%).[2] Compared with high-volume regimens, low-volume regimens had higher odds for patient completion of the prescribed laxative (86.8% vs. 92.8%; RR 1.06; 95% CI 1.02 to 1.10; p<0.01; I^2 = 85%).[2] When adverse effects (AEs) were evaluated, low-volume regimens had less bloating (RR 0.66, 95% CI 0.48 to 0.92), nausea (RR 0.86, 95% CI 0.46 to 1.00), and vomiting (RR 0.68, 95% CI 0.46 to 1.00) compared with high-volume regimens.[2] Abdominal pain was less likely with high-volume regimens compared with low-volume regimens (RR 1.22; 95% CI 0.73 to 2.03).[2]
- A 2022 systematic review evaluated the efficacy of ultra-low volume (< 1 L) bowel preparation products compared with high-volume (> 2 L) and low-volume (1-2 L) products.[3] In single-arm RCTs, bowel preparation with SPMC 300 mL (milliliters), 1 L PEG with ascorbate (PEG-ASC), sodium phosphate 240 mL, and sodium sulfate solution 354 mL was adequate in 75.2%, 82.9%, 81.9%, and 92.1%, of patients, respectively.[3] However, heterogeneity between studies was considerable (I^2 range: 86 to 98%).[3] Ultra-low volume bowel preparation fluids do not always meet the 90% quality standard for adequate bowel preparation as defined by 2017 European Society of Gastrointestinal Endoscopy (ESGE) guidelines.[3,8]
- A 2023 meta-analysis of 9 RCTs evaluated the safety and effectiveness of 1 L PEG-ASC compared with other bowel preparation products.[4] The comparators included: 2 L PEG-ASC, 4 L PEG, a trisulfate product (magnesium, potassium, and sodium salts), SPMC, and SPMC plus PEG.[4] The meta-analysis showed a higher bowel cleansing rate with 1 L PEG-ASC than with the other preparations (odds ratio [OR] 1.50; 95% CI 1.25 to 1.81; p<0.01, I^2 = 0%, n=6,720).[4] In addition, a higher right-colon high-quality cleansing rate was found with 1 L PEG-ASC than with the other preparations (OR 1.67; 95% CI 1.21 to 2.31; p<0.01, I^2 = 43%, n= 3,221).[4] The pooled estimate of the adenoma detection rate did not significantly differ between the 2 groups (OR 1.02; 95% CI 0.87 to 1.20; p=0.79, I^2 = 0%, n=3,984).[4] More patients reported AEs with 1 L PEG-ASC than with the other laxatives (OR 1.51; 95% CI 1.23 to 1.84; p<0.01, I^2 = 0%, n=3,500).[4]

- A 2016 systematic review and meta-analysis evaluated the safety and efficacy of SPMC versus PEG-based regimens for colonoscopy preparation.[5] In the meta-analysis of 21 RCTs, adequate bowel preparation favored PEG compared with SPMC (RR 0.93; 95% CI 0.86 to 1.01; p=0.07; I^2 = 87%).[5] Pooled data from 7 RCTs showed no difference between SPMC and PEG in adenoma detection rate (RR 0.88; 95% CI 0.74 to 1.05; p=0.16; I^2 = 37%).[5] Pooled data from 13 RCTs showed less AEs with SPMC compared with PEG (RR 0.78; 95% CI 0.66 to 0.93; p=0.004; I^2 = 88%).[5] When analyzing individual AEs, more patients in the PEG group had nausea, vomiting and abdominal bloating while more patients in the SPMC group developed dizziness. There was no significant difference between the two groups in the incidence of abdominal pain.[5]
- A 2022 meta-analysis of 8 RCTs evaluated the efficacy of oral sulfate solution versus PEG-based solutions (volume ranged from 1L to 4L)for polyp and adenoma detection during colonoscopy.[9] Meta-analysis of 6 RCTs suggested that oral sulfate solutions increased the polyp detection rate compared with PEG-based laxatives (47.34% vs. 40.14%, RR 1.13, 95% CI 1.03 to 1.24; p=0.01; I^2 = 69%).[9] In pooled data from 5 RCTs, the adenoma detection rate was higher with oral sulfate solutions compared with PEG-based laxatives (44.60% vs. 38.14%; RR 1.17; 95% CI 1.03 to 1.33; p=0.01; I^2 = 73%).[9]
- Guidance for adequate bowel preparation prior to colonoscopy was published in 2014 by a multi-society task force comprised of the American College of Gastroenterology, the American Gastrological Association, and the American Society for Gastrointestinal Endoscopy.[6] Strong recommendations based on moderate- to high quality-evidence include:
    - Use of a split-dose bowel cleansing regimen is strongly recommended for elective colonoscopy (strong recommendation, high-quality evidence).[6]
    - A same-day regimen is an acceptable alternative to split dosing, especially for patients undergoing an afternoon examination (strong recommendation, high-quality evidence).[6]
    - The second dose of split preparation ideally should begin 4–6 hours before the time of colonoscopy with completion of the last dose at least 2 hours before the procedure time (strong recommendation, moderate-quality evidence).[6]
    - Selection of a bowel-cleansing regimen should take into consideration the patient's medical history, medications, and, when available, the adequacy of bowel preparation reported from prior colonoscopies (strong recommendation, moderate-quality evidence).[6]
- In 2019, the European Society Of Gastrointestinal Endoscopy (ESGE) Guideline Committee updated 2013 guidance on the efficacy and safety of bowel preparation products prior to endoscopy.[7] Most of the recommendations are similar to the 2014 U.S. multi-task force guidance, but include data for the safety and efficacy of formulations which received FDA-approval after 2013. Strong recommendations based on low- to high-quality evidence include:
    - The use of high-volume or low-volume PEG-based regimens as well as that of non-PEG-based agents that have been clinically validated for routine bowel preparation are recommended.[7] In patients at risk for electrolyte disturbances, the choice of laxative should be individualized (strong recommendation, moderate-quality evidence).[7]
    - Do not routinely use oral sodium phosphate for bowel preparation (strong recommendation, low-quality evidence).[7]
    - High volume or low volume PEG-based bowel preparations are recommended in patients with inflammatory bowel disease (strong recommendation, high-quality evidence).[7]
- Both guidelines recommend the selection of a bowel preparation product should take into consideration patient risk factors. For most people, PEG-electrolyte lavage solutions (ELS) are preferred.[6,7] For people that cannot tolerate the large volume of solution that must be consumed, saline-based laxatives are available. Saline-based laxatives are recommended for use in people under 65 years of age without risk factors for electrolyte disturbances (i.e., heart failure, renal impairment, end-stage hepatic disease).[6,7] Products that contain magnesium should be avoided in older patients, patients with renal disease and people taking medications (i.e., diuretics) that impact renal blood flow or electrolyte excretion.[7] The PEG- electrolyte lavage solutions (ELS) formulations that contain ascorbic acid should be avoided in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as ascorbic acid can trigger hemolysis.[10]
- Colorectal cancer disease burden varies across racial groups, with the highest incidence and mortality rates in Blacks, American Indians, and Alaska Natives.[11]

Health-care providers should make extra efforts to promote access for these populations to get the follow-up they need, including access to clear information and colonoscopy.[12]

Recommendations:

- Create a PDL class entitled "Bowel Preparations" and include PEG 3350 products and saline-laxatives approved for colonoscopy preparation in this drug class.
- Make at least one PEG product and one saline-laxative preferred on the PDL.
- Evaluate drug costs in executive session.

Background:

According to the World Health Organization, colorectal cancer has the fourth highest incidence of non-cutaneous cancer worldwide, affecting 32.3 per 100,000 people in 2020.[13] By the year 2070, colorectal cancer is projected to be the most common cancer globally with 4.7 million expected cases.[14] In the U.S., colorectal cancer is the second leading cause of cancer death, leading to 50,000 deaths annually.[15] Colorectal cancer disease burden varies across racial groups, with the highest incidence and mortality rates in Blacks, American Indians, and Alaska Natives.[11] Colorectal cancer can be prevented by the detection and removal of precancerous polyps, and survival is significantly better when colorectal cancer is diagnosed early, while still localized.[16]

Colorectal cancer screening includes guaiac-based fecal occult blood testing, flexible sigmoidoscopy, and colonoscopy.[16] Fecal blood testing can be completed at home, but only indicates the presence of blood in the rectum or intestine, as polyps cannot be detected with this test. Sigmoidoscopy can be performed with a simple bowel preparation, without sedation, and by a variety of practitioners including nurses and physician assistants in office-based settings.[16] The major limitation of sigmoidoscopy is that it only examines a portion of the large intestine (i.e., the rectum, sigmoid, and descending colon).[16] Colonoscopy requires extensive bowel preparation, patient sedation, and is conducted in a hospital or outpatient surgical setting by a specialist. In contrast to sigmoidoscopy, colonoscopy allows direct mucosal inspection of the entire colon and biopsy sampling or polypectomy in the case of precancerous polyps and some early-stage cancers.[16] Indications for colonoscopy include screening for colon cancer, evaluating signs and symptoms of possible colonic disease, assessing a response to treatment in patients with known colonic disease (e.g., inflammatory bowel disease), evaluating unexplained gastrointestinal bleeding, and evaluating abnormalities found on imaging studies.[17] Therapeutic indications for colonoscopy include stricture dilation, stent placement, colonic decompression, and foreign body removal.[17]

A successful colonoscopy requires cleansing of the large bowel to permit clear visualization of the mucosal surface.[16] Current options for bowel preparation include polyethylene glycol-electrolyte lavage solutions (PEG-ELS) and various saline laxatives.[18] Polyethylene glycol-electrolyte lavage solutions are isosmotic, which minimizes fluid exchange across the colonic membrane.[19] Some PEG-ELS formulations (i.e., MOVIPREP, PLENVU) contain ascorbic acid to improve palatability.[18] These products should be avoided in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as ascorbic acid can trigger hemolysis.[20] Some PEG-ELS products contain magnesium (i.e., SUFLAVE) and should be avoided in patients with renal impairment.[21] In 2016, the Food and Drug Administration (FDA) issued a safety communication due the risk of phosphate-induced nephropathy associated with oral sodium phosphate products used for bowel preparation.[22] As of 2019, oral sodium phosphate tablets and liquids have been removed from the U.S. market due to safety concerns. **Table 1** provides a list of bowel preparation products which are FDA-approved prior to colonoscopy. A summary of relevant drug information is included in **Appendix 2**, which includes pharmacology, pharmacokinetics, contraindications, warnings and precautions.

Table 1. FDA-Approved Bowel Preparations Prior to Colonoscopy.

Generic Drug Name (BRAND NAME)	FDA-Approved Indication(s)	How Supplied	Total Volume of Adult Dose and Additional Fluid Requirements	Total Volume of Pediatric Dose and Additional Fluid Requirements	Comments
Polyethylene Glycol Laxatives					
PEG 3350 with 4 Electrolytes (Potassium Chloride; Sodium Bicarbonate; Sodium Chloride; Sodium Sulfate) (COLYTE, GOLYTELY)[23]	-Barium Enema Preparation -Colonoscopy Preparation	• Oral Powder for Solution. • Reconstitute with water to a final volume of 4000 mL.	• Laxative dose: 4000 mL • No additional fluids are required.	• Safety and efficacy not established in pediatrics	• Gold standard for bowel preparation efficacy.
PEG 3350 with 3 Electrolytes (Potassium Chloride; Sodium Bicarbonate; Sodium Chloride) (NULYTELY)[24]	Colonoscopy Preparation	• Oral Powder for Solution. • Reconstitute with water to a final volume of 4000 mL.	• Laxative dose: 4000 mL • No additional fluids are required.	• Approved in pediatric patients 6 months and older. • Drink at a rate of 25 mL/kg/hour orally or via NGT until stool is watery, clear and free of solid matter (usually within 4 hours). Total dose not included in prescribing information.	• Gold standard for bowel preparation efficacy.
PEG 3350/Sodium Ascorbate/Ascorbic Acid with 3 Electrolytes (Potassium Chloride; Sodium Chloride; Sodium Sulfate) (MOVIPREP, PLENVU)[10]	Colonoscopy Preparation	• Oral Powder for Solution. • Supplied in 2 separate pouches, which are combined and reconstituted with water to a final volume of 960 mL.	• Laxative dose: 1920 mL (Two 960 mL doses) • Additional total volume of clear liquids: 960 mL (Two 480 mL doses)	• Safety and efficacy not established in pediatrics	• Avoid in people with G6PD deficiency due to ascorbic acid component, which can cause hemolysis.
PEG 3350/Magnesium Sulfate with 3 Electrolytes (Potassium Chloride; Sodium Sulfate; Sodium Chloride) (SUFLAVE)[21]	Colonoscopy Preparation	• Oral Powder for Solution. • Supplied as active ingredients and flavor packet, which are combined and reconstituted with water to a final volume of 1000 mL.	• Laxative dose: 2000 mL (Two 1000 mL doses) • Additional total volume of water: 960 mL (Two 480 mL doses)	• Safety and efficacy not established in pediatrics	• Use with caution in people with renal impairment due to magnesium component.

PEG 3350 OTC product (MIRALAX)	Constipation *Off-Label Indication: Colonoscopy Preparation*	• Oral Powder for Solution.	• Laxative dose: Dilute 238 g in 2000 mL of a sports drink (Two 1000 mL doses) • No additional fluids are required	• Safety and efficacy not established in pediatrics	• May precipitate severe hyponatremia because not osmotically balanced.
Saline-Based Laxatives					
Sodium Sulfate; Potassium Sulfate; Magnesium Sulfate (SUPREP)[25]	Colonoscopy Preparation	• Oral Solution supplied in adult (180 mL) and pediatric (135 mL) doses. • Each 180 mL dose must be diluted with water to a final volume of 480 mL • Each 135 mL dose diluted to a final volume of 360 mL.	• Laxative dose: 960 mL (Two 480 mL doses) • Additional total volume of water: 1920 mL (Two 960 mL doses)	• Approved in pediatric patients aged 12 years and older. • Laxative dose: 720 mL (Two 360 mL doses) • Additional total volume of water: 1440 mL (Two 720 mL doses)	• If taking tetracycline or fluoroquinolone antibiotics, iron, digoxin, chlorpromazine, or penicillamine, take these medications at least 2 hours before and not less than 6 hours after administration.
Sodium Picosulfate; Magnesium Oxide; Citric Acid (CLENPIQ)[26]	Colonoscopy Preparation	• Oral Solution supplied as 175 mL	• Laxative dose: 350 mL (Two 175 mL doses) • Additional total volume of clear liquids: 1920 mL (Two 960 mL doses)	• Approved in pediatric patients aged 9 years and older. • Pediatric dosing is the same as the adult dose.	• If taking tetracycline or fluoroquinolone antibiotics, iron, digoxin, chlorpromazine, or a penicillamine, take these medications at least 2 hours before and not less than 6 hours after administration. • Avoid in severe renal impairment (Cr Cl < 30 mL/min.
Sodium Sulfate; Magnesium Sulfate; Potassium Chloride (SUTAB)[27]	Colonoscopy Preparation	• Oral Tablets • 1 dose = 12 tablets. Total dose = 24 tablets.	• Laxative dose: 12 tablets. • Additional total volume of water: 2800 mL (Two 1400 mL doses)	• Safety and efficacy not established in pediatrics	• If taking tetracycline or fluoroquinolone antibiotics, iron, digoxin, chlorpromazine, or penicillamine, take these medications at least 2 hours before and not less than 6 hours after administration.
Abbreviations: Cr Cl = creatinine clearance**;** FDA = Food and Drug Administration**;** G = grams; G6PD = glucose-6-phosphate dehydrogenase; kg = kilogram; L = liter; min = minute; mL = milliliter; NGT = nasogastric tube; OTC = over-the-counter; PEG = polyethylene glycol					

Up to one-quarter of patients who present for colonoscopies have inadequate bowel preparation.[28] Proper bowel cleansing is defined as one that allows the detection of colonic polyps 5 millimeters (mm) or larger.[29] In 2017, the Quality Committee of the European Society of Gastrointestinal Endoscopy (ESGE) recommended the minimum standard for adequate bowel preparation achieve least 90% or greater stool cleansing.[8] Insufficient bowel preparation may result in: an increased risk of adverse events related to the procedure; increased procedure time; reduced interval between procedures; and reduced adenoma detection rates.[30] Medical predictors of inadequate bowel preparation include: previous failed preparation, obesity, chronic constipation, use of constipating medications (i.e. opioids, tricyclic antidepressants), people with diabetes, and previous colonic resection.[30] People with low health literacy may not be equipped to follow the bowel preparation instructions which could lead to inadequate bowel preparation.[30]

Other factors which may influence the quality of the bowel cleansing include volume of the bowel preparation medication, timing of medication administration, and dietary factors.[30] Poor patient adherence prompted recommendations to split the dose administration of large volume PEG (> 3 L) products into 2 doses.[30] Dose splitting consists of taking half the preparation the evening before and the remaining half on the day of the procedure.[30] Day before bowel preparations instruct the patient to consume up to 4 L of the medication the day before the colonoscopy. A shorter interval between the last dose of bowel preparation and the examination is associated with improved bowel preparation quality.[31] To maximize preparation quality, colonoscopy should be performed within 3 to 5 hours of the last dose of preparation.[31] Every hour the interval is extended is associated with a 10% decrease in adequate bowel preparation.[31]

Five scoring systems have been used to assess the quality of bowel preparation.[32] The Aronchick Bowel Preparation Scale provides a single score reflecting the overall quality of the bowel preparation (i.e., excellent, good, fair, poor, or inadequate) depending on the volume of clear liquid or stool present in the intestine and the percentage of intestinal surface that can be observed during the procedure.[33] The Ottawa Bowel Preparation Scale uses 3 separate colonic segment scores which are rated 0 to 4 and summed as part of a total score ranging from 0 (excellent) to 14 (inadequate).[34] Cleanliness and fluid volume are separately assessed in this instrument and then combined into the total score. The Boston Bowel Preparation Scale (BBPS), provides scores ranging from 0 (unprepared colon) to 3 (entire segment of colon well seen) for 3 individual segments of the colon (right, transverse, and left) for a total score of 0 to 9 points.[35] Adequate preparation is defined as an overall BBPS score of 6 or greater, with each segment scored 2 points or greater.[35] The BBPS has been validated in multiple clinical studies.[32] The reliability and validation data for BBPS is more extensive compared with the Aronchick and Ottawa Bowel Preparation scales and include good supporting data correlating scores with key clinical outcomes.[32] Other instruments that have been validated, but are less commonly used, include the Harefield Cleansing Scale and the Chicago Bowel Preparation Scale.[32] A comparison of all 5 instruments is presented in **Table 2**.

Table 2. Instruments for Quality of Bowel Preparation Assessment.[32]

Scale Name	Score/Rating Description	Other Scale Properties
Aronchick Bowel Preparation Scale	*Total Colon:* 1. Excellent: Small volume of liquid; > 95% of mucosa seen 2. Good: Clear liquid covering 5-25% of mucosa, but >90% of mucosa seen 3. Fair: Semisolid stool could not be suctioned or washed away, but 90% of mucosa seen 4. Poor: Semisolid stool could not be suctioned or washed away and < 90% of mucosa seen 5. Inadequate: Repeat preparation/screening needed	• Total score range: Minimum 1 (excellent) to maximum 5 (inadequate). • Scoring performed before washing or suctioning. • No separate ratings for segments; global colon rating only. • No threshold for adequate/inadequate provided.
Ottawa Bowel Preparation Scale	*By Colon Segment:* 0. Excellent: Mucosal detail clearly visible, almost no stool residue; if fluid present, it is clear, almost no stool residue.	• Total score (obtained by adding scores for each segment + total colon fluid score) range: Minimum 0 (excellent) to

	1. Good: Some turbid fluid or stool residue, but mucosal detail still visible without need for washing/suctioning. 2. Fair: Some turbid fluid of stool residue obscuring mucosal detail; however, mucosal detail becomes visible with suctioning, washing not needed. 3. Poor: Stool present obscuring mucosal detail and contour; a reasonable view is obtained with suctioning and washing. 4. Inadequate: Solid stool obscuring mucosal detail and not cleared with washing and suctioning. *Total Colon Fluid:* 0. Small amount of fluid 1. Moderate amount of fluid 2. Large amount of fluid	maximum 14 (inadequate due to solid stool throughout with lots of fluid). • Scoring performed before washing or suctioning. • Rates cleansing by colon segment: Right colon, mid-colon, and rectosigmoid colon. • No threshold for adequate/inadequate provided.
Boston Bowel Preparation Scale (BBPS)	*By Colon Segment:* 0. Unprepared colon segment with mucosa not seen because of solid stool that cannot be cleared. 1. Portion of mucosa of the colon segment seen, but other areas of segment not well seen because of staining, residual stool, and/or opaque liquid. 2. Minor amount of residual staining, small fragments of stool, and/or opaque liquid, but mucosa of colon segment is well seen. 3. Entire mucosa of colon segment well seen, with no residual staining, small fragments of stool, or opaque liquid.	• Total score (obtained by adding scores for each segment) range: Minimum 0 (very poor) to maximum 9 (excellent). • Scoring performed after washing or suctioning. • Segments separately rated: Right colon (including cecum and ascending colon); transverse (includes hepatic and splenic flexures); and left colon (descending and sigmoid colon, and rectum). • Optimal threshold is a total score of ≥ 6 AND ≥ 2 per segment.
Harefield Cleansing Scale	*By Colon Segment:* 0. Irremovable, heavy, hard stools 1. Semisolid, only partially removable stools 2. Brown liquid/fully removable semi-solid stools 3. Clear liquid 4. Empty and clean	• Total score (obtained by adding scores for each segment) range: Minimum 0 (very bad) to maximum 20 (very good). • Scoring performed after washing or suctioning. • Segments separately rated: Rectum, sigmoid, left, transverse, right colon. • Threshold for successful cleansing: ○ Successful cleansing: ▪ Grade A: no segment scored < 3 or 4 or ▪ Grade B: ≥ 1 segment scored 2 but no segment < 2 ○ Unsuccessful cleansing: ▪ Grade C: ≥ 1 segment scored 1 but no segment < 1 or ▪ Grade D: ≥ 1 segment scored 0
Chicago Bowel Preparation Scale	*Total Colon:* 0. Little fluid (≤ 50 mL) 1. Minimal amount of fluid (51-150 mL) 2. Moderate amount of fluid (151-300 mL) 3. Large amount of fluid (> 300 mL)	• Total score range: Minimum 0 (little fluid) to maximum 3 (large amount of fluid). • Scoring performed before washing or suctioning. • No threshold for adequate/inadequate provided. • Not incorporated into total score for segments.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canadian Agency for Drugs and Technologies in Health (CADTH), and Scottish Intercollegiate Guidelines Network (SIGN), resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Efficacy of Split-Dose Bowel Preparations
A 2019 systematic review and meta-analysis evaluated the efficacy of polyp detection for split-dose bowel preparation versus single dose administration.[1] Literature was searched through June 2017 for RCTs conducted in adults aged 18 to 85 years of age undergoing elective outpatient colonoscopy.[1] Studies that were limited to inpatients, pediatrics, or people with inflammatory bowel disease were excluded from the review.[1] Medications of interest included high- and low-volume PEG solutions, sodium phosphate, oral sulfate solutions, and the combination product of sodium picosulfate, magnesium oxide, and citric acid (SPMC).[1] Although oral sodium phosphate solutions are no longer recommended for bowel preparation in the U.S., they continued to be available through 2019.

Twenty-eight RCTs (n=8,842) met inclusion criteria.[1] Seven RCTs (n=1,834) evaluated split-dose versus day-before preparation, 7 trials (n=1,587) evaluated split-dose versus same-day preparation, and 14 trials (n=5,496) compared different split-dose regimens.[1] Most of the trials (16 of 28) had a low risk of bias.[1] Twelve trials had an unclear risk of bias; of these 12 trials, 8 did not describe the measures taken to prevent bias in the allocation assignment, 5 trials did not report whether there were withdrawals, 3 trials did not describe how a random sequence generation occurred, and 1 trial did not describe a method to ensure the endoscopist remained blinded to the intervention.[1]

Detection of adenomas was the primary outcome for the meta-analysis, measured as the number of patients with at least one adenoma detected.[1] In 4 RCTs comparing split-dose versus day-before bowel preparation regimens, there was an increased detection rate of adenomas in the split-dose groups (RR 1.26; 95% CI 1.10 to 1.44; I^2 = 0%; n = 1,258).[1] Eleven patients would be required to use a split-dose bowel preparation regimen for 1 patient to have an adenoma detected that otherwise would not have been detected through the use of a day-before, single-dose regimen.[1] A meta-analysis of 3 RCTs showed there was an increased rate of adenomas detected among participants who received a split-dose regimen of 2 L PEG compared with 2 L PEG the day before the procedure (RR 1.22; 95% CI 1.00–1.48; I^2 = 57%; n= 1,155).[1]

One small RCT (n=103) evaluated a split-dose regimen of 4 L PEG with 2 L PEG the day before colonoscopy and found no evidence of a statistically significant difference between groups for the number of adenomas detected.[1] Pooled estimates from 8 trials (n=1,587) evaluating split-dose versus same-day bowel preparations yielded no evidence of statistical difference in adenoma detection.[1] For 14 RCTs (n=5,496) which evaluated split-dose versus other split-dose regimens (i.e., PEG split high-volume (≥3 L) vs. PEG split low-volume (<3 L); PEG split high-volume (≥3 L) vs. split PEG 3350 + sports drink; PEG split high-volume (≥3 L) vs. sodium phosphate split; PEG split vs. SPMC split; and PEG split vs. oral sulfate solution split), no superior split-regimen was identified to detect adenomas.[1]

Secondary outcomes were detection of advanced adenomas and sessile serrated polyp (SSPs). Sessile serrated polyps are believed to be responsible for a higher proportion of interval colorectal cancers (cancers occurring between surveillance colonoscopies) than sporadic cancers.[1] This may be due to the challenging phenotypic characteristics of SSPs because they are often located in the right colon (where bowel preparation is often worse than when compared with the left colon), or slightly elevated above the colonic mucosa and covered in mucus, which makes them difficult to detect.[1] When split-dose administration was compared with day-before administration, there was increased detection of advanced adenomas (RR 1.53; 95% CI 1.22 to 1.92; 3 trials; I^2 = 0%; n=1,155).[1] Twelve patients would be required to use a split-dose regimen of 2 L PEG to detect an advanced adenoma in 1 patient, that otherwise would not have been detected through the use of a 2 L PEG day-before regimen.[1] Split-dose regimens also improved SSP detection (RR 2.48; 95% CI 1.21 to 5.09; 2 RCTs; I^2 = 0%; n=1,045).[1] No trials reported advanced adenoma detection or SSP detection for a split-dose regimen versus a different split-dose regimen.[1]

In summary, this review found that compared with day-before bowel preparation regimens, split-dose bowel preparations regimens increase the detection of adenomas, advanced adenomas, and have the greatest benefit in SSP detection.[1]

Efficacy Of High- Versus Low-Volume Split Dose PEG Bowel Cleansing Regimens for Colonoscopy

A 2020 systematic review and meta-analysis evaluated efficacy of high-volume PEG laxatives (> 2 L) versus low-volume laxatives (≤ 2 L) administered in split-dose regimens for bowel preparation prior to colonoscopy.[2] Literature was searched through January 2019 for RCTs that included adults undergoing elective colonoscopy.[2] Trials that included pediatric patients, patients with a history of colorectal resection, patients with inflammatory bowel disease, or patients with previous poor bowel preparation we excluded.[2] Low volume laxatives included: 2 L PEG-ASC (9 RCTs), a combination of 2 L PEG with citrate and simethicone in 4 studies (with the addition of oral bisacodyl in 2 RCTs), SPMC (3 RCTs), and oral sulfate solution (2 RCTs).[2] Excluded products were sodium phosphate and over-the-counter (OTC) PEG regimens.[2] After review, 17 RCTs (n=7,528) met inclusion criteria.[2] Baseline characteristics in terms of age and gender were comparable between the 2 groups.[2] Risk of bias was low for all except for allocation concealment (i.e., blinding of endoscopists at randomization) and incomplete outcome data (i.e., for excluded patients).[2] The overall quality of evidence was moderate.[2]

The primary outcome was bowel preparation efficacy in the overall colon and the right colon based on validated instruments (see **Table 2**).[2] In the pooled analysis of 17 RCTs, comprising 7,528 patients, no significant differences in adequacy of bowel cleansing were identified between the low- versus high-volume split-dose regimens (86.1% vs 87.4%; RR 1.00; 95% CI 0.98 to 1.02; p=0.2; I^2 = 17%).[2] In the RCTs reporting on right colon cleansing (10 studies, n=5,288), no difference in efficacy between low-volume PEG and non-PEG versus high-volume PEG regimens was found in the meta-analysis (91.2% vs 89.6%; RR 1.01; 95% CI 0.99 to 1.03; I^2 = 18%; p=0.2).[2] In 13 RCTs (n=6,593) that compared split-dose 2 L PEG-ASC with high-volume split-dose PEG, in differences were observed in the percentage of patients who presented with adequate bowel preparation (84.9% vs 86.3%; RR 1.0; 95% CI 0.95 to 1.02; I^2 = 38%; p=0.09).[2]

Secondary outcomes included adenoma detection rates, regimen compliance (defined as consumption of 75 to 100% of the prescribed solution) and AEs such as abdominal bloating, nausea, vomiting, and abdominal pain.[2] In pooled data from 4 RCTs (n=5,399), no difference in adenoma detection rate between low- and high-volume split dose regimens was found (RR 0.96; 95% CI 0.87–1.08; p-value not reported; I^2 = 0%).[2] Compared with high-volume split-dose regimens, low-volume split-dose regimens had higher odds for compliance of regimen completion (86.8% vs 92.8%; RR 1.06; 95% CI 1.02 to 1.10; p<0.01; I^2 = 85%).[2] For AEs, low-volume split dose-regimens had less risk for bloating (RR 0.66, 95% CI 0.48 to 0.92), nausea (RR 0.86, 95% CI 0.46 to 1.00), and vomiting (RR 0.68, 95% CI 0.46 to 1.00) compared with high-volume split dose regimens.[2] Abdominal pain was not statistically different with high-volume regimens compared with low-volume split dose regimens(RR 1.22; 95% CI 0.73 to 2.03).[2]

In summary, this review did not find statistically significant differences in bowel cleansing and adenoma detection rates between low- and high-volume regimens, when split-dose administration is adopted.[2] Low-volume regimens had higher odds of patient adherence to regimen completion and less incidence of bloating, nausea, and vomiting.[2]

Efficacy Of Ultra-Low Volume Bowel Preparation Fluids

A 2022 systematic review evaluated the efficacy of ultra-low volume bowel preparation products (< 1 L) compared with high-volume (> 2 L) and low-volume (1 to 2 L) products.[3] Literature was searched through April 2020 for RCTs that evaluated comparative efficacy of ultra-low volume bowel preparation products.[3] Forty-three studies met inclusion criteria.[3] All RCTS were single or multi-center assessor-blinded trials in outpatients with various indications for colonoscopy.[3] Of the 43 included studies, 26 RCTs evaluated SPMC, 12 RCTs evaluated 1 L PEG-ASC, 4 RCTs evaluated oral sulfate solution, 4 RCTs evaluated oral sodium phosphate solution, 2 RCTs evaluated sennosides, and one RCT evaluated magnesium citrate.[3] The small number of studies evaluating sennosides and magnesium citrate reflects their limited use in clinical practice.[3] The mean age of the included patients ranged from 47 years to 62 years.[3] Other patient demographics were not described in the report. Fourteen studies were sponsored by pharmaceutical companies.[3] The overall risk of bias was low in 58.1%, intermediate in 23.3%, and high in 16.3% of the included studies.[3]

The primary endpoint for this systematic review was the proportion of patients with adequate bowel cleansing for each studied product.[3] Adequate bowel cleansing was defined using validated bowel preparation instruments (see **Table 2**). If the outcome was reported with more than one preparation scale, BBPS and Ottawa Bowel Preparation Scores were preferred over the Aronchick Scale, as previous studies have shown better interrater consistency with these scales.[3] Additionally, BBPS was preferred over the Ottawa Bowel Preparation Scale because of more extensive validation and more frequent use in clinical practice with this instrument.[32] Secondary outcomes included adenoma detection rate and AEs.

Thirty-two RCTs were included in single arm meta-analyses of adequate bowel cleansing rates.[3] For SPMC 300 mL, the percentage of adequately cleaned patients was reported in 19 studies comprising 10,287 patients, with a pooled percentage of 75.2% (95% CI 67.6 to 81.4, I^2 = 96%).[3] Ten studies (n=1,717) reported the proportion of adequately prepared patients using 1 L PEG-ASC, with a pooled percentage of 82.9% (95% CI 74.4 to 90.1, I^2 = 94%).[3] Two studies (n=621) reported the efficacy of sodium phosphate, with a pooled percentage of adequately prepared patients equal to 81.9% (95% CI 36.7 to 97.2, I^2 = 98%).[3] For oral sodium sulfate, 3 studies (n=597) reported on the primary endpoint, with a pooled percentage of 92.1% (95% CI 79.7 to 97.2, I^2 = 86%).[3] The pooled outcome did not change significantly for any of the formulations when excluding the studies classified as high risk of bias, except for the 1 L PEG-ASC group, as a drop from 83.0% (95% CI 74.4 to 90.1) to 75.3% (95% CI 73.0 to 77.3) was identified.[3] In summary, bowel preparation with SPMC, 1 L PEG-ASC, sodium phosphate, and oral sulfate solution was adequate in 75.2%, 82.9%, 81.9%, and 92.1% of patients, respectively.[3] However, heterogeneity between studies was considerable (I^2 range: 86 to 98%).[3]

Adenoma detection rate was reported in 10 SPMC studies with a pooled detection rate of 31.0% (95% CI 25.6 to 36.7, I^2 = 83%).[3] The pooled adenoma detection rate with 1 L PEG was 32.4% (95% CI 26.6 to 38.4, I^2 = 83%, 8 RCTs). Adenoma detection rate was reported in one study in the sodium phosphate group and was 30.4% (95% CI 20.6 to 41.2). Adenoma detection rate was reported in 2 studies in the sodium sulfate group with a pooled adenoma detection rate of 40.9% (95% CI 28.3 to 54.2, I^2 = 81%).[3] Temporary electrolyte changes were seen with all ultra-low volume bowel preparation fluid solutions but without sustained effects in most patients.[3] All included studies reported gastrointestinal symptoms such as abdominal pain and distention, anal irritation, nausea, and to a lesser extent vomiting as most frequent adverse events.[3] Headache, dizziness, and general malaise were reported with the use of all fluids.[3]

The authors concluded ultra-low volume bowel preparation fluids do not always meet the 90% quality standard for adequate bowel preparation as defined by 2017 ESGE guidelines.[3,8] However, ultra-low volume products may be considered in patients intolerant for higher-volume laxatives and without risk factors for inadequate bowel preparation or dehydration-related complications.[3] Hyperosmotic ultra-low volume laxatives may be less suitable for elderly patients or patients with renal dysfunction.[3]

Effectiveness and Safety of 1-Liter Polyethylene Glycol Plus Ascorbate Versus Other Bowel Preparations for Colonoscopy

A 2023 meta-analysis evaluated the safety and effectiveness of 1 L PEG-ASC compared with other bowel preparation products.[4] Literature was searched through July 2022, and 9 RCTs met inclusion criteria.[4] In all included studies, cleansing success was defined as a total BBPS score of ≥6 with a partial BBPS score of ≥2 in each segment.[4] Right colon high-quality cleansing was defined as a partial BBPS score of 3.[4] The adenoma detection rate was defined as the percentage of patients with at least one adenoma in the analyzed population.[4] Safety of the preparations was assessed through occurrence of AEs.

Two different dosing regimens were used: split-dosing regimen in 8 RCTs and day-before regimen in one RCT.[4] One L PEG-ASC was compared with 2 L PEG-ASC in 5 RCTs , 4 L PEG in one RCT, trisulfate (magnesium, potassium, and sodium) solution in one RCT, SPMC in one RCT, and SPMC plus PEG in one RCT.[4] None of the studies were of poor methodological quality.[4] The assignment to the intervention domain remained at a low risk of bias, although all studies reported absence of patient blinding for the intervention owing to differences between the treatments.[4] All other domains were at a low risk of bias.[4] The mean body mass index (BMI) of the patients across the included studies ranged from 24.1 to 29.8 kg/m^2 while the mean age of the patients across the included studies ranged from 45.6 to 70.9 years.[4] Additional patient demographics (i.e., race, ethnicity) were not described in the report.

The meta-analysis showed a significantly higher cleansing success rate with 1 L PEG-ASC than with the other preparations both in the overall group (OR 1.50; 95% CI 1.25 to 1.81; p<0.01; I^2 = 0%; n=6,720) and split-dosing regimen subgroup (OR 1.44; 95% CI 1.16 to 1.80; p<0.01; I^2 = 0%; n=5,958).[4] Similar to the cleansing success rate, a significantly higher right colon HQC rate was found with 1 L PEG-ASC than with the other preparations both in the overall group (OR 1.67; 95% CI 1.21 to 2.31; p<0.01; I^2 = 43%; n= 3,221) and split-dosing regimen subgroup (OR 1.59; 95% CI 1.17 to 2.14; p<0.01; I^2 = 38%; n=2,708).[4] The pooled estimate of the adenoma detection rate did not significantly differ between the two groups either in the overall (OR 1.02; 95% CI 0.87 to 1.20; p=0.79; I^2 = 0%; n=3,984) or split-dosing regimen subgroup analysis (OR 0.99; 95% CI 0.84 to 1.18; p=0.94; I^2 = 0%; n=3,381).[4]

More patients with AEs were observed with 1 L PEG-ASC than with the other preparations (OR 1.51; 95% CI 1.23 to 1.84; p<0.01; I^2 = 0%; n=3,500).[4] A similar result was observed when only the studies with the split-dosing regimen were considered (OR 1.46; 95% CI 1.18 to 1.81; p<0.01; I^2 = 0%; n=2960).[4] When analyzing number and type of AEs, more nausea and vomiting were associated with 1 L PEG-ASC than with the other for specific AEs: nausea (incidence risk ratio [IRR] 1.45; 95% CI 1.24 to 1.70; p <0.01; I^2 = 0%, n=6720) and vomiting (IRR 2.22; 95% CI 1.60 to 3.07; p <0.01; I^2 = 8%, n=5962).[4] The incidence of abdominal pain was similar between 1 L PEG-ASC and other preparations (IRR 1.02; 95% CI 0.78 to 1.33; p <0.90; I^2 = 0%, n=4594).[4] No serious AEs or deaths were reported.[4]

In summary, compared to other preparations, 1-L PEG-ASC yielded higher overall cleansing success rates, higher right-colon high-quality cleansing rates, and similar adenoma detection rates.[4] The number of patients with AEs and incidence of AEs were higher with 1-L PEG-ASC compared with other products.[4] Nausea and vomiting occurred with 1 L PEG-ASC more often than with other products, while the incidence of abdominal pain was similar between the two groups.[4]

Sodium Picosulfate-Magnesium Citrate Versus PEG Laxatives for Colonoscopy Preparation

A 2016 systematic review and meta-analysis evaluated the safety and efficacy of SPMC with PEG-based regimens for colonoscopy preparation.[5] Literature was searched through July 2015 for RCTs that enrolled adult patients undergoing elective colonoscopy.[5] Twenty-five, single-blinded (due to differences in

administration schedules and product packaging) RCTs met inclusion criteria.[5] Ten RCTs compared full-dose SPMC versus full-dose PEG, 6 RCTs compared split-dose SPMC versus split-dose PEG, one RCT compared split-dose SPMC versus full-dose PEG, 4 RCTs evaluated full-dose SPMC versus split-dose PEG, and 4 RCTs evaluated multiple administration schedules.[5] The primary outcome was bowel cleanliness as defined as the proportion of patients attaining a satisfactory preparation.[5] Satisfactory preparation was specified based on validated instrument scores (see **Table 2**).[5] If 2 bowel preparation scales were both used in one study, the authors selected BBPS or the Ottawa Preparation Scale as the preferred instrument.[5] Secondary outcomes included adenoma detection rate, patient tolerability, and AEs.[5] The quality of evidence of RCTs was evaluated as high-quality.[5]

Bowel cleanliness was examined in all 25 trials, regardless of dosage, administration, and preparation cleanliness scale.[5] However, data of satisfactory preps could not be extracted from 4 RCTs according to the defined parameters.[5] In the meta-analysis of 21 RCTs, no differences in adequate bowel preparation were found with PEG compared with SPMC (RR 0.93; 95% CI 0.86 to 1.01; p=0.07; I^2 = 87%).[5] Pooled data from 7 RCTs showed no differences between SPMC and PEG in adenoma detection rate (RR 0.88; 95% CI 0.74 to 1.05; p=0.16; I^2 = 37%).[5]

Pooled data from 13 RCTs showed less AEs with SPMC compared with PEG (RR 0.78; 95 % CI 0.66 to 0.93; p=0.004; I^2 = 88%).[5] When analyzing individual AEs, more patients in the PEG group reported nausea (RR 0.63; 95% CI 0.51 to 0.77; p<0.001; I^2 = 70%), vomiting (RR 0.48; 95% CI 0.33 to 0.69; p<0.001; I^2 = 54 %), and abdominal bloating (RR 0.60; 95% CI 0.48 to 0.76; p<0.001; I^2 = 72 %) while more patients in the SPMC group developed dizziness (RR 1.64; 95% CI 1.34 to 2.01; p<0.001; I^2 = 0%). No significant difference was found between the two groups in development of abdominal pain (RR 0.83; 95% CI 0.65 to 1.07; p=0.15; I^2 = 66%).[5]

In summary, no differences in adequate bowel preparation or adenoma detection rate were found with PEG over SPMC. More patients reported nausea, vomiting, and abdominal bloating with PEG, while more patients developed dizziness with SPMC.

Efficacy of Oral Sulfate Solution versus PEG-Based Solutions for Polyp and Adenoma Detection During Colonoscopy

A 2022 meta-analysis of RCTs evaluated the efficacy of oral sulfate solution versus PEG-based solutions for polyp and adenoma detection during colonoscopy.[9] Literature was searched through October 2021 and 8 RCTs (n=2,059) meet inclusion criteria.[9] Most of the RCTs were conducted in Korea (6 of 8); the other 2 RCTs were conducted in the U.S. and India.[9] The sample size of all eligible RCTs ranged between 167 and 556, with a total sample size of 2,059.[9] Two RCTs specifically enrolled elderly individuals, 5 RCTs used 2 L PEG-ASC, 2 RCTs used 4 L PEG- ASC and one RCT used 1 L PEG-ASC as comparators.[9] Three RCTs were conducted in patients scheduled for a morning colonoscopy, and 4 RCTs specifically considered outpatients.[9]

Six RCTs clearly reported the methods to generate a random sequence, but only 2 RCTs clearly reported the approaches of concealing allocation.[9] Seven studies blinded investigators but not participants and were therefore judged as unclear risk in performance bias except for one RCT, which did not blind either investigators or participants.[9] Regarding outcome assessment, 5 studies were judged as low risk of bias because it was evaluated by either blinded independent trained central readers or blind investigators; however, another 3 studies did not clearly describe detailed information on outcome assessment and were therefore rated as unclear risk.[9] For the remaining items, all RCTs were considered as low risk.[9]

The primary outcome was polyp and adenoma detection. Meta-analysis of 6 RCTs suggested that oral sulfate solution significantly increased the polyp detection rate compared with PEG-based laxatives (47.34% vs. 40.14%, RR 1.13, 95% CI 1.03 to 1.24; P=0.01; I^2 = 69%).[9] In the pooled data from 5 RCTs, the adenoma detection rate was higher with oral sulfate solution compared with PEG-based laxatives (44.60% vs. 38.14%; RR 1.17; 95% CI 1.03 to 1.33; P=0.01; I^2 = 73%).[9]

A secondary outcome was effective bowel preparation using the Ottawa Preparation Scale or BBPS.[9] Pooled analyses suggested that, compared with the PEG-based solutions group, the BBPS in the oral sulfate group was greater (mean difference [MD] 0.32, 95% CI 0.03 to 0.62; P=0.03; 5 RCTs), and the Ottawa Preparation Scale in the oral sulfate group was lower (MD −1.28; 95% CI −1.95 to -0.62, P< 0.001; 2 RCTs), demonstrating that the quality of bowel preparation in the oral sulfate group was better than that of PEG-based solutions group.[9]

In summary, compared with PEG-based regimens, the oral sulfate solution bowel preparation regimen increased the polyp and adenoma detection rates and effectiveness of bowel preparation in patients undergoing colonoscopy.[9] However, there was substantial heterogeneity between trials, and AEs were not assessed in this analysis.

After review, 5 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). [36-40]

Guidelines:

Optimizing Adequacy of Bowel Cleansing for Colonoscopy: Recommendations from an American Multi-Society Task Force on Colorectal Cancer

Guidance for adequate bowel preparation was published in 2014 by a multi-society task force comprised of the American College of Gastroenterology, the American Gastrological Association, and the American Society for Gastrointestinal Endoscopy.[6] This publication was supported in part by resources from the U.S. Veterans Health Administration.[6] Ineffective bowel cleansing for colonoscopy results in missed precancerous lesions and increased costs related to early repeat procedures.[6] The rate of adequate bowel cleansing should be at least 85%, and higher whenever possible.[6] Evidence and rationale for strong recommendations are summarized below.

- *Use of a split-dose bowel cleansing regimen is strongly recommended for elective colonoscopy (strong recommendation, high-quality evidence).*[6] Six trials showed significantly increased cleanliness for the PEG-ELS split-dose regimen (2 L + 2 L) compared with the PEG-ELS same-day dose (OR, 4.38; 95% CI, 1.88–10.21).[6] Consistent data show superior efficacy with a split dose compared with the traditional regimen of administering the preparation the day before the procedure.[41-43] Split dosing leads to higher adenoma detection rates.[44] Four previously published guidelines endorsed split dosing of preparations for colonoscopy.[45-48]

- *A same-day regimen is an acceptable alternative to split dosing, especially for patients undergoing an afternoon examination (strong recommendation, high-quality evidence).*[6] Several studies have shown that same-day bowel cleansing is an effective alternative to split dosing for patients with an afternoon colonoscopy.[6] One single-blind, prospective study in 277 participants showed same-day preparation provided better mucosal cleansing, less sleep disturbance, better tolerance, less impact on activities of daily living, and greater patient preference scores compared with split dosing.[49]

- *The second dose of split preparation ideally should begin 4–6 hours before the time of colonoscopy with completion of the last dose at least 2 hours before the procedure time (strong recommendation, moderate-quality evidence).*[6] This recommendation is based upon guidance from the American Society of Anesthesiologists, which states that ingestion of clear liquids until 2 hours before sedation does not affect residual gastric volume.[50] Two endoscopic studies found that ingestion of bowel cleansing agents on the day of colonoscopy did not affect residual gastric volumes, indicating that the rate of gastric emptying of bowel preparations is similar to other clear liquids.[51,52]

- *Selection of a bowel-cleansing regimen should take into consideration the patient's medical history, medications, and, when available, the adequacy of bowel preparation reported from prior colonoscopies (strong recommendation, moderate-quality evidence).*[6]

Because they are isosmotic, PEG-ELS regimens often are considered preferred regimens in patients who are less likely to tolerate fluid shifts, including patients with renal insufficiency, congestive heart failure, and advanced liver disease.[6] When sodium picosulfate was compared to PEG-ELS in 10 RCTs, the sodium picosulfate preparation showed similar efficacy in bowel cleansing to PEG-ELS formulations (OR 0.92; 95% CI 0.63 to 1.36).[6] At the time of this guideline publication, 2 comparative studies were available that evaluated oral sulfate solutions with 4 L and 2 L PEG-ELS products. The combined results of 923 patients found that oral sulfate solutions showed no difference in bowel cleanliness compared with PEG-ELS (OR 1.12; 95% CI, 0.77 to 1.62).[6] The use of magnesium-based preparations in patients with chronic kidney disease should be avoided because of possible magnesium toxicity.[6]

PEG-3350 powder (MIRALAX), an over-the-counter (OTC) laxative marketed for constipation, is available as an 8.3-oz bottle (238 g). When used for a pre-colonoscopy bowel preparation, the contents of 1 bottle often are mixed with 64 ounces of Gatorade (PepsiCo, Chicago, IL) to create a 2-L PEG formulation.[6] In some instances, clinicians prescribe bisacodyl tablets or magnesium citrate in conjunction with the PEG-3350 powder.[6] Five randomized controlled trials (total, 1556 patients) compared OTC PEG-3350 powder, either alone or combined with an adjunct, with 4 L PEG-ELS.[6] In one study, satisfactory colon cleansing was less frequent with OTC PEG-3350 powder than with 4 L PEG-ELS (68% vs. 83%; p=0.018).[6] In the remaining 4 studies, including 1 study that used 306 g rather than 238 g, the proportion of patients with adequate bowel preparation was comparable with OTC PEG-3350 powder and 4 L PEG-ELS.[6] Reports of hyponatremia have occurred when OTC PEG-3350 powder was administered the evening before, but not with split-dose regimens.[6] Widespread use of OTC PEG-3350 for bowel preparation seems to have been remarkably safe, but additional evaluation of safety and is warranted.[6]

- *Recommendations for Specific Populations:*
    - *Pediatrics*: There is insufficient evidence to recommend specific bowel preparation regimens for children and adolescents undergoing colonoscopy (strong recommendation, very-low quality evidence).[6]
    - *Pregnancy*: Strongly consider deferring colonoscopy until second trimester and consider risks of bowel preparation regimen.[6] Tap water enemas should be used to prepare the colon for sigmoidoscopy in pregnant women (strong recommendation, very low-quality evidence).[6]

Bowel Preparation For Colonoscopy: European Society Of Gastrointestinal Endoscopy

In 2019, the ESGE Guideline Committee updated 2013 guidance to incorporate additional evidence on the efficacy and safety of bowel preparation prior to endoscopy.[7] Most of the recommendations are similar to the 2014 U.S. multi-task force guidance, but are based upon more recently published evidence not evaluated in the U.S. guidance. The rate of adequate bowel cleansing should be at least 90%, and higher whenever possible.[8] Recommendations regarding selection and administration of medications are summarized below.

- *ESGE recommends split-dose bowel preparation for elective colonoscopy (strong recommendation, high quality evidence).*[7] A meta-analysis (47 RCTs, 13, 478 patients) found that split-dose regimens, regardless of the type and dose of the cleansing agent, provided excellent/good colon cleansing more frequently than day-before bowel preparation (OR 2.51 95% CI 1.86 to 3.39).[53] This result was confirmed in sub-analyses restricted to PEG (OR 2.60, 95 % CI 1.46 to 4.63), sodium phosphate (OR 9.34, 95 % CI 2.12 to 41.11), and picosulfate (OR 3.54, 95 % CI 1.95 to 6.45).[53] Split dosing was associated with a higher proportion of patients willing to repeat the preparation (OR 1.90, 95 % CI 1.05 to 3.46).[53]

- *ESGE recommends, for patients undergoing afternoon colonoscopy, a same-day bowel preparation as an acceptable alternative to split dosing (strong recommendation, high quality evidence).*[7] Two meta-analyses (11 and 14 RCTs) compared split-dose with same-day bowel preparation and showed similar results regarding the quality of bowel preparation, patient willingness to repeat it, and overall tolerability.[54,55] Patients taking the same-day

regimen reported less bloating (OR 0.68, 95% CI 0.40 to 0.94)[54] and better sleep quality (OR 0.44, 95% CI 0.24 to 0.82).[55] The adverse effect rate was similar for the two regimens.[54] Most of the people enrolled in the included studies were scheduled for afternoon procedures.[7]

- *ESGE recommends to start the last dose of bowel preparation within 5 hours of colonoscopy, and to complete it at least 2 hours before the beginning of the procedure (strong recommendation, moderate quality evidence).*[7] A meta-regression analysis of 29 RCTs comparing split versus day-before regimens showed that the clinical gain of the split-dose regimen was highest within 3 hours from last dose intake, progressively decreased after 4 to 5 hours, and became statistically not significant at 5 hours.[56]

- *ESGE recommends the use of high volume or low volume PEG-based regimens as well as that of non-PEG-based agents that have been clinically validated for routine bowel preparation. In patients at risk for electrolyte disturbances, the choice of laxative should be individualized (strong recommendation, moderate quality evidence).*[7]
  In a 2015 meta-analysis, split-dose high volume (≥3 L) PEG appeared to be superior to split-dose low volume PEG (6 studies; 1305 patients; OR 1.89, 95% CI 1.01 to 3.46).[53] This confirmed a previous meta-analysis showing the superiority of split-dose high volume PEG versus other alternatives (9 studies; 2477 patients; OR 3.46, 95 % CI 2.45 to 4.89) including low volume PEG with different adjuvants and sodium phosphate, regardless of the adoption of the split regimen.[43] After the meta-analyses were published, several trials compared high-volume PEG vs. low-volume PEG or non-PEG split regimens.[7] Overall, such trials showed an equivalence or superiority of the high-volume versus low-volume PEG or non-PEG regimens in terms of efficacy, while confirming the worse tolerability of the high volume PEG regimens.[7] Studies have not demonstrated significant alterations in vital or biochemical parameters (e. g., sodium, potassium, chloride, bicarbonates) linked to these formulations.[7]

  In order to reduce the volume of PEG solutions, with the aim of improving tolerability, a formulation of 2 L PEG-ASC was developed.[7] One meta-analysis, including 11 RCTs comparing 2 L PEG plus ascorbate versus 4 L PEG preparations for elective colonoscopies, showed noninferior efficacy for bowel cleansing (OR 1.08, 95% CI 0.98 to 1.28) but better compliance for 2 L PEG-ASC (OR 2.23, 95% CI 1.67 to 2.98), with reduced nausea and vomiting.[57] Solutions containing aspartame and ascorbate are contraindicated in patients with phenylketonuria or G6PD deficiency.[7] These products are not recommended in patients with renal insufficiency and creatinine clearance less than 30 mL/min and in patients with New York Heart Association (NYHA) III or IV congestive heart failure.[7] A high rate of hypernatremia has been observed following the administration of 1 L PEG plus ascorbate, primarily due to the sodium content of the product.[7] For this reason, additional clear liquids are recommended. Hyponatremia cases have been described with 2 L PEG-ASC; this prompted caution in patients at risk of electrolyte disturbances.[7]

  Sodium picosulfate, magnesium oxide, and citric acid was compared with PEG and with oral sodium phosphate in two meta-analyses, including 6 and 13 studies.[58,59] In the smaller meta-analysis, SPMC provided satisfactory colon cleansing in a similar proportion of patients compared with PEG, with less frequent adverse events. However oral sodium phosphate produced better colon cleansing than SPMC.[59] In the second meta-analysis, which included only RCTs in which colon cleansing was rated according to a validated scale, SPMC provided a slightly better quality of bowel cleansing compared with PEG (RR 1.06, 95% CI 1.02 to 1.11); this was lost, however, when SPMC was compared with 4 L PEG only.[59] In addition, SPMC was better tolerated than PEG, with a higher probability of completing the preparation.[59] In the most recent meta-analysis, including 25 RCTs that compared SPMC with PEG (but with different regimens), no difference was found in colon cleansing or polyp detection rate.[5] However AEs, including nausea, vomiting, bloating, but not dizziness, were less frequent in the SPMC group (RR 0.78, 95 % CI 0.66 to 0.93), and a higher proportion of patients were likely to complete the SPMC regimen (RR 1.08, 95 %CI 1.04 to 1.13) and willing to repeat the same regimen (RR 1.44, 95% CI, 1.25 to 1.67).[5] Because of hyperosmolarity and

magnesium content, solutions containing SPMC are contraindicated in patients with congestive heart disease, hypermagnesemia, rhabdomyolysis, gastrointestinal ulcerations, and severe impairment of renal function, which can lead to magnesium accumulation.[7]

There is insufficient evidence to recommend a specific product for elderly people. Osmotically balanced PEG solutions are theoretically the safest, and are preferred in these patients.[7] However, high volume products are thought to be particularly poorly tolerated in elderly patients.[7] Hyperosmotic saline laxatives may increase the risk of dehydration and electrolyte imbalances in at-risk populations, such as patients with chronic renal insufficiency, congestive heart failure, or liver failure with ascites.[7] Although the majority of RCTs exclude such patients, PEG solutions with osmotically balanced electrolytes are often selected, on account of their safety profiles, for patients in these categories.[7]

- *ESGE recommends against the routine use of oral sodium phosphate for bowel preparation (strong recommendation, low quality evidence).*[7] Between January 2006 and December 2007, 171 cases of renal failure were reported to the U.S. FDA following the use of oral sodium phosphate and 10 cases were reported following the use of PEG.[60]

- *ESGE recommends high volume or low volume PEG-based bowel preparation in patients with inflammatory bowel disease (strong recommendation, high quality evidence).*[7] In an RCT of patients without colitis, sodium phosphate- or sodium picosulfate-based preparations resulted in a 10-fold increase in mucosal inflammation compared to PEG-based bowel preparation.[61] However, limited comparative data are available for bowel preparation efficacy and tolerability in colitis.[7]

- *ESGE found insufficient evidence to determine for or against the use of specific regimens in pregnant/breastfeeding women. However, if colonoscopy is strongly indicated, PEG regimens may be considered, with tap water enemas preferred for sigmoidoscopy. (Insufficient evidence to determine net benefits or risks).*[7] The use of PEG in pregnancy has not been extensively studied and it is unknown whether it can cause fetal harm; when used for treating constipation during pregnancy it is considered relatively safe.[7]

After review, 3 guidelines were excluded due to poor quality.[62-64]

Randomized Controlled Trials:
A total of 296 citations were manually reviewed from the initial literature search. After further review, 294 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Enestvedt BK, et al.[65] Single-center, single-blinded RCT Duration: 7/1/2009 to 6/29/2010	1. PEG 236 g dissolved in 4 L water administered as a split dose (n=103) vs. 2. PEG 238 g dissolved in 2 L sports drink administered as a split dose + 4 bisacodyl 5 mg tablets the day before the procedure (n=87)	Adult patients 50 yo and older undergoing routine outpatient colorectal screening Exclusions: -Chronic constipation -Use of chronic narcotics N=190	Excellent bowel preparation as assessed by the BBPS score as 8 or 9 on 10-point scale ranging from 0 to 9 points	Percent of patients achieving BBPS score of 8 or 9 1. 70% (n=72) 2. 55% (n=48) Difference: 25% P=0.036 *Confidence intervals not reported	-PEG 236 g in 4 L provided effective bowel cleansing prior to colonoscopy compared with PEG 238 in 2 L -Small sample size -Side effects such as electrolyte changes and kidney function were not assessed -Bowel cleansing is a surrogate endpoint for polyp detection -Patients not blinded to treatment assignment due to differences in products and volume of fluids
Hjelkrem M, et al.[66] Single-center, single-blinded RCT Duration: 7/1/2009 to 7/1/2010	1. PEG 236 g dissolved in 4 L water administered as a split dose (n=102) vs 2. PEG 238 g dissolved in 2 L sports drink administered as a split dose (n=100) vs 3. PEG 238 g dissolved in 2 L sports drink administered as a split dose + lubiprostone 24 mcg the day before the procedure (n=101) vs. 4. PEG 238 g dissolved in 2 L sports drink administered as a split dose + bisacodyl 10 mg	Adult patients 18 yo and older undergoing routine outpatient colorectal screening Exclusions: -Congestive heart failure -Kidney disease -Solid organ transplant -Bowel obstruction N=404	Excellent bowel preparation as assessed by the OBPS score less than 5 points on 15-point scale ranging from 0 to 14 points	Mean total OBPS score 1. 5.1 2. 6.9 3. 6.3 4. 6.8 1 vs. 2: Difference = 1.8; P<0.001 1 vs. 3: Difference = 1.2; P<0.001 1 vs. 4: Difference = 1.7; P<0.001 *Confidence intervals not reported Percent of patients achieving OPBS score <5 1. 49% (n=40) 2. 15% (n=15) 3. 19% (n=20) 4. 20% (n=21) P <0.001 for all comparisons with PEG 4 L	-No differences were found in the number of polyps detected with each regimen (p=0.346) -No differences were reported in adverse event reporting

	the day before the procedure (n=101)				
Abbreviations: BBPS = Boston Bowel Preparation Scale; g = grams; L = liters; mcg = micrograms; OBPS = Ottawa Bowel Preparation Scale; PEG = polyethylene glycol; yo = years old					

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Appendix 1: PDL Status: Laxatives, Bowel Preparation

Generic Name	Brand Name	Form	PDL Status
peg3350/sod sul/NaCl/KCl/asb/C	PEG3350-SOD SUL-NACL-KCL-ASB-C	POWD PACK	
peg3350/sod sul/NaCl/KCl/asb/C	MOVIPREP	POWD PACK	
peg3350/sod sul/NaCl/KCl/asb/C	PLENVU	POWD PK SQ	
peg3350/sod sulf, bicarb, Cl/KCl	PEG-3350 AND ELECTROLYTES	SOLN RECON	
peg3350/sod sulf, bicarb, Cl/KCl	GOLYTELY	SOLN RECON	
peg3350/sod sulf, bicarb, Cl/KCl	GAVILYTE-G	SOLN RECON	
peg3350/sod sulf, bicarb, Cl/KCl	GAVILYTE-C	SOLN RECON	
sod picosulf/mag ox/citric ac	CLENPIQ	SOLUTION	
sod sulf/pot chloride/mag sulf	SUTAB	TABLET	
sodium chloride/NaHCO3/KCl/peg	NULYTELY	SOLN RECON	
sodium chloride/NaHCO3/KCl/peg	PEG 3350-ELECTROLYTE	SOLN RECON	
sodium chloride/NaHCO3/KCl/peg	GAVILYTE-N	SOLN RECON	
sodium phosphate, mono-dibasic	PREPARATION CLEANSING	LIQUID	
sodium, potassium, mag sulfates	SOD SULF-POTASS SULF-MAG SULF	SOLN RECON	
sodium, potassium, mag sulfates	SUPREP	SOLN RECON	

Appendix 2: Specific Drug Information

Clinical Pharmacology and Pharmacokinetics:
Almost all of the FDA-approved bowel preparation products are osmotic laxatives and not absorbed systemically; therefore, pharmacokinetic properties have not been assessed. The only product that contains an osmotic laxative and stimulant laxative is CLENPIQ. The sodium picosulfate component acts as a stimulant laxative while the magnesium oxide serves as the osmotic laxative.[26]

Summary of Warnings and Precautions:
All of the FDA-approved bowel preparations carry similar precautions. Because MOVIPREP contains sodium ascorbate and ascorbic acid, it should be used cautiously in patients with G6PD deficiency, especially in patients with active infection, history of hemolysis, or concomitant use of medication known to precipitate hemolytic reaction.[10] MOVIPREP also contains phenylalanine 2.33 mg per treatment, so it should be used cautiously in patients with phenylketonuria.[10] CLENPIQ is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) as magnesium accumulation may occur.[26]

Precautions:
- Fluid and electrolyte disturbances may occur and can lead to cardiac arrhythmias, seizures and renal impairment; correct abnormalities prior to use.
- Patients with a history of QT prolongation, uncontrolled arrhythmias, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy are at increased risk of serious arrhythmias; monitoring is recommended.
- Patients with impaired renal function or those taking concomitant drugs that may affect renal function (e.g., diuretics, ACE inhibitors, angiotensin receptor blockers, or NSAIDs) are at increased risk for adverse effects. Maintain adequate hydration; monitoring is recommended.

Contraindications:
- Bowel perforation
- Gastric retention
- Gastrointestinal obstruction
- Ileus
- Toxic colitis
- Toxic megacolon
- Severe acute inflammatory bowel disease

Appendix 3: Abstracts from Comparative Randomized Controlled Trials

Miralax Vs. Golytely - A Controlled Study Of Efficacy And Patient Tolerability In Bowel Preparation For Colonoscopy[65]

BACKGROUND: MiraLAX is gaining acceptance as a bowel cleanser for colonoscopy. We hypothesize that MiraLAX/Gatorade is as efficacious for bowel cleansing as Golytely and is more tolerable for patients undergoing screening colonoscopy.
AIM: To compare bowel preparation scores of MiraLAX/Gatorade vs. Golytely and examine differences in patient tolerability.
METHODS: Patients undergoing screening colonoscopy were randomized to 4 L Golytely or 238 g MiraLAX in 64 ounces Golytely and four bisacodyl tablets. Efficacy in bowel cleansing was assessed using the Boston Bowel Preparation Scale (BPPS). Subjects completed a brief survey assessing patient tolerability.
RESULTS: A total of 190 patients were enrolled (85 male, 105 female; mean age 56.9 years, s.d. 6.3); 87 were randomized to MiraLAX, 103 to Golytely. There was no difference in age, gender or timing of colonoscopy between the bowel preparation groups. Golytely's median total BBPS score was significantly higher than that of MiraLAX [9 (IQR 7-9) vs. 8 (IQR 6-9), P = 0.034]. Golytely had a higher rate of an excellent equivalent BBPS score of 8 or 9 than MiraLAX (70% vs. 55%, P = 0.036). There was no difference in patient tolerability (P = 0.857).
CONCLUSIONS: Golytely was more efficacious than MiraLAX/Gatorade in bowel cleansing; both preparations were equally tolerated by patients.

Miralax Is Not As Effective As Golytely In Bowel Cleansing Before Screening Colonoscopies[66]

BACKGROUND & AIMS: Successful colonoscopies require good bowel preparations-poor bowel preparations can increase medical costs, rates of missed lesions, and procedure duration. The combination of polyethylene glycol (PEG) 3350 without electrolytes (MiraLAX; Schering-Plough Healthcare Products, Inc, Kenilworth, NJ) and 64 oz of Gatorade (PepsiCo, Inc, Purchase, NY) has gained popularity as a bowel preparation regimen. However, the efficacy and tolerability of this approach has not been compared with standard bowel preparations in clinical trials. We compared split-dose (PEG) 3350 with electrolytes (GoLytely; Braintree Laboratories, Inc, Braintree, MA) with split-dose MiraLAX alone and in combination with pretreatment medications (bisacodyl or lubiprostone) to determine the efficacy and patient tolerability of MiraLAX as an agent for bowel preparation.
METHODS: We performed a prospective, randomized, blinded, controlled trial at a tertiary care center. Patients (n=403) were randomly assigned to groups given GoLytely, MiraLAX, MiraLAX with bisacodyl (10 mg), or MiraLAX with lubiprostone (24 mug). MiraLAX was combined with 64 oz of Gatorade. All patients were surveyed regarding preparation satisfaction and tolerability. The Ottawa bowel preparation scale was used to grade colon cleanliness.
RESULTS: GoLytely was more effective at bowel cleansing (average Ottawa score, 5.1) than MiraLAX alone (average Ottawa score, 6.9) or in combination with lubiprostone (average Ottawa score, 6.8), or bisacodyl (average Ottawa score, 6.3) (P<.001). MiraLAX was associated with a trend toward longer procedure duration (P=.096). Groups given MiraLAX rated the overall experience as more satisfactory than those given GoLytely (P<.001). There were no differences between polyp detection rates (P=.346) or adverse events (P=.823).
CONCLUSIONS: Split-dose MiraLAX in 64 oz of Gatorade is not as effective as 4 L split-dose GoLytely in bowel cleansing for screening colonoscopies.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to November Week 4 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to November 29, 2023

1	sodium phosphate.mp.	4638
2	Picolines/ or sodium picosulfate.mp.	913
3	moviprep.mp.	53
4	golytely.mp.	100
5	colyte.mp.	19
6	miralax.mp.	52
7	suprep.mp.	10
8	sodium sulfate.mp.	3900
9	polyethylene glycol electrolyte lavage.mp. or Therapeutic Irrigation/	8817
10	Polyethylene Glycols/	49705
11	Laxatives/	1515
12	Cathartics/	3132
13	Colonoscopy/	28197
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	70339
15	13 and 14	1581
16	limit 15 to (english language and humans)	1448
17	limit 16 to (guideline or meta-analysis or practice guideline or "systematic review")	70
18	limit 16 to (comparative study or controlled clinical trial)	296

Appendix 5: Key Inclusion Criteria

Population	Children and Adults
Intervention	Sodium Salts, Polyethylene Glycol Lavage Solutions
Comparator	Other bowel preparation products
Outcomes	Successful bowel preparation
Timing	Split-dose versus one dose the evening prior to procedure
Setting	Outpatients

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Drug Class Review: COVID-19 Antivirals

Date of Review: April 2024 **End Date of Literature Search:** 10/04/2023

Purpose for Class Review:
Evaluate the efficacy, effectiveness and safety of antivirals approved or authorized to treat coronavirus disease 2019 (COVID-19) in non-hospitalized patients.

Plain Language Summary:
- Coronavirus disease 2019 (COVID-19) is caused by a virus called SARS-CoV-2. Most people who get infected with the virus will have mild to moderate symptoms and recover without needing treatment. People over 50 years of age, those that are not vaccinated, and people with certain medical conditions such as cancer, asthma, diabetes, obesity, or heart disease may be at risk for getting severe COVID-19 and may benefit from treatment with medicine.
- Two medicines called PAXLOVID (nirmatrelvir with ritonavir) and LAGEVRIO (molnupiravir) are pills that can be taken by mouth twice a day over 5 days. A third medicine called VEKLURY (remdesivir) must be given through a vein by infusion once a day over 3 days.
- These medicines have shown to lower the risk of getting hospitalized or dying from COVID-19 in people who have mild or moderate symptoms of COVID-19 and are at risk of severe disease. Real world studies continue to show how effective these medicines are as the virus continues to evolve and people's immunity to the virus changes, either from vaccination or past infections.
- PAXLOVID and LAGEVRIO should be started no later than 5 days after symptoms first appear. Remdesivir should be started no later than 7 days after the first symptoms appear. All 3 medicines must be prescribed by a healthcare provider. Pharmacists have Food and Drug Administration approval to prescribe PAXLOVID if the infection is confirmed by testing.
- There are special considerations that the healthcare provider uses to determine which treatment is best for each person. For example, PAXLOVID can interact with several other medicines in ways that can cause dangerous side effects. LAGEVRIO can harm an unborn baby and is not recommended for use during pregnancy. LAGEVRIO may affect bone growth and cannot be used in growing children.
- It is recommended that these medicines be available for people enrolled in the Oregon Health Plan (OHP) fee-for-service program.

Research Questions:
1. What is the evidence for efficacy of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir in treating COVID-19 infections?
2. What are the harms associated with the use of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir when used to treat COVID-19 infections?
3. Are there specific subpopulations that would be more likely to benefit from the use of one antiviral agent over another to treat COVID-19 infections?

Conclusions:
- Two systematic reviews[1,2] and 3 clinical guidelines[3-5] provide high-quality evidence for the efficacy and safety of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir for treatment of COVID-19 infection.

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- A 2023 Cochrane systematic review evaluated all published evidence for the effects of remdesivir on improving clinical outcomes in COVID-19.[1] However, only one RCT (n=562) was conducted in non-hospitalized patients. Participants of that RCT had mild or moderate symptoms that had started 4 days or less prior to screening, and were at risk of progression to severe COVID-19.[1] The primary outcome was a composite of hospitalization related to COVID-9 or death from any cause by day 28. This trial showed that remdesivir decreased the risk of hospitalization up to day 28 compared with placebo (RR 0.28, 95% CI, 0.11 to 0.75; moderate-certainty evidence).[1] No deaths were reported in either arm of this study, so it was not possible to determine if remdesivir impacts 28-day mortality.[1] There were less serious adverse events in the remdesivir arm compared with placebo arm (RR 0.27, 95% CI, 0.10 to 0.70; low-certainty evidence), but no differences in AE of any grade were found between arms (RR 0.91, 95% CI 0.76 to 1.10; moderate-certainty evidence).[1]
- A 2022 Cochrane systematic review assessed the efficacy and safety of ritonavir-boosted nirmatrelvir in treating mild or moderate COVID-19 infection.[2] One RCT (n=2,246) conducted in non-hospitalized patients that compared ritonavir-boosted nirmatrelvir with placebo met inclusion criteria.[2] Trial participants were unvaccinated, without previous confirmed SARS-CoV-2 infection, onset of symptoms of no longer than 5 days, and were at high risk for progression to severe disease.[2] The trial found that ritonavir-boosted nirmatrelvir may reduce all-cause mortality at 28 days versus placebo (RR 0.04, 95% CI, 0.00 to 0.68; low-certainty evidence), and reduce admission to hospital or death within 28 days (RR 0.13, 95% CI, 0.07 to 0.27; low-certainty evidence).[2] There were less serious adverse events with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 0.24, 95% CI, 0.15 to 0.41; low-certainty evidence).[2] No difference in overall treatment-emergent adverse events were found between arms (RR 0.95, 95% CI, 0.82 to 1.10; moderate-certainty evidence).[2] However dysgeusia and diarrhea were more likely to occur with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 2.06, 95% CI, 1.44 to 2.95; moderate-certainty evidence).[2]
- The National Institute of Health (NIH) recommendations for treatment of non-hospitalized adults with COVID-19 are as follows:
    - Oral ritonavir-boosted nirmatrelvir is favored in most high-risk, non-hospitalized adults with mild to moderate symptoms of COVID-19 (Strong Recommendation, Moderate-quality Evidence).[3]
    - Intravenous remdesivir is recommended when ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions) (Moderate Recommendation, Moderate-quality Evidence).[3]
    - Oral molnupiravir is an alternative therapy, for use when the preferred therapies are not available, feasible to use, or clinically appropriate (Weak Recommendation, Moderate-quality Evidence).[3] The NIH panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (Strong Recommendation, Expert Opinion).[3]
- The Infectious Diseases Society of America (IDSA) recommendations for treatment of non-hospitalized people with COVID-19 are as follows:
    - Remdesivir if initiated within 7 days of symptom onset rather than no remdesivir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - Ritonavir-boosted nirmatrelvir if initiated within 5 days of symptom onset rather than no ritonavir-boosted nirmatrelvir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - For adults age 18 years or older who have no other treatment option, molnupiravir if initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional Recommendation, Low Certainty of Evidence).[4]
- The National Institute of Health and Care Excellence (NICE) guidance is similar to the NIH and IDSA recommendations. Ritonavir-boosted nirmatrelvir or remdesivir are considered first- and second-line treatments, respectively, in non-hospitalized adults with mild-to-moderate COVID-19 who are at high risk for progression to severe disease.[5] Molnupiravir is considered a third-line treatment in adults who have no other treatment option.[5]
- Guidance for use in special populations is as follows:
    - Remdesivir is Food and Drug Administration (FDA)-approved for treatment of COVID-19 in pediatric patients aged 28 days and older.[6]
    - Ritonavir-boosted nirmatrelvir is FDA-approved for treatment of COVID-19 in adults.[7]
    - Ritonavir-boosted nirmatrelvir is approved via an FDA emergency use authorization (EUA) for use in pediatric patients aged 12 years and older.[8]

- Ritonavir-boosted nirmatrelvir should not be initiated in patients taking concomitant medications highly dependent on CYP3A4 metabolism until the risk for significant drug interactions is assessed and a plan implemented to prevent adverse reactions.[7]
- The dose of ritonavir-boosted nirmatrelvir should be reduced in patients with impaired renal function (i.e., estimated glomerular filtration rate [eGFR] 30 to 60 mL/min).[7] Ritonavir-boosted nirmatrelvir is not recommended for patients with severe renal impairment (i.e., eGFR < 30 mL/min).[7]
- Molnupiravir is available via an FDA EUA for treatment of COVID-19 in adults.[9]
- Molnupiravir is not authorized under the FDA EUA for use in patients younger than 18 years of age because it may affect bone and cartilage growth.[9]
- Molnupiravir is not recommended for pregnant individuals due to the risk of fetal harm observed in animal models.[9]

- People who are members of racial and ethnic minority groups have higher rates of hospitalization and death from COVID-19 than people who are White.[3] Disparities in the use of antiviral treatments in patients who are not White have been reported; therefore, attention to equitable access is critical.[3] In outpatient studies of the 3 COVID-19 antivirals, Black, Asian, Hispanic, and American Indian populations were underrepresented (see **Table 2**).

Recommendations:

- Create a Preferred Drug List (PDL) class for the antivirals FDA-approved to treat COVID-19 infection and designate ritonavir-boosted nirmatrelvir and remdesivir as preferred agents on the PDL. Ritonavir-boosted nirmatrelvir is only FDA-approved in adults, therefore access for pediatric patients aged 12 to 18 years is only available through the FDA EUA.
- Since molnupiravir is only available through EUA, it will not have PDL status until it is FDA-approved. If it receives FDA-approval, recommend making molnupiravir preferred on the PDL with age restrictions in patients aged 17 years and younger due to risk of adverse effects.

Background:

COVID-19 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] According to the Centers for Disease Control and Prevention (CDC), over one million people have died from COVID-19 in the United States.[10] The NIH has stratified the severity of COVID-19 into four levels:

1. Mild disease: Individuals have symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.[3]
2. Moderate disease: Individuals show evidence of lower respiratory tract disease and have oxygen saturation measured by pulse oximetry (SpO_2) ≥ 94% on room air.[3]
3. Severe disease: Individuals have pneumonia and one of the following: SpO2 < 94% on room air, respiratory rate > 30 breaths/minute, or lung infiltrates > 50%.[3]
4. Critical disease: Individuals have respiratory failure, septic shock, and/or multiple organ dysfunction.[3]

Most symptomatic COVID-19 patients have mild or moderate disease and do not require hospitalization.[11] Patients who develop severe or critical disease require hospitalization with respiratory support.[11] Many factors can increase the risk for developing severe or critical COVID-19 disease.[11] Some of the most common risk factors are age over 50 years, obesity, cardiovascular disease, asthma, and chronic obstructive pulmonary disease.[3,11] Communities that have been historically marginalized or made socially vulnerable due to a lack of access to health care or an inability to socially isolate are at increased risk of SARS-CoV-2 acquisition, COVID-19–related hospitalization, and death.[3,11] These communities include racial and ethnic minorities, essential non-health care workers, and some people with disabilities.[3,11] The severity of COVID-19 is changing as the proportion of individuals who are vaccinated increases and the prevalence of different SARS-CoV-2 variants changes.[12]

Three antiviral agents are currently available for treatment of SARS-CoV-2 infection. Ritonavir-boosted nirmatrelvir (PAXLOVID) is a combination oral drug that inhibits 3-chymotrypsin-like cysteine protease, an enzyme necessary to produce other functional SARS-CoV-2 proteins.[12] Ritonavir does not have anti-SARS-COV-2 activity, but is used as a pharmacokinetic booster to slow the metabolism of nirmatrelvir and allow for twice daily dosing.[12] Ritonavir-boosted nirmatrelvir tablets are FDA-approved for treatment of adults with mild-to-moderate COVID-19 infection who are at risk for severe COVID-19 and hospitalization.[7] Ritonavir-boosted nirmatrelvir is available via the FDA EUA for pediatric patients aged 12 to 17 years, and its use must be consistent with the terms and conditions of the EUA.[8]

A second oral antiviral, molnupiravir (LAGEVRIO) is a prodrug of N-hydroxycytidine (NHC), an oral ribonucleoside analog that causes viral genome replication errors.[12] Molnupiravir has FDA EUA for use in adults with mild-to-moderate symptoms of COVID-19 who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.[9]

The third antiviral, remdesivir (VEKLURY) is administered via intravenous (IV) infusion. Remdesivir is a nucleotide prodrug of an adenosine analog, and binds to the viral RNA-dependent RNA polymerase which inhibits viral replication by prematurely terminating RNA transcription.[6] Remdesivir is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are: 1) hospitalized, or 2) not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[6]

A comparison of the 3 antiviral indications and dosing is presented in **Table 1**. Additional details including pharmacology, pharmacokinetics, warnings, precautions and use in special populations for each drug are summarized in **Appendix 1**.

Table 1. Antivirals to Treat Mild-to-Moderate COVID-19 in People at High Risk for Progression to Severe COVID-19 Disease.

Drug Name (Brand Name, Manufacturer)	FDA Approval or FDA EUA	Age Range	Route/Strength	Dose and Frequency
Molnupiravir[9] (LAGEVRIO, Merck)	• EUA effective 12/23/2021.	• Adults	• Oral • 200 mg capsules	• Four x 200 mg capsules orally every 12 hours x 5 days • Start within 5 days of symptom onset.
Nirmatrelvir (Ritonavir-boosted)[7,8] (PAXLOVID, Pfizer)	• FDA approval 5/25/2023 for adults. • EUA effective 12/22/2021 and continues to authorize eligible pediatric patients not covered under the FDA approval.	• FDA-approved: Adults • EUA: Children aged 12 to 18 years weighing at least 40 kg	• Oral • Nirmatrelvir 150 mg with Ritonavir 100 mg tablets co-packaged	• Two nirmatrelvir 150 mg tablets with one ritonavir 100 mg tablet orally twice daily x 5 days. • For patients with moderate renal impairment (eGFR 30 to 59 mL/min): Reduce dose to one nirmatrelvir 150 mg with one ritonavir 100 mg tablet orally twice daily for 5 days. • Not recommended in patients with severe renal impairment (eGFR <30 mL/min).

				• Not recommend in patients with severe hepatic impairment (Child-Pugh Class C). • Start within 5 days of symptom onset.
Remdesivir[6] (VEKLURY, Gilead)	• FDA approval 10/22/2020.	• Adults and children 28 days of age and older and weighing at least 3 kg	• Intravenous infusion • 100 mg vial	• 200 mg IV on day 1 followed by 100 mg IV for 2 consecutive days. • Pediatric dose is 5 mg/kg on day 1 followed by 2.5 mg/kg on days 2 and 3. • Start within 7 days of symptom onset.
Abbreviations: eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; kg = kilograms; mg = milligrams; mL = milliliters; min = minutes.				

Differences in participants studied across the COVID-19 antiviral RCTs do not permit direct comparisons or formal quantitative indirect comparisons of safety and effectiveness between the 3 antivirals currently recommended for COVID-19 treatment.[12] For example, the molnupiravir trial enrolled substantially larger proportions of individuals with obesity compared to the nirmatrelvir/ritonavir trial.[13] In addition, there were variabilities in the timing of trial enrollment which affected the primacy causal variant observed in the trials and impacted the vaccination status of study participants between trials.[12] Factors that must be considered when reviewing these trials include: 1) the rapid evolution of SARS-CoV-2 leading to variants with treatment resistance and with different morbidity and mortality impacts; 2) the enrollment of predominantly unvaccinated patients in early trials; and 3) the uncertain generalizability of data related to hospitalization rates and other health care resource utilization from studies conducted prior to the advent of the Omicron variant and based predominately or exclusively in countries outside of the United States (US).[12] An overview of the pivotal trials that provided safety and efficacy evidence for use of antivirals in treating COVID-19 is provided in **Table 2**. Currently, there are no comparative head-to-head trials for the 3 antivirals approved or authorized to treat COVID-19.

Table 2. Key RCTs in Outpatient Adults with Mild-to-Moderate COVID-19 at High Risk for Severe Disease.

Trial Details	Intervention	Inclusion/Exclusion Criteria	Outcomes	Baseline Characteristics	Results
Bernal A, et al.[13] MOVe-OUT • DB, MC, Phase 2/3 RCT • N=1,433 • 107 sites in 20 countries • Enrollment: 5/6/2021-10/2/2021	1. Molnupiravir 800 mg orally twice daily x 5 days (n=709) Vs. 2. Placebo orally twice daily x 5 days (n=699)	**Inclusion:** • Age ≥18 yrs • Mild or moderate symptom onset within 5 days • Not vaccinated • ≥1 risk factor for severe disease **Exclusion:** • Unwillingness to use contraception during treatment and at least 4 days after treatment completion • Prior COVID-19 vaccination • HBV or HCV infection with complications	**Primary Endpoints:** • Incidence of hospitalization or death from any cause through day 29 • Incidence of adverse events	Age (median): 43 yrs Gender (female): 51% US enrollment: 6% Race/ethnicity: • 57% White • 7% American Indian • 7% Alaska Native • 5% Black • 3% Asian Risk factors: • BMI ≥30: 74% • Age >60 years: 17% • Diabetes: 16%	**Hospitalization or Death from any Cause through Day 29** 1. 6.8% (n=48) 2. 9.7% (n=68) Difference: -3.0% 95% CI, -5.9 to -0.1 **Mortality** 1. 0.1% (n=1) 2. 1.3% (n=9) **Adverse Events** 1. 1.4% (n=10) 2. 2.9% (n=20)

					Serious Adverse Events 1. 0.7% (n=5) 2. 1.9% (n=13)
Hammond J, et al.[14] EPIC-HR • DB, MC, Phase 2/3 RCT • N=2,246 • 343 sites in 21 countries • Enrollment: 7/16/2021-12/9/2021	1. Nirmatrelvir 300 mg with ritonavir 100 mg orally every 12 hours x 5 days (n=1039) Vs. 2. Placebo orally every 12 hours x 5 days (n=1046)	**Inclusion:** • Age ≥18 yrs • Mild or moderate symptom onset within 5 days • Not vaccinated • ≥1 risk factor for severe disease **Exclusion:** • Prior COVID-19 infection or vaccination • HIV infection	**Primary Endpoint:** • COVID-19-related hospitalization or death from any cause through day 28 **Secondary Endpoints:** • Adverse events	Age (median): 46 yrs Gender (female): 49.5% US enrollment: 41% Race/ethnicity: • 72% White • 5% Black • 14% Asian • 9% American Indian or Alaska Native Risk factors: • BMI ≥30: 33% • Age >60 years: 12% • Diabetes: 12% • Hypertension: 33%	**Hospitalization or Death from any Cause through Day 28** 1. 0.77% (n=8) 2. 6.31% (n=65) Difference: 5.62% 95% CI, 7.21 to 4.03 P< 0.001 **Mortality** 1. 0% (n=0) 2. 1.15% (n=12) **Adverse Events** 1. 7.8% (n=86) 2. 3.8% (n=42) **Serious Adverse Events** 1. <0.1% (n=1) 2. 0% (n=0)
Gottlieb RL, et al.[15] PINETREE • DB, MC Phase 3 RCT • N=562 • 64 sites in 4 countries • Enrollment: 9/18/2020-4/8/2021	1. Remdesivir 200 mg IV on Day 1 followed by 100 mg IV on Days 2 and 3 (n=279) Vs. 2. Placebo (n=283) IV on days 1-3	**Inclusion:** • Laboratory-confirmed SARS-CoV-2 infection ≤4 days from screening • Aged ≥12 yrs • ≥1 risk factor for disease progression or 60 yrs and older • Symptom onset ≤7 days from randomization • ≥1 ongoing COVID-19 symptom **Exclusion:** • COVID-19 vaccination • Receipt of supplemental oxygen • Previous hospitalization or treatment for COVID-19	**Primary Endpoints:** • COVID-19-related hospitalization or death from any cause by Day 28 • Occurrence of AEs	Age (median): 50 yrs Gender (female): 48% Adolescents: 1.4% (n=8) US enrollment: 94% Race/ethnicity: • 80% White • 8% Black • 6% American Indian • 3% Asian • 42% Hispanic Risk factors: • BMI ≥30: 55% • Age >60 years: 30% • Diabetes: 62% • Hypertension: 48%	**Hospitalization or Death from any Cause through Day 28** 1. 0.7% (n=2) 2. 5.3% (n=15) HR: 0.13 95% CI, 0.03 to 0.59 P=0.0008 **Mortality** 1. 0 2. 0 **Adverse Events** 1. 12.2% (n=34) 2. 8.8% (n=25) **Serious Adverse Events** 1. 1.8% (n=5) 2. 6.7% (n=19)

Abbreviations: BMI = body mass index; CI = Confidence Interval; COVID-19 = coronavirus disease; DB = double blind; HR = Hazard Ratio; HBV = hepatitis B; HCV = hepatitis C; IV = intravenous; LOS = length of stay; MC = multi-center; n = number; RCTs = randomized controlled trials; US = United States; WHO = World Health Organization; yrs = years

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, and warnings and precautions.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Remdesivir for Treatment Of COVID-19
A 2023 Cochrane systematic review evaluated all evidence from RCTs on the effect of remdesivir on clinical outcomes in COVID-19.[1] Literature was searched through May 21, 2022.[1] Non-hospitalized individuals with asymptomatic or mild COVID-19 infection were differentiated from hospitalized individuals with moderate to severe COVID-19.[1] Nine RCTs (n=11,218) met inclusion criteria, however only one (n=562) of the 9 RCTs was conducted in the outpatient setting in symptomatic people with a risk of progression to severe disease.[1] The population in the outpatient RCT differed significantly from the hospitalized population in terms of baseline disease severity, clinical course, and duration of the treatment (3 days versus 10 days, respectively), so the data were analyzed separately.[1] Risk of bias for the outpatient RCT was considered to be low for risk of hospitalization (clinical worsening) and safety outcomes.[1] Risk of bias for clinical improvement by day 14 was estimated as high as a large number of missing values and analyses were not performed as pre-defined by protocol, with a high risk of selective reporting.[1]

Data from this RCT showed that remdesivir decreased the risk of hospitalization up to day 28 compared with placebo (RR 0.28, 95% CI, 0.11 to 0.75; risk difference [RD] 46 fewer per 1000, 95% CI, 57 fewer to 16 fewer; n=562; moderate-certainty evidence).[1] No deaths were reported in either arm of this study, so it was not possible to determine if remdesivir impacts 28-day mortality.[1] There were less serious adverse events (in the remdesivir arm compared with placebo arm (RR 0.27, 95% CI, 0.10 to 0.70; low-certainty evidence), but no differences in AE of any grade were found between arms (RR 0.91, 95% CI 0.76 to 1.10; moderate-certainty evidence).[1] The applicability of this evidence to current practice may be limited by the recruitment of participants from mostly unvaccinated populations exposed to early variants of the SARS-CoV-2 virus at the time the study was undertaken.[1]

Nirmatrelvir Combined with Ritonavir for Treatment of COVID-19
A 2022 Cochrane systematic review assessed the efficacy and safety of ritonavir-boosted nirmatrelvir in treating COVID 19.[2] Literature was searched through July 11, 2022. Only one trial (n=2,246) met inclusion criteria, an RCT conducted in outpatients with mild to moderate COVID-19 which compared ritonavir-boosted

nirmatrelvir with standard of care plus placebo.[2] Trial participants were unvaccinated, without previous confirmed SARS-CoV-2 infection, had a symptom onset of no more than 5 days before randomization, and were at high risk for progression to severe disease.[2] No evidence is currently available on ritonavir-boosted nirmatrelvir to treat hospitalized people with COVID-19 or to prevent a SARS-CoV-2 infection.

Ritonavir-boosted nirmatrelvir compared to standard of care plus placebo may reduce all-cause mortality at 28 days (RR 0.04, 95% CI, 0.00 to 0.68; 1 study, n= 2,224; estimated absolute effect: 11 deaths per 1000 people receiving placebo compared to 0 deaths per 1000 people receiving nirmatrelvir/ritonavir; low-certainty evidence), and may reduce hospitalization or death within 28 days (RR 0.13, 95% CI, 0.07 to 0.27; estimated absolute effect: 61 admissions or deaths per 1000 people receiving placebo compared to 8 admissions or deaths per 1000 people receiving nirmatrelvir/ritonavir; low-certainty evidence).[2]

There were less serious adverse events with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 0.24, 95% CI, 0.15 to 0.41; low-certainty evidence).[2] No difference in overall treatment-emergent adverse events were found between arms (RR 0.95, 95% CI, 0.82 to 1.10; moderate-certainty evidence).[2] However dysgeusia and diarrhea were more likely to occur with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 2.06, 95% CI, 1.44 to 2.95; moderate-certainty evidence).[2]

In summary, there is low-certainty evidence that ritonavir-boosted nirmatrelvir reduces the risk of all-cause mortality and hospital admission or death based on one trial investigating unvaccinated COVID-19 participants with symptom onset of no more than 5 days, without previous infection, who were at high risk for progression to severe disease.[2]

After review, 10 systematic reviews were excluded due to poor quality (e.g., network meta-analyses),[16-22] or wrong study design of included trials (e.g., observational).[23-26]

Guidelines:

National Institute of Health: Therapeutic Management of Nonhospitalized Adults with COVID-19

The most recent NIH update on treatment of outpatients with COVID-19 was issued July 21, 2023.[3] The NIH recommends that several factors be considered before treatment is selected for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications, the potential for significant drug-drug interactions, the patient's pregnancy status, time from symptom onset, and the *in vitro* activity of the available drug against currently circulating SARS-CoV-2 variants and subvariants.[3] Most of the data that support the use of the recommended treatment options come from clinical trials that enrolled individuals who were at high risk of disease progression and who had no pre-existing immunity from COVID-19 vaccination or prior SARS-CoV-2 infection.[3] The proportion of hospitalizations and deaths in the placebo arms of these trials was high compared to what is observed currently in populations where most people are vaccinated or have had prior SARS-CoV-2 infection.[3] Although these trials demonstrated the efficacy of using antiviral drugs in high-risk populations, it is difficult to know their precise effectiveness in the current real-world settings.[3]

Available therapies remain beneficial in people who continue to have an increased risk of disease progression.[3] These risk factors of severe disease include older people (i.e., those aged >50 years, but especially those aged ≥65 years) and people who are unlikely to have an adequate immune response to COVID-19 vaccines due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications.[3] Other risk factors include lack of vaccination or incomplete vaccination; a prolonged amount of time since the most recent vaccine dose (e.g., >6 months); and conditions such as obesity, diabetes, and chronic respiratory, cardiac, or kidney disease.[1] [3] Recommendations for patients who are at high risk for progressing to severe COVID-19 are as follows in order of preference:

- Oral ritonavir-boosted nirmatrelvir is favored in most high-risk, nonhospitalized patients with mild to moderate COVID-19 (Strong Recommendation, Moderate-quality Evidence).[3]
    - Ritonavir-boosted nirmatrelvir has high efficacy and has been shown to reduce hospitalization and death when administered to high-risk, unvaccinated, nonhospitalized patients within 5 days of symptom onset.[3,14]
    - Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions.[3]
    - The use of ritonavir-boosted nirmatrelvir may be challenging in patients with severe renal impairment and in patients receiving certain transplant-related immunosuppressants or chemotherapy.[3]
- Intravenous remdesivir is recommended when ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions) (Moderate Recommendation, Moderate-quality Evidence).[3]
- Oral molnupiravir is recommended to be reserved as alternative therapy when preferred therapies are not available, feasible to use, or clinically appropriate (Weak Recommendation, Moderate-quality Evidence).[3]
    - Molnupiravir appears to have lower efficacy[13] than the other options recommended by the NIH Panel, although no RCTs have directly compared these therapies.[3]
    - The NIH panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (Strong Recommendation, Expert Opinion).[3]

Infectious Diseases Society of America: Treatment of Patients with COVID-19

In March 2020, the IDSA formed a multidisciplinary guideline panel of infectious diseases clinicians, pharmacists, and methodologists with varied areas of expertise to regularly review the evidence and make recommendations about the treatment and management of persons with COVID-19.[4] The process used a living guideline approach and followed a rapid recommendation development checklist.[4] The most recent treatment update was published April 12, 2023. After a review of published evidence, medications that are **not** recommended for outpatient treatment of COVID-19 include: hydroxychloroquine, chloroquine, azithromycin, lopinavir/ritonavir, inhaled corticosteroids, famotidine, ivermectin, and colchicine.[4] The antidepressant, fluvoxamine, is recommended only in the context of a clinical trial (no recommendation; insufficient evidence).[4] In 2 RCTs that studied symptomatic ambulatory patients with COVID, fluvoxamine failed to demonstrate a beneficial effect on mortality at 28 days compared to no fluvoxamine (RR 0.69; 95% CI, 0.38 to 1.27; low-quality evidence).[4]

The overall certainty of evidence for the use of remdesivir in patients with mild-to-moderate COVID-19 was low due to concerns about imprecision, as less than half of the original projected sample size was enrolled leading to few events and fragility of the effect estimate.[4] However, compared to prior trials, giving remdesivir early in the course of infection appears to have a robust effect within the limitation of a small sample size.[4] The panel agreed that benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk for severe disease.[4] The evidence confirms that using remdesivir early in the disease process when viral loads are high confers maximum benefit.[4] The evidence for the use of remdesivir in children is limited.[4] For ambulatory children at risk for severe disease, one RCT included 8 children aged 12 to 18 years, limiting confidence in the available direct evidence for ambulatory care.[4] A report of 77 children who received remdesivir through compassionate use early in the pandemic found good tolerability in this population with a low rate of serious adverse events.[4]

The overall certainty of the evidence for the use of ritonavir-boosted nirmatrelvir in ambulatory patients is low. There are concerns with the inability to exclude potential risks to bias because of limited availability of study details, and there is imprecision due to a low number of events reported.[4] The panel agreed that the benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk of severe disease; however, recognized concerns with drug

interactions must be considered.[4] The evidence confirms that using ritonavir-boosted nirmatrelvir early in the disease process when viral loads are high confers maximum benefit.[4] Recurrence of symptoms associated with viral rebound has been estimated to occur in ritonavir-boosted nirmatrelvir- treated patients in 0.8% to 6.6% in various trials, including the EPIC-HR trial.[4,14] More data are needed on the potential adverse effects of this medication.[4] In addition, future studies are important to inform the impact of ritonavir-boosted nirmatrelvir in hospitalized patients, in vaccinated high-risk patients with mild-to-moderate COVID-19 and in symptomatic immunocompromised patients with persistently elevated viral loads.[4]

The overall certainty of evidence for the use of molnupiravir in ambulatory patients is low given concerns with data imprecision, driven by few reported events and a relatively small effect size.[4] The use of molnupiravir presents additional considerations and potential concerns regarding viral mutagenesis in immunocompromised persons and safety in persons of reproductive age, for which more data are needed to quantify such effects.[4] The panel recognized that alternative treatment options exist with the possibility of greater benefit with a smaller known safety profile.[4] The guideline panel suggests the use of molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who are within 5 days of symptom onset and have no other treatment options.[4] More data are needed on the potential adverse effects of molnupiravir.[4]

Conditional recommendations supporting the use of remdesivir, ritonavir-boosted nirmatrelvir, and molnupiravir based on low-quality evidence are summarized below. Patient-specific factors (e.g., patient age, symptom duration, renal function, drug interactions), product availability, and institutional capacity and infrastructure should drive decision-making regarding choice of agent.[4] It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.[4] Data for combination of treatments do not currently exist.[4]

- Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at high risk for progression to severe disease (e.g., patients with $Sp0_2 \leq 94\%$ on room air), the IDSA guideline panel suggests remdesivir initiated within 7 days of symptom onset rather than no remdesivir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - Dosing for remdesivir in mild-to-moderate COVID-19 is 200 mg on day one followed by 100 mg on days two and three. Pediatric dosing is 5 mg/kg on day 1 and 2.5 mg/kg on subsequent days.[4]
- In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests ritonavir-boosted nirmatrelvir initiated within 5 days of symptom onset rather than no ritonavir-boosted nirmatrelvir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - Drug/supplement screening needed for potential drug interactions.[4]
    - Dosing based on renal function per manufacturer's guidance.[4]
    - In ambulatory patients (≥18 years of age) with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment option, the IDSA guideline panel suggests molnupiravir initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional Recommendation, Low Certainty of Evidence).[4]
        - Molnupiravir is not authorized under the FDA EUA for use in pediatric patients less than 18 years because it may affect bone and cartilage growth.[4]
        - Molnupiravir is not authorized under the FDA EUA for use during pregnancy.[4]

National Institute for Health and Care Excellence: Managing COVID-19 Rapid Guideline

The NICE guidance was published in March 2021 and most recently updated June 22, 2023.[5] Risk factors for progression to severe COVID-19 in adults were defined by the independent advisory group and include: people with Down's syndrome and other genetic disorders, solid cancer, hematological diseases and

recipients of hematological stem cell transplant, renal disease, liver diseases , solid organ transplants, immune-mediated inflammatory disorders, asthma, chronic pulmonary obstructive disease, immune deficiencies, HIV/AIDS, and neurological disorders.[5] Most of the RCTs reviewed for the NICE guidance were in unvaccinated patients prior to the emergence of the Omicron variant (see **Table 2** above).[5]

- Ritonavir-boosted nirmatrelvir is recommended as first-line treatment initiated as soon as possible and within 5 days of symptom onset (benefits outweigh harms for almost everyone) for treating COVID-19 in adults, only if the patient is at increased risk for progression to severe COVID-19, as described earlier, and supplemental oxygen for the infection is not needed.[5]
- Remdesivir is recommended as a second-line treatment option (Conditional recommendation; benefits outweigh harms for most people). A 3-day course of remdesivir may be considered for children and young people who weigh at least 40 kg and adults with COVID-19 who:
    - do not need supplemental oxygen for COVID-19, and
    - are within 7 days of symptom onset, and
    - are thought to be at high risk of progression to severe COVID-19. [5]
- Molnupiravir may be considered as a third-line treatment option (Conditional recommendation) for adults with COVID-19 who:
    - do not need supplemental oxygen for COVID-19, and
    - are within 5 days of symptom onset, and
    - are thought to be at high risk of progression to severe COVID-19.[5]

Randomized Controlled Trials:

A total of 365 citations were manually reviewed from the initial literature search. After further review, 365 citations were excluded because of wrong study design, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Specific Drug Information

Table 1. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption/Distribution	Metabolism/Excretion	Pharmacokinetics (mean)
Molnupiravir (LAGEVRIO)[9]	• Prodrug metabolized to NHC, a nucleoside analog which inhibits RNA replication.	• Median T_{max} = 1.5 hrs • 0% protein bound	• Major route of elimination is hepatic.	• Half-life: 3.3 hrs • Cmax: 2330 ng/mL • AUC: 8260 ng/hr/ml • Vd: 142 L
Nirmatrelvir/Ritonavir (PAXLOVID)[7]	• Nirmatrelvir: protease inhibitor which blocks viral replication. • Ritonavir: inhibits metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. It does not have viral activity against the SARS-CoV-2 virus.	• Median T_{max} = 3 hrs • 69% protein bound	• Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal. • Major route of elimination is renal.	• Half-life: 6.05 hrs • Cmax: 3.43 mcg/mL • AUC: 30.4 mcg/hr/mL • Vd: 104.7 L

Remdesivir (VEKLURY)[6]	• Nucleotide analog RNA polymerase inhibitor which reduces RNA transcription.	• T_{max} = 0.67 to 0.68 hrs
		• 88-93.6% protein bound
			• Major route of elimination is hepatic.
			• Metabolic Pathways
			  ○ CES1 80%
			  ○ Cathepsin A (10%)
			  ○ CYP3A 10%
				• Half-life: 1 hr
				• Cmax: 2229 ng/L
				• AUC: 1585 ng/hr/mL
				• Vd: NR

Abbreviations: AUC = area under the curve; C = concentration; CYP = cytochrome P450; hrs = hours; L = liters; mcg = micrograms; mL = milliliters; ng = nanograms; NHC = N-hydroxycytidine; NR = not reported; T = time; Vd = volume of distribution				

Table 2. Use in Specific Populations.

Drug Name	Pediatric Patients	Patients with Renal Impairment	Patients with Hepatic Impairment	Pregnancy/Lactation
Molnupiravir (LAGEVRIO)[9]	• Not authorized for use in patients < 18 yo as it may affect bone and cartilage growth.	• No dose adjustment is recommended.	• No dose adjustment is recommended.	• Based on animal data, may cause fetal harm. Use is not recommended during pregnancy. • Breast feeding is not recommended during treatment and up until 4 days after last dose.
Nirmatrelvir/Ritonavir (PAXLOVID)[7]	• EUA permits use in pediatric patients > 12 yo and older weighing at least 40 kg • Not FDA approved in patients < 18 yo	• Moderate renal impairment (eGFR 30 to 59 mL/min): reduce dose to 2 tablets (nirmatrelvir 150 mg with 1 tablet of ritonavir 100 mg) orally twice daily for 5 days. • Not recommended in severe renal impairment (eGFR <30 mL/min)	• No dose adjustment is recommended in mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. • Not recommended for use in severe hepatic impairment (Child-Pugh Class C) due to lack of data.	• Insufficient data to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse fetal outcomes. • Insufficient data in breast fed infants. • Consider risk versus benefit.
Remdesivir (VEKLURY)[6]	• Approved in pediatric patients 28 days of age and older and weighing at least 3 kg.	• No dose adjustment is recommended.	• No dose adjustment is recommended. • Discontinue if ALT/AST increase to > 10 times the upper limit of normal	• Insufficient pregnancy data is available during first trimester. • No drug-associated risks have been identified in second and third trimesters. • Consider risk versus benefit in lactation.
Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration; EUA = Emergency Use Authorization; FDA = Food and Drug Administration kg = kilograms; mg = milligram; mL = milliliters; min = minutes; yo = years old				

Table 3. Summary of Warnings and Precautions.

Drug Name	Drug Interactions	Hepatic Disease	Risk of HIV-1 Resistance
Molnupiravir (LAGEVRIO)[9]	N/A	N/A	N/A
Nirmatrelvir/Ritonavir (PAXLOVID)[7]	• Contraindicated for co-administration with drugs metabolized by CYP3A hepatic pathway.	• Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Caution should be exercised in patients with pre-existing hepatic disease, liver enzyme abnormalities, or hepatitis.	• Due to coadministration with ritonavir, there may be a risk of developing resistance to HIV protease inhibitors in people with uncontrolled or undiagnosed HIV-1 infection.
Remdesivir (VEKLURY)[6]	• Avoid co-administration with chloroquine or hydroxychloroquine due to risk of reduced antiviral activity.	• Increased risk of transaminase elevations.	N/A
Abbreviations: HIV = Human Immunodeficiency Virus; N/A = Not Applicable			

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to September Week 4 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 04, 2023

1	COVID-19/ or SARS-CoV-2/ or COVID-19 Drug Treatment/	247189
2	molnupiravir.mp.	421
3	remdesivir.mp.	2492
4	Ritonavir/ or nirmatrelvir.mp.	5572
5	2 or 3 or 4	8009
6	1 and 5	3306
7	limit 6 to (english language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	365

Appendix 3: Key Inclusion Criteria

Population	Patients with mild-to-moderate COVID-19
Intervention	Molnupiravir, nirmatrelvir/ritonavir, and remdesivir
Comparator	Placebo or standard of care
Outcomes	Hospitalization or mortality
Timing	Within 5 to 7 days of symptom onset, depending on antiviral selection
Setting	Outpatients

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

New Drug Evaluations: pegcetacoplan (SYFOVRE) injection, for intravitreal use
avacincaptad pegol (IZERVAY) injection, for intravitreal use

Date of Review: April 2024

End Date of Literature Search: 12/31/2023

Generic Name:
pegcetacoplan
avacincaptad pegol

Brand Name (Manufacturer):
Syfovre (Apellis Pharmaceuticals, Inc)
Izervay (IVERIC bio, Inc)

Dossier Received:
Yes (SYFOVRE)
No (IZERVAY)

Plain Language Summary:

- The United States (US) Food and Drug Administration (FDA) approved two new medicines, pegcetacoplan and avacincaptad pegol, to treat adults with age-related macular degeneration (AMD). These medicines are known as complement inhibitors.
- Age-related macular degeneration is a condition that affects older people of both sexes but is more common in fair-skinned people and those who smoke. Even though the cause is unknown, the condition often runs in families.
- There are two forms of AMD, dry and wet. The macula is part of an area near the center of the back of the eye, called the retina. The macula allows a person to see fine details and colors in the center of their vision.
- In dry AMD, the macula tissue is damaged, becomes thin, and gets a buildup of protein and fat products called drusen. As the body tries to repair damaged tissue, other cells and protein helpers cause inflammation. Over time, too much inflammation leads to additional tissue damage. Although there may not be noticeable bleeding, scarring, or pain right away, the patient's vision slowly gets worse. A doctor may notice these changes around the macula at an eye-exam even before patients has visual complaints.
- In wet AMD, abnormal blood vessels develop in the layer of tissue under the macula. The vessels often leak fluid that may cause immediate scarring and damage. Wet AMD is a medical emergency that may lead to complete blindness if not treated quickly.
- Dry AMD usually does not result in complete blindness but may lead to blind spots. However, the patient can still see around the outer edge of the visual field and see colors. When the patient has advanced dry AMD, or geographic atrophy (GA), it makes tasks of daily living difficult because it is hard to see things clearly especially in dim light.
- There is no cure for AMD but the complement inhibitors pegcetacoplan and avacincaptad pegol have been studied to stop some of the damage caused by inflammation in order to treat advanced AMD. These medicines must be injected directly into the eye with a special needle by a trained clinician.
- Evidence from one study shows that pegcetacoplan resulted in a small change in GA growth rate compared to a false (placebo) injection at 12 months, but the other study did not show any difference. Both of the studies did not show any improvement in eye function (for example, ability to see better or read better).

Author: David Engen, PharmD

- Evidence from two studies show that avacincaptad pegol resulted in a small change in GA growth rate compared to a false (placebo) injection at 12 months but did not show any improvement in eye function (for example, ability to see better or read better).
- Both pegcetacoplan and avacincaptad pegol may increase the risk of eye infection, eye bleeding, elevated eye pressure, retinal separation (detachment), or harmful blood vessel formation in the retinal area. Patients who used pegcetacoplan also had reports of eye inflammation.
- We recommend that pegcetacoplan and avacincaptad pegol be non-preferred, and that providers explain why someone needs one of these complement inhibitors before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the evidence for comparative efficacy of complement inhibitors pegcetacoplan and avacincaptad pegol for the treatment of age-related macular degeneration?
2. What is the evidence for comparative safety of complement inhibitors pegcetacoplan and avacincaptad pegol for the treatment of age-related macular degeneration?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed by treatment with a complement inhibitor for AMD?

Conclusions:

- The efficacy and safety of pegcetacoplan was studied in 2 parallel, phase 3 randomized, placebo-controlled trials (APL2-303 "DERBY" and APL2-304 "OAKS") in adult patients with AMD.[1-3]
- There is low quality evidence from one fair quality study (OAKS) that pegcetacoplan administered monthly (PM) or every other month (EOM) resulted in a statistically significant reduction in GA lesion growth compared to sham injection at 12 months (PM: -21% change; mean size difference -0.41 mm^2; 95% confidence interval (CI) -0.64 to -0.18; p=0.0004; and EOM: -16% change [mean size difference –0.32 mm^2, 95% CI, –0.54 to –0.09; p=0.0055).[1-3] The DERBY trial did not demonstrate a statistically significant difference in GA lesion growth for pegcetacoplan compared to sham injection.[1-3] The clinical significance of the change reported in the OAKS trial is unclear and neither trial showed benefit in functional measures or quality-of-life in pegcetacoplan-treated patients compared to sham injection.[1-3]
- The efficacy and safety of avacincaptad pegol was evaluated in 2 randomized, double-blind, sham-controlled trials. The first study was an 18-month, phase 2/3 trial (OPH2003 "GATHER1") and the second a 24-month, phase 3 trial (ISEE2008 "GATHER2").[4-8]
- There is low-quality evidence from two moderate-quality studies that avacincaptad pegol 2 mg administered monthly resulted in a statistically significant reduction in rate of GA lesion growth compared to sham injection at 12 months (GATHER1: -35% change; mean difference (MD) = 0.67mm^2/year;95% CI, 0.21 to 1.13; p <0.01 and GATHER2: -18% change; MD 0.38 mm^2/year; 95% CI, 0.12 to 0.63; p=0.0039).[4-8] The clinical significance of the change reported in GATHER1 and GATHER2 is unclear and neither trial was able to show any benefit in functional measures including visual acuity in avacincaptad pegol-treated patients.[4-8]
- Treatment with either pegcetacoplan or avacincaptad pegol has been associated with conjunctival hemorrhage and development of neovascular (wet) AMD.[1-8]
- Treatment with either pegcetacoplan or avacincaptad pegol is contraindicated in patients with ocular or periocular infections and those with active intraocular inflammation.[1,2,4,5]
- There is insufficient direct comparative evidence between the complement inhibitors pegcetacoplan and avacincaptad pegol for safety and efficacy in treating AMD.

- Evidence for pegcetacoplan and avacincaptad pegol is primarily limited to White populations at least 50 years of age or older.[1,3,4,6-8] There is insufficient evidence on efficacy or harms data for other subgroups.

Recommendations:
- Create a new preferred drug list (PDL) class: Ophthalmologic Complement Inhibitors.
- Designate pegcetacoplan and avacincaptad pegol as non-preferred on the PDL.
- Implement prior authorization (PA) criteria for complement inhibitors (pegcetacoplan and avacincaptad pegol) to ensure appropriate and safe use in FDA-approved indications.

Background:
Age-related macular degeneration (AMD) is a chronic, progressive, retinal disease that eventually leads to visual impairment.[9,10] Age-related macular degeneration is among the leading causes of blindness worldwide and the foremost cause of legal blindness is the US.[11] The incidence of AMD increases with age and is more common in fair-skinned individuals.[11] It affects approximately 2-6% of older adults in the US and is most prevalent in adults greater than 50 years of age. [11-13] The pathogenesis of AMD has not been fully elucidated; however, contemporary research has indicated advanced age and smoking are significant risk factors.[14-17] Other risk factors for AMD may include genetic predisposition, cardiovascular disease history, sedentary lifestyle, and increased BMI $\geq$30 kg/m^2.[11-13] There is no cure available for AMD, but the goal of treatment is to slow disease progression and prevent blindness.[18] Supportive therapy is used to preserve visual acuity through lifestyle modifications to help patients maintain maximum independence and quality of life.[19,20]

Age-related macular degeneration is characterized by degenerative changes in the light-sensitive retinal neurons and surrounding supportive cells referred to as the retinal pigment epithelium (RPE).[21,22] The RPE is a continuous single layer of epithelial cells situated between the retina and choroid.[23] Deterioration and dysfunction of the RPE results in hyperpigmentation, atrophy, macular thinning, and accumulation of extracellular drusen deposits between the RPE and the area known as Bruch's membrane.[21,23] Drusen are lipid- and protein-rich deposits that do not usually affect visual function unless they enlarge and coalesce.[23] Early AMD may be asymptomatic, but with chronic inflammation and infiltration of mononuclear phagocytes, disease may begin to progress toward later stages that are more conspicuous.[21,23] At the intermediate stage, clustering of drusen and waste deposits in the RPE leads to more central vision distortions.[21,-23] Since the destructive process takes place mostly in the macular region (the area with the highest spatial resolution) there may be increased difficulty with reading and facial recognition but generally little to no effects on peripheral vision.[22] As the areas of atrophy enlarge and coalesce, the patient may experience worsened overall vision with centralized blurred or blind spots, or scotoma, which typically have negative impacts on daily function.[21-23]

Late-stage AMD typically presents either as dry form AMD (nonexudative; non-neovascular) or the less common wet AMD (exudative; neovascular).[21] Although it is believed that dry and wet AMD share certain pathological mechanisms, there are also some notable contrasts. In both forms, drusen accumulates, induces RPE inflammation and causes photoreceptor degeneration.[21] In dry AMD, drusen deposition and photoreceptor degeneration occur relatively slowly and, when combined with natural aging process, cause eventual atrophy ("geographic atrophy" [GA]) of the macula.[21,24] However, in wet AMD, abnormal growth of choroidal vessels causes the vessels to break through the Burch membrane and invade the retina.[21,22,24] The newly formed choroidal vessels are not as well-established as the normal vasculature and tend to leak fluid, blood, and lipids into the surrounding tissue.[24] This leakage attracts microglia and macrophages that result in inflammatory damage, fibrovascular scar formation, and photoreceptor dysfunction.[21,23,24] As the vessels bleed into the macula, wet AMD becomes a medical emergency that, if untreated, may result in rapid, irreversible vision loss.[24] In roughly 10-15% of cases, patients with the dry form of AMD may progress to the wet form.[21] The risk of central vision loss is highest in wet-form AMD.[21]

Although the pathogenesis of AMD is poorly understood, chronic inflammation and the activation of complement have been implicated in the initiation and progression of AMD and geographic atrophy.[10,25] The complement system is a controlled network of more than 30 proteins within the innate immune system that may be activated in a cascade fashion to provide protection against tissue pathogens.[21] The complement cascade is activated in multiple interconnected proteolytic pathways and culminates in the formation of the membrane attack complex (MAC) .[10,25] All of the complement cascade pathways converge at the cleavage of C3 and C5 to bring about the MAC which leads to cell lysis.[10,22,25] Under normal conditions, complement activation and MAC formation are highly regulated by a number of cell-surface proteins and feedback loops to prevent complement-mediated intravascular hemolysis and injury to surrounding tissues.[22] Oxidative stress may leave retinal pigment epithelium cells vulnerable to injury from the complement system and is hypothesized to be a key factor in the development and progression of AMD.[22,26,27] In patients with AMD, a higher concentration of complement activation products has been observed in aqueous and vitreous humor samples.[22,26] There have been other findings that may indicate complement dysregulation in patients with AMD such as C3a observed in drusen, decreased regulatory complement protein in retinal pigment epithelium, and increased levels of membrane attack complex in the retina.[22,26,28]

Changes in drusen location, size, and growth rate may be helpful indicators of AMD progression.[23] The presence of geographic atrophy in a single eye is highly indicative that both eyes will be affected, typically within a 7-year time period.[29] However, the presence of small deposits of drusen do not automatically indicate the presence of AMD, but larger deposits of drusen have been correlated with increased risk of AMD progression.[30,31] Therefore, obtaining baseline drusen size is of clinical importance.[23] Size of drusen may be classified as small (<63 µm in diameter), intermediate >63 µm but ≤ 125 µm diameter), or large (>125 µm diameter). [23,30,31] Only the intermediate and large drusen have been correlated directly with AMD.[31] Extrafoveal lesions and faster lesion growth rates tend to result in a more rapid GA progression toward central vision loss, or blindness.[31] There is no consensus for a standard AMD classification scheme but the system frequently used by practitioners is the Age-Related Eye Disease Study (AREDS) or the Beckman Classification system.[30,31] The AREDS/Beckman stages AMD is based on the number, size, and location of drusen, as well as pigmentary changes (see **Table 1**).[30,31] AREDS scores range from 0 to 4 with higher scores indicative of more severe disease.[30] As the size and number of drusen size increases and both eyes become affected, the 5-year rate of developing advanced AMD can be calculated.[31]

Table 1. AREDS/Beckman Classification of AMD (modified)[30,31]

Beckman		**AREDS simplified score**	**AREDS classification/ categories**
No Disease	• No drusen • No AMD pigmentary abnormalities	0	No disease
Normal Aging	• Only drupelets (small ≤63 micrometer drusen) • No AMD pigmentary abnormalities	0	No disease or early stage
Early	• >63 to ≤125 micrometer drusen • No AMD pigmentary abnormalities	0	Early or intermediate
Intermediate	• >125 micrometer drusen and/or Pigmentary abnormalities	1-4	Intermediate
Advanced	• Neovascular AMD and/or Any geographic atrophy	n/a, 5	Advanced
Abbreviations: AREDS = Age-Related Eye Disease Study; AMD = age-related macular degeneration			

There are many methods employed to diagnose and monitor geographic atrophy progression. Indirect ophthalmoscopy allows for fundus examination through a dilated pupil which enables the clinician to see gross changes in the macula.[32-34] For detailed visualization of the AMD lesions, clinicians use techniques such as color fundus photography (CFP), fundus autofluorescence (FAF), and optical coherence tomography (OCT).[32,33] Each provide a unique perspective to help gain a better understanding of AMD disease mechanisms.[34] Each imaging technique is briefly described in **Table 2**.

Table 2. Common Imaging Techniques used in Diagnosis and Monitoring of Geographic Atrophy (GA) Progression [18,23,32-34,37]

Imaging Technique	Abbreviation	Description
Fluorescein Angiography	FA	Takes sequential photographs of chorioretinal circulation after fluorescein dye is injected which allows detection of leakage from neovascular lesions
Color Fundus Photography	CFP	Useful for defining GA lesion size and provides a 30- to 50-degree colored image of the macular region
Fundus Autofluorescence	FAF	Enables topographic visualization of the retina with the use of a scanning laser ophthalmoscope to detect retinal pigments and metabolic byproducts to track GA
Optical Coherence Tomography	OCT	Produces two-dimensional (2-D) views for retinal assessment, and 3-D views that can be used to compare fundus autofluorescence

Besides tracking GA lesion size and form, measuring visual function is a crucial component of monitoring geographic atrophy progression.[36] The Snellen chart is an often used test of visual acuity at a distance of 20 feet.[20] The Snellen chart has fewer letters in the upper portion of the chart and the number of letters increase as the test of visual acuity becomes finer at the lower portion of the chart.[20] With normal vision, subjects should be able to read the 20/20-foot line with each eye without correction.[20] Best-corrected VA (BCVA) is the patient's best distance vision when using optimal refraction correction.[20] Since measurement of BCVA is relatively straightforward, it is a commonly utilized endpoint for later stages of AMD.[36] Patients with a BCVA of 20/200 or worse are considered to be legally blind.[35] Low luminance BCVA (LL-BCVA) is measured by simply adding a filter to the refraction for BCVA while keeping the vision chart and lighting conditions of the room constant.[36] Clinical trials of GA have reported a difference of 20 letters between LL-BCVA and BCVA measurements is clinically significant.[38] Visual acuity may also be evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.[36] The EDTRS chart is an accurate measurement at low levels of acuity due to its flexibility in working distance and font readability.[36] The minimal clinically important difference referenced in the literature may vary, but a change of 5 letters (corresponding to 1 line on the chart or 0.1 logMAR) is typically considered to be the minimum clinically detectable change.[39] Moderate visual loss correspond to losses of 15-30 letters on the ETDRS chart and severe vision loss is typically defined as a loss of greater than 30 letters (or 6 lines on the ETDRS chart).[39,40]

The impact of GA progression on quality of life is also an important consideration for clinicians to monitor in their patients with AMD. Even with adequate visual acuity measured by BCVA, more than half of patients with GA may have compromised reading ability.[41] The functional reading independence (FRI) index score is used to measure the ability to complete everyday reading activities and has been used in various studies of patients with geographic atrophy.[18,41] The FRI Index identifies seven functional items (e.g. reading written print from books or magazines; reading to pay bills; reading a prescription bottle label, etc.) that are scored from 1 (unable to perform) to 4 (totally independent).[41] Index scores are totaled and averaged to provide a mean score.[41] The mean score is then rounded to the nearest integer (1, 2, 3, or 4) which corresponds to a functional reading independence level: Level 1 (unable to do); Level 2 (help required some or most of the time); Level 3 (moderately independent); and Level 4 (totally independent).[41]The minimal clinically important difference (MCID) on the functional reading independence index has not been established.

Anti-vascular endothelial growth factor A (anti-VEGFA) agents have been used successfully to treat vision loss in patients with wet AMD, but there are very few approved therapies for dry AMD, and new strategies and targets are currently under exploration.[22,42] Several studies with antioxidant vitamins (Vitamins C, E), minerals (zinc, copper) and other supplements (beta-carotene) have reported some benefit for slowing progression to late AMD, however evidence is inconclusive.[43] Complement inhibitors such as pegcetacoplan and avacincaptad pegol have been studied for use in AMD with GA.[44-48] Other therapeutic strategies taking place in clinical trials include visual cycle modulators, laser therapy, stem cell therapy and gene therapy.[22] With the increasing prevalence of AMD, there is a significant unmet need to find therapies that not only reduce the rate of GA progression, but also restore retinal function.[49-51]

NEW DRUG EVALUATION: Pegcetacoplan intravitreal injection

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Pegcetacoplan (SYFOVRE) received FDA approval in February 2023 for the treatment of adult patients with GA secondary to AMD.[2] Pegcetacoplan binds to complement protein C3 to prevent cleavage into its active components and also binds/inactivates C3b.[1,2] It is believed that by binding C3, pegcetacoplan may help to reduce chronic inflammation and oxidative stress to slow GA progression and enhance cell survival.[2,3] The recommended pegcetacoplan dosage is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days.[2] Pegcetacoplan must be administered by a qualified provider.[2]

Pegcetacoplan was studied in two parallel, phase 3, randomized, placebo-controlled trials (APL2-303 "DERBY" and APL2-304 "OAKS").[1-3] The OAKS and DERBY study details are described and evaluated below in **Table 5.**[1-3] Each trial was a similarly designed 24-month, multicenter study that evaluated the efficacy and safety of pegcetacoplan compared to a sham-control in patients aged 60 years and older with GA secondary to AMD.[1-3] Patients were screened for up to 28 days prior to treatment.[1-3] Eligible patients were randomized 2:2:1:1 to receive pegcetacoplan 15 mg/0.1 mL once per month (PM), once every other month (EOM), or matching sham injection (PM or EOM) procedure without actual eye penetration.[1,3] Any study eyes that developed exudative AMD were administered a VEGF inhibitor (either ranibizumab or aflibercept) in the study eye at least 30 minutes prior to but on the same day as pegcetacoplan (or sham) injection.[3] The decision to initiate VEGF therapy was at the sole discretion of the investigator.[3] The intent-to-treat (ITT) set included all randomized subjects.[1,3] Subjects were to be analyzed in the treatment arm assigned at randomization with the 2 sham treatment arms being combined into a single "control" group.[1,3] The modified ITT (mITT) set included all randomized subjects who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion in the study eye as assessed by fundus autofluorescence (FAF).[1,3] In both studies, the primary endpoint was change from baseline to month 12 in the total area of geographic atrophy lesions in the study eye based on FAF image analysis.[1,3] Secondary endpoints included differences in visual function endpoints of best-corrected visual acuity, functional reading independence index scores, monocular maximum reading speed, and change in mean threshold sensitivity (OAKS only). The FDA requested that the applicant provide additional 24-month follow-up data beyond the original 12 and 18-month data submission to demonstrate conclusive efficacy.[1]

A total of 2661 patients were screened in both trials of whom 1403 (53%) were excluded due to not meeting lesion size requirements (GA area ≥ 2.5 and ≤ 17.5 mm^2), evidence of choroidal neovascularization, or study noncompliance.[1,3] Of the ITT population (N=1258), 1115 (89%) completed assessment at month 12.[1,3] The mITT population used to assess the primary outcome was generally balanced with regard to baseline characteristics in both studies. Except in the DERBY trial participants in the pegcetacoplan groups had lower rates of unifocal GA and intermediate/large drusen compared to combined sham groups (roughly 27% vs

34% and 39% vs 51%, respectively).[1,3] Additionally, patients in the OAKS trial had higher rates of extrafoveal GA in the pegcetacoplan PM and EOM groups compared to the combined sham groups (43% and 36% vs 29%, respectively).[1,3] Roughly 20% of all included patients had evidence of choroidal neovascularization in the non-study eye.[3]

For pegcetacoplan-treated subjects, there were GA lesion growth reductions over 12 months in both dosing regimens.[1,3] In the OAKS trial, pegcetacoplan given PM and EOM resulted in a reduction in extrafoveal geographic atrophy lesion area compared to sham (-21% change; mean size difference -0.41 mm^2 ; 95% CI, -0.64 to -0.18 mm^2; p=0.0004; and -16% change ; mean size difference –0.32 mm^2, 95% CI, –0.54 to –0.09 mm^2; p=0.0055, respectively).[1,3] The reported benefit was of a similar magnitude at 24 months.[1,3] However, in the DERBY trial, no statistically significant difference was demonstrated in extrafoveal geographic atrophy lesion area with pegcetacoplan administered PM or EOM versus sham-treated patients (MD: -0.23 and -0.21 mm^2; p=0.062 and 0.085, respectively).[1,3] A small, but statistically significant benefit was reported at 24 months for pegcetacoplan monthly and pegcetacoplan every other month as each slowed geographic atrophy lesion growth by 22% compared to sham (MD –0.90 mm^2, 95% CI, –1.30 to –0.50; p<0.0001) and 18% (MD –0.74 mm^2, 95% CI, –1.13 to –0.36; p=0.0002) in OAKS, and by 19% (MD –0.75 mm^2, 95% CI, –1.15 to –0.34; p=0.0004) and 16% (MD –0.63 mm^2, 95% CI, –1.05 to –0.22; p=0.0030) in DERBY, respectively.[1,3]

In the OAKS trial, the difference of GA lesion growth between the treatment groups and sham was approximately 0.3 to 0.4 mm^2. The FDA reviewers did not consider this difference clinically significant because it was less than one fifth the size of the normal blind spot.[1] In DERBY, the difference between the treatment groups and sham was approximately 0.2 mm^2, which is approximately one tenth the size of the normal blind spot.[1] The difference for the primary endpoint in DERBY was not statistically or clinically significant. At 24 months, all other secondary functional endpoint data that compared pegcetacoplan to sham did not reach statistical significance.[1,3]

In the OAKS trial, the difference of GA lesion growth between the treatment groups and sham was approximately 0.3 to 0.4 mm^2. The FDA reviewers did not consider this difference clinically significant because it was less than one fifth the size of the normal blind spot.[1] The Study APL2-303 (DERBY) failed to meet its primary endpoint for both groups (PM and PEOM) as the difference between the treatment groups and sham was approximately 0.2 mm^2, which is approximately one tenth the size of the normal blind spot.[1] The difference for the primary endpoint in DERBY was not statistically or clinically significant.

Only one of two trials with pegcetacoplan met its primary endpoint and neither OAKS or DERBY reported statistically significant benefits in functional improvements or quality of life measures. With higher rates of neovascular AMD noted in pegcetacoplan treated patients compared to sham, it is uncertain whether pegcetacoplan therapy increases risk of or hastens conversion to exudative AMD in certain patient subpopulations. Routine injections or as needed use of certain anti-VEGF agents have been utilized in patients with neovascular AMD which has helped preserve (and even improve) functional outcomes such as visual acuity. Complement inhibitors do not have data to support improvements in functional outcomes, and guidelines for use while undergoing VEGF inhibitor therapy is not available. In the OAKS and DERBY studies, there were a large proportion of patients who had discontinued the study by month 24 so long-term efficacy (and safety) of pegcetacoplan treatment is unknown. The FDA review noted that at week 18, both studies reported around 26% of subjects randomized to pegcetacoplan monthly had missing efficacy data and that by Month 24, the number had increased to 30% (DERBY) and 33% (OAKS). More data is needed to determine the long-term safety of pegcetacoplan and to demonstrate that minor changes in rate of GA lesion growth correlate to a clinically significant functional benefit.

Clinical Safety:

Common adverse reactions experienced with pegcetacoplan are presented in **Table 3.**[2] Rates of intraocular inflammation were higher in pegcetacoplan-treated patients compared to sham (3% versus <1%, respectively) over 24 months in the OAKS and DERBY studies.[2] According to labeling, pegcetacoplan administration is contraindicated in patients with active intraocular inflammation or with ocular or periocular infections.[2] At 12 months, OAKS and DERBY reported new-onset exudative AMD in 5-7% of patients given pegcetacoplan monthly, 3-5% of those on EOM dosing, and from 1-3% of sham-treated patients.[3] By month 24, rates of neovascular (wet) AMD or choroidal neovascularization appeared to increase in the pegcetacoplan-treated groups compared to sham (12% when administered monthly, 7% when administered every other month and 3% in the sham group).[1-3] Roughly 96-98% of pegcetacoplan-treated patients with new wet AMD were co-administered a VEGF inhibitor compared to about 85% of those on sham.[3] It was reported that the mean anti-VEGF injection frequency was once monthly but details regarding the number of injections in each group were not available nor the identification of which VEGF-inhibiting agent was chosen by the investigator.[3] Overall study discontinuations through month 24 were highest in the pegcetacoplan once monthly groups followed by pegcetacoplan every other month and pooled sham (29%, 22%, and 21% respectively) and mostly due to consent withdrawal and adverse events.[1,3] Patient discontinuations in both trials were mainly due to withdrawal after an adverse event and were highest in the monthly pegcetacoplan group.[1] Combined incidence of ocular inflammation was 3.8% in the PM group and 2.1% in the EOM group.[1,3] If episodes of intraocular inflammation (e.g. vitritis, iridocyclitis, uveitis, iritis, etc.) are observed during treatment, FDA prescribing information suggests holding treatment and then resuming after inflammation resolves.[2] FDA labeling warns of the possibility of an acute increase in intraocular pressure (IOP) within minutes of pegcetacoplan administration, therefore perfusion of the optic nerve head should be monitored following the injection and managed as needed.[2]

Table 3. Adverse Reactions in Study Eye Reported in ≥5% of Patients Treated with Pegcetacoplan Through Month 24 in OAKS and DERBY Studies[2]

Adverse Reactions	Pegcetacoplan once monthly (N = 419)	Pegcetacoplan every other month (N = 420)	Sham pooled (N = 417)
ocular discomfort	13%	10%	11%
neovascular (wet) AMD	12%	7%	3%
vitreous floaters	10%	7%	1%
conjunctival hemorrhage	8%	8%	4%
vitreous detachment	4%	6%	3%
retinal hemorrhage	4%	5%	3%
punctate keratitis	5%	3%	<1%

Pooled results of both studies showed there was a higher number of patient deaths in the pegcetacoplan monthly group (7%) compared to pegcetacoplan every other month (4%) or patients assigned to sham (4%) but rates and causes were reported to be consistent with the elderly population.[1] The FDA review noted that less than 20% of the subjects in the pegcetacoplan monthly treatment group received the total 24 injections allowed in the 24-month period.[1] Therefore, the actual incidence of adverse events with a full monthly treatment regimen is unknown and could be higher than what was observed in the studies. A small proportion of patients received both anti-VEGF and complement therapy.[3] Certain VEGF inhibitors as well as pegcetacoplan currently list similar warnings of intraocular inflammation and/or retinal vein occlusion (which can cause blindness) on their respective FDA labeling.[2,22] Without longer-term data, it is unclear whether anti-VEGF therapy administered with complement inhibitors have a combined increased risk of adverse effects over time.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual symptom improvement
2) Visual function
3) Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total area of geographic atrophy lesions

Table 4. Pharmacology and Pharmacokinetic Properties.[1,2]

Parameter	
Mechanism of Action	Complement protein C3 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 1.85 L; Protein Binding N/R
Elimination	Clearance is 0.284 L/day
Half-Life	4.5 days
Metabolism	Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathway

Abbreviations: C3=complement 3; L=liters; N/A=not available; N/R=not reported

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. DERBY[1-3] (APL2-303) Phase 3, RCT, Sham-control, MC	1. Pegcetacoplan (PEG) 15 mg/0.1 ml IVI once monthly 2. Pegcetacoplan 15 mg/0.1 ml IVI once every other month 3. Sham pooled 2:2:1:1 randomization	Demographics: -Mean Age: 78 years -Female: 61% -White: 94% -Mean size GAL: 8.3 mm^2 ->20 medium to large drusen in study eye: 1. 39% 2. 39% 3. 50% -Mean number study eye BCVA, ETDRS letters: 59 -Mean number study eye LLD, ETDRS letters: 26 Key Inclusion Criteria: -Age ≥ 60 years	ITT: 1. 206 2. 208 3. 207 mITT: 1. 201 2. 201 3. 195 Attrition Month 12: 1. 11% 2. 10% 3. 14% Month 24:	Primary Endpoint: Change from baseline to month 12 in the total area of GA lesions in the study eye based on FAF image analysis. 1. 1.73 mm^2 2. 1.76 mm^2 3. 1.96 mm^2 MD PEG monthly vs sham: -0.23 mm^2 95% CI, -0.47 to 0.01, P = 0.062 MD PEG EOM vs sham: -0.21 mm^2 95% CI, -0.44 to -0.03, P = 0.085	NA NS NS	TEAEs: 1. 86% 2. 87% 3. 82% Ocular TEAEs: 1. 61% 2. 52% 3. 46% Non-ocular TEAEs: 1. 79% 2. 68% 3. 71%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Central web-based randomization with stratified permuted block by GA lesion area at screening. Eye with worst visual acuity (or right eye if same visual acuity) selected. Baseline characteristics generally similar between groups. Performance Bias: (Low) Blinded participants and investigators/care givers. External, independent data monitoring committee reviewed all data across the conduct of the studies on an ongoing basis. Sham procedure same as IVI procedure without actual injection (touch with blunt syringe). Detection Bias: (Low) FAF images evaluated in a central reading center by a minimum of two certified readers with independent manual measurements of features of the GA lesions. At 12 months, only the sponsor personnel

		-BCVA 24 letters or better using ETDRS charts -Clinical diagnosis of GA of the macula secondary to AMD -GA lesion criteria via FAF imaging at screening: • Total GA area ≥ 2.5 and ≤ 17.5 mm^2 • If GA multifocal, ≥ 1 focal lesion must be ≥ 1.25 mm^2 • Entire GA lesion must be able to be imaged • No evidence of prior or active CNV in the study eye or presence of RPE tear Key Exclusion Criteria: -Geographic atrophy secondary to condition other than AMD -History or active CNV, associated with AMD or any other cause, including evidence of neovascularization -Active ocular disease that compromises visual function -History of intraocular surgery or laser therapy in the macular region -Contraindication to IVI injection including current ocular or periocular infection	1. 29% 2. 20% 3. 22%	Secondary Endpoints: Change from baseline to month 24 in the total area of GA lesions in the study eye based on FAF image analysis. 1. 3.27 mm^2 2. 3.26 mm^2 3. 3.98 mm^2 MD PEG monthly vs sham: -0.75 mm^2 95% CI, -1.15 to -0.34, P=0.0004 MD PEG EOM vs sham: -0.63 mm^2 95% CI, -1.05 to -0.22, p = 0.003 Change in BCVA from baseline to month 24: 1. -7.89 2. -8.83 3. -6.94 MD PEG vs Sham: *Not statistically significant* Change from baseline in FRI composite score at month 24: 1. -0.35 2. -0.37 3. -0.32 MD PEG vs. Sham: *Not statistically significant*	NA NS NS	New-onset exudative AMD: 1. 13% 2. 6% 3. 4% Intraocular inflammation: 1. 2% 2. 3% 3. 0%		responsible for analyzing, interpreting, and reporting data were unmasked to treatment assignment. Physicians administering treatment for active CNV were unblinded after blinded reading center provided report. Attrition Bias:(Unclear) Missing outcome data balanced at 12 months with similar TEAEs reported. At 24 months >20% did not complete trial for all groups. No imputation for missing data. Reporting Bias: (Low) Full protocol available online as supplement. No protocol deviations noted. Other Bias: (Unclear) Manufacturer funded the study and contributed to report writing. Multiple authors received grants, funding, consultant fees from, or are paid employees of manufacturer. **Applicability**: Patient: Age appropriate; racial and ethnic makeup not necessarily reflective of overall Medicaid population but disease more common in fair-skinned individuals. Intervention: Pegcetacoplan 15 mg IVI every 4 or 8 weeks appropriate based on earlier phase testing. Comparator: Sham injection is appropriate. No standard available. Outcomes: Change in the GA lesion area is a surrogate marker but rational measure of photoreceptor loss. Longer term outcomes needed, particularly those that correlate with improved function. Setting: Multicenter at 110 clinical sites and 122 clinical sites worldwide, including United States, Canada, Europe, and Australia.
2. OAKS [1-3] (APL2-304) Phase 3, RCT, Sham-control, MC	1. Pegcetacoplan 15 mg/0.1 ml IVI once monthly 2. Pegcetacoplan (PEG) 15 mg/0.1 ml IVI once every other month 3. Placebo/Sham	Demographics: -Mean Age: 78 years -Female: 61% -White: 93% -Mean size GAL: 8.3 mm^2 -Extrafoveal GAL: 39% -Unifocal GAL: 30% ->20 medium to large drusen in study eye: -Mean BCVA, ETDRS letters baseline: 59	ITT: 1. 213 2. 212 3. 212 mITT: 1. 202 2. 205 3. 207 Attrition: Month 12	Primary Endpoint: CFB to month 12 in the total area of GALs in the study eye based on FAF image analysis. 1. 1.56 mm^2 2. 1.65 mm^2 3. 1.97 mm^2 MD PEG monthly vs sham: -0.411 mm^2 95% CI, -0.640 to -0.183 P=0.0004	NA NA	TEAEs: 1. 90% 2. 88% 3. 83% Ocular TEAEs: 1. 62% 2. 58% 3. 46% Non-ocular TEAEs:	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see DERBY Performance Bias: see DERBY Detection Bias: see DERBY Attrition Bias; see DERBY Reporting Bias: see DERBY Other Bias: see DERBY **Applicability**: Patient: see DERBY Intervention: see DERBY Comparator: see DERBY

	2:2:1:1 randomization	-Mean number study eye ETDRS letters: <u>Key Inclusion Criteria</u>: -see DERBY <u>Key Exclusion Criteria</u>: -see DERBY	1. 10% 2. 10% 3. 10% Month 24 1. 32% 2. 20% 3. 25%	-21% difference vs sham MD PEG EOM vs sham: -0.318 95% CI, -0.542 to -0.094 P = 0.0055 -16% difference vs sham <u>Secondary Endpoints</u>: CFB to month 24 in the total area of GALs in the study eye based on FAF image analysis: 1. 3.12 mm^2 2. 3.28 mm^2 3. 4.03 mm^2 MD PEG monthly vs sham: -0.90 mm^2 95%CI, -1.30 to -0.50; P < 0.0001 MD PEG EOM vs sham: -0.74 mm^2 95% CI, -1.13 to -0.36; p= 0.0002	 NA NA	1. 82% 2. 78% 3. 73% <u>New-onset exudative AMD:</u> 1. 11% 2. 8% 3. 2% <u>Intraocular inflammation:</u> 1. 5% 2. 1% 3. 0% <u>Infectious endophthalmitis</u> 1. 1% 2. 1% 3. 0%		<u>Outcomes</u>: see DERBY <u>Setting</u>: see DERBY
<u>Abbreviations</u>: AMD = Age-related macular degeneration; ARR = absolute risk reduction; BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; EOM = every other month; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = Fundus Autofluorescence; FRI = functional reading independence; GA = geographic atrophy; ITT = intention to treat; IVI = intravitreally; MC = multicenter; MD = mean difference; mITT = modified intention to treat; mm = millimeters; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PEG = pegcetacoplan; PM = per month; PP = per protocol; TEAE = treatment emergent adverse event; RCT = randomized controlled trial								

NEW DRUG EVALUATION: Avacincaptad pegol intravitreal injection

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Avacincaptad pegol (IZERVAY) received FDA approval in August 2023 for the treatment of adult patients with GA secondary to AMD.[4,5] Avacincaptad pegol binds to complement protein C5 to prevent cleavage into its active components of C5a and C5b.[4] It is believed that C5a fragments may contribute to formation of the membrane attack complex and cell apoptosis.[4] The recommended dose of avacincaptad pegol intravitreal solution is 2 mg (0.1 mL) into affected eye(s) once monthly (or every 21 to 35 days) for up to 12 months administered by a qualified health provider.[4]

Avacincaptad pegol was studied in two randomized, double-blind, sham-controlled trials.[4-8] The first study was an 18-month, phase 2/3 trial (OPH2003 "GATHER1") and the second a 24-month, phase 3 trial (ISEE2008 "GATHER2").[4-8] Both were multicenter studies that evaluated the efficacy and safety of avacincaptad pegol in patients aged 50 years and older with GA secondary to AMD.[4,6-8] Inclusion and exclusion criteria were similar for both trials.[4,6-8] In GATHER2, patients who developed confirmed macular neovascularization in the study eye were treated with either ranibizumab or aflibercept per their label and remained in the trial.[8] Study details for GATHER1 and GATHER2 are described and evaluated below in **Table 8.**[4-8] For the purposes of this review, only the FDA-approved dose of avacincaptad pegol 2 mg compared to sham will be highlighted in the evidence table.

In Part 1 of GATHER1, 77 patients were randomized 1:1:1 to receive monthly avacincaptad pegol 1 mg, 2 mg, or sham administered via intravitreal (IVI) injection.[4,6,7] In Part 2, patients were then randomized 1:2:2 to receive avacincaptad pegol 2 mg once monthly (plus sham), 4 mg monthly (2 x 2 mg injections), or monthly (2x) sham injection.[4,6,7] In GATHER2 (N=448) patients were randomized 1:1 to avacincaptad pegol 2 mg monthly (2 injections: 1 drug, 1 sham) or sham monthly (2 injections: both sham) for 12 months. The primary endpoint of GATHER1 and GATHER2 was the mean rate of change in GA from baseline over 12 months (as measured by FAF).[4,8] Secondary endpoints included the mean change in BCVA (ETDRS letters) from baseline to month 12 and the mean change in low luminance BCVA (ETDRS letters) from baseline to month 12.[4,6-8]

Baseline demographics were similar between treatment and sham groups in both trials.[4,6-8] In GATHER1, the mean patient age was 78 years, about 71% were female, and almost all patients (97–100%) were White.[4,6,7] The mean total GA area was about 7.3 – 7.4 mm^2.[4,6,7] Mean baseline BCVA was about 70 letters and the mean low luminance BCVA at baseline was roughly 35 letters.[4,6,7] In GATHER2 the mean patient age was 76 years, 68% were female, and roughly 81% were White.[4,8] The mean GA area at baseline was 7.48 mm^2 in avacincaptad pegol group (compared to 7.81 mm^2 for sham), while the mean BCVA and low luminance BCVA were roughly 71 and 41 letters, respectively.[4,8]

The mean rate of change in GA area was reduced for both avacincaptad pegol treatment cohorts compared to sham.[4-8] At 12 months, GATHER1 reported a reduced mean rate of square-root-transformed GA growth in the avacincaptad pegol 2 mg compared to sham (0.292 mm and 0.402 mm, respectively) with a MD 0.110 mm (95% CI 0.030–0.190; p = 0.0072).[4-7] In a mixed model repeated measures (MMRM) analysis of observed data at 12 months, the treatment difference was 0.67 mm^2/year (95% CI 0.21–1.13; p < 0.01), corresponding to a relative reduction of 35% compared with sham.[5] In GATHER2, similar results were observed from baseline to month 12 with a lower mean rate of square-root-transformed geographic atrophy growth in the avacincaptad pegol 2 mg group compared to sham (0.34 mm/year and 0.39 mm/year, respectively) and an absolute difference of 0.06 mm/year [(95% CI, 0.02–0.1); 14% difference, P=0.0064].[4,7,8] The

MMRM analysis of observed data for GATHER2 at 12 months reported a reduced rate of GA growth in avacincaptad pegol 2 mg compared to sham (1.75 mm^2/year and 2.12 mm^2/year, respectively) with a mean difference of 0.38 mm^2/year [(95% CI, 0.12 to 0.63); 18% relative difference, p<0.01].[5]

Although the surrogate marker of reduced GA growth showed a very modest but statistically significant difference, the clinical significance of such a minor difference has not been established. There was no correlation of reduced GA growth rate and functional outcome studied as both functional measures, BCVA and LL-BCVA, showed no benefit in either GATHER1 or GATHER2.[4,6-8] GATHER1 and GATHER2 excluded patients with fellow-eye choroidal neovascularization so the benefit of therapy in patients with this history is unknown. Longer term data is needed to demonstrate that minor changes in rate of GA lesion growth correlate to a clinically significant functional benefit.

Clinical Safety:

Common adverse reactions experienced by patients in the 2 trials are presented in **Table 6.**[4,5] In GATHER1, ocular treatment emergent adverse events (TEAEs) in the treated eye were reported in 52% of avacincaptad pegol 2 mg recipients (*n* = 67), 69% of avacincaptad pegol 4 mg recipients (*n*= 83) and 35% of sham recipients (*n* = 110).[4,5] In GATHER2, ocular TEAEs occurred in 49% and 37% of avacincaptad pegol and sham recipients, respectively.[4] In a pooled analysis of GATHER1 and GATHER2, the most frequent ocular adverse events occurring in more than 2% of subjects and at a higher rate with avacincaptad pegol 2 mg compared to sham were conjunctival hemorrhage (13% vs. 9%), increased intraocular pressure (9% vs. 1%), blurred vision (8% vs. 5%), and choroidal neovascularization (7% vs. 4%).[4,5] In GATHER1 there were systemic TEAEs reported in 58% and 55% of the avacincaptad pegol 2 mg versus sham-treated patients, respectively.[4,5] The most common systemic TEAEs in avacincaptad pegol 2 mg compared to sham, respectively, were urinary tract infection (10% vs. 8%), falls (9% vs. 5%), nasopharyngitis (9% vs. 4%), and atrial fibrillation (6 vs. <1%).[4,5] No patients discontinued treatment due to an AE in GATHER1.[4,5] In GATHER2, TEAEs were more common in the avacincaptad pegol group compared to sham (79% and 71%, respectively), and discontinuations due to TEAEs were reported in 3% of the avacincaptad pegol patients and <1% of sham recipients.[4,5] No serious ocular AEs were reported in either eye in all treatment groups for the GATHER1 trial.[4,5] Although avacincaptad pegol is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation, no cases of endophthalmitis or intraocular inflammation were observed in the trials.[4,5] There were 3 deaths (2 in the avacincaptad pegol 2 mg group and one in the sham group) to month 12, none of which was determined by the investigator to be related to injection procedure or the study drug.[4] No deaths were reported in GATHER1.[4,6,7] More studies are needed to assess long-term safety of avacincaptad pegol.

Table 6. Common Ocular Adverse Reactions (>2%) and greater than Sham in Study Eye [4,5]

Adverse Reactions	**avacincaptad pegol (N = 292)**	**Sham pooled (N = 332)**
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Blurred vision*	8%	5%
Choroidal neovascularization	7%	4%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

***Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual symptom improvement
2) Visual function
3) Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total area of geographic atrophy lesions

Table 7. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5.
Oral Bioavailability	N/A
Distribution and Protein Binding	Max concentration in vitreous humor 500 µg/mL after first injection; Protein Binding N/R
Half-Life	12 days
Metabolism/Elimination	Avacincaptad pegol is catabolized by endonucleases and exonucleases to oligonucleotides of shorter lengths and excreted renally

Abbreviations: C5=complement 5; µg/mL=micrograms per milliliter; N/A=not applicable; N/R=not reported

Table 8. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. GATHER1[4-7] (OPH2003) Phase 2/3, RCT, PC (Sham), MC	1. avacincaptad pegol (AP) 2 mg IVI once monthly 2. Sham 1:2 randomization* (* = part 2 excluded 4 mg dose)	Demographics: -Mean Age: 78 years -Female: 70% -White: 98% -Mean size GAL: 7.4 mm^2 -Active smoker: 34% -Mean BCVA, ETDRS letters baseline: 70 -Mean LL-BCVA: 35 Key Inclusion Criteria: -Age 50 years or greater -BCVA between 20/25 and 20/320 in study eye -GA secondary to AMD -Total GA area ≥2.5 and ≤17.5 mm^2 -For multifocal GA lesions ≥1 focal lesion ≥1.25 mm^2 Key Exclusion Criteria: -GA secondary to condition other than AMD -Active or history of CNV in either eye -Prior treatment for AMD -Intraocular inflammation -Uveitis in either eye -Significant media opacities, including cataract -Diabetic retinopathy in either eye -History of intraocular surgery or laser therapy in the macular region -Contraindication to IVI injection including current ocular or periocular infection -Hx of stroke (prior 12 months), PAD, cardiac dysfunction -Pregnant or nursing women	ITT: 1. 67 2. 110 Attrition (month 12): 1. 18% 2. 13%	Primary Endpoint: Change in the (square root transformed) GA lesion area from baseline to month 12: 1. 0.292 mm 2. 0.402 mm MD = 0.110 mm 95% CI, 0.030 to 0.190; P = 0.0072 -27% difference from sham FDA label: Change in the mean rate of GA lesion area growth from baseline to month 12: 1. 1.22 mm^2/year 2. 1.89 mm^2/year MD = 0.67 mm^2/year (95% CI, 0.21 to 1.13); P <0.01 -35% difference from sham Secondary Endpoint: Mean change from baseline to month 12 in BCVA: 1. -7.9 2. -9.3 MD = 1.4 (95% CI, -1.5 to 4.3) Mean Change from baseline to month 12 in LL-BCVA (ETDRS Letters): 1. -1.0 2. -1.4 MD = 0.4 (95% CI, -3.3 to 4.1)	NA NS NS	Ocular TEAEs: 1. 52% 2. 35% Systemic TEAEs: 1. 58% 2. 57% Systemic SAEs: 1. 10% 2. 18% p-value and 95% CI NR for all	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Central web-based randomization with minimization method used to maintain balance between groups and for each stratification criterion. Baseline characteristics similar between groups. Performance Bias: (Low) Blinded participants, investigators, reading center personnel and sponsor personnel. Method of blinding not described but masking reported to be preserved through trial. Detection Bias: (Low) Masked, trained readers independently analyzed and graded the FAF images. More than a 10% discrepancy in results measurements were arbitrated by Reading Center Director. Attrition Bias (Unclear) Substantial overall attrition with a slightly larger proportion of patients in treatment group unable to complete the trial. Treatment effects compared with MMRM using only observed data. Multiple prespecified imputation methods used to replace missing values and treatment effects remained statistically significant. Reporting Bias: (Unclear) No CIs or p-values reported in secondary outcome data tables. Other Bias: (High) Manufacturer funded the study and contributed to study design, data collection, data management, data analysis, data interpretation, and report writing. **Applicability**: Patient: Study population was mostly older, white females. Racial and ethnic makeup not necessarily reflective of overall Medicaid population but disease more common in fair-skinned individuals. Mean age appropriate as condition largely affects adults >50 yrs Intervention: Lower monthly dose (2 mg) consistent with FDA approval. Comparator: Sham control appropriate for safety and efficacy comparisons. Outcomes: Change in the GA lesion area is a surrogate marker but rational measure of photoreceptor loss. Longer term outcomes needed notably those that correlate with improved function. Setting: Multicenter at 63 sites in United States, Europe, and Israel.

2. GATHER2[4,5,8] (ISEE2008) Phase 3, RCT, PC (Sham), MC	1. avacincaptad pegol 2 mg IVI once monthly 2. Sham 1:1 randomization*	Demographics: -Mean Age: 76 years -Female: 69% -White: 82% -Active Smoker: 48% -Mean size GAL: 7.65 mm^2 -Mean BCVA, ETDRS letters baseline: 71 -Mean LL-BCVA: 40 Key Inclusion Criteria: -see GATHER1 Key Exclusion Criteria: -see GATHER1	ITT: 1. 225 2. 222 Attrition: 1. 11% 2. 8%	Primary Endpoint: Change in GA lesion from baseline to month 12 (slope analysis of square-root-transformed data): 1. 0.336 mm/year 2. 0.392 mm/year MD 0.056 mm/year 95% CI, 0.016 to 0.096 P = 0.0064 Change in the mean rate of GA lesion area growth from baseline to month 12: 1. 1.75 mm^2/year 2. 2.12 mm^2/year MD 0.376 mm^2/year 95% CI, 0.122 to 0.63 P = 0.0039 -18% difference from sham Secondary Endpoints: Mean change in BCVA (ETDRS letters) in the study eye from baseline to month 12: 1. 1.34 2. 0.96 MD 0.38 95% CI, -1.43 to 2.19 P = 0.68 Mean change in LL-BCVA (ETDRS letters) in the study eye from baseline to month 12: 1. -4.35 2. -2.29 MD -2.06 95% CI, -4.86 to 0.75 P = 0.15	NA NS NS	TEAEs: 1. 79% 2. 71% Conjunctival hemorrhage 1. 12% 2. 8% Increased ocular pressure 1. 9% 2 1% Choroidal neovascularization 1. 7% 2. 4% Serious TEAEs 1. 13% 2. 17% Discontinuations due to TEAE: 1. 3% 1. 1% Death: 1. 0.9% 2. 0.5%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see GATHER1 Performance Bias: see GATHER1 Detection Bias: see GATHER1 Attrition Bias: see GATHER1 Reporting Bias: Protocol was available. Also see GATHER1. Other Bias: see GATHER1 **Applicability**: Patient: see GATHER1 Intervention: see GATHER1 Comparator: see GATHER1 Outcomes: see GATHER1 Setting: see GATHER1

Abbreviations: AMD = Age-related macular degeneration; ARR = absolute risk reduction; BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; EOM = every other month; ETDRS = Early Treatment Diabetic Retinopathy Study; GA = geographic atrophy; ITT = intention to treat; IVI = intravitreally; LL-BCVA = low luminance best-corrected visual acuity MC = multicenter; MD = mean difference; mm = millimeters; MMRM = mixed model repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PAD = peripheral arterial disease; PEG = pegcetacoplan; PM = per month; PP = per protocol; SAE = serious adverse event; TEAE = treatment emergent adverse event; RCT = randomized controlled trial

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYFOVRE safely and effectively. See full prescribing information for SYFOVRE.

SYFOVRE ™ (pegcetacoplan injection), for intravitreal use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Retinal Vasculitis and/or Retinal Vascular Occlusion (5.2) 11/2023

----------INDICATIONS AND USAGE----------
SYFOVRE is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dose for SYFOVRE is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 150 mg/mL in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
- Ocular or Periocular Infections (4.1)
- Active Intraocular Inflammation (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and Retinal Detachments (5.1)
- Retinal Vasculitis and/or Retinal Vascular Occlusion (5.2)
- Neovascular AMD (5.3)
- Intraocular inflammation (5.4)
- Increased Intraocular Pressure (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apellis Pharmaceuticals, Inc. at 1-833-866-3346 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Appendix 2: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IZERVAY safely and effectively. See full prescribing information for IZERVAY.

IZERVAY™ (avacincaptad pegol intravitreal solution)
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
IZERVAY is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) (1).

----------DOSAGE AND ADMINISTRATION----------
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately 28 ± 7 days) for up to 12 months (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
Intravitreal solution: 20 mg/mL in a single-dose vial (3).

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1).
- Active intraocular inflammation (4.2).

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and Retinal Detachments (5.1).
- Neovascular AMD (5.2)
- Increase in Intraocular Pressure (IOP) (5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions were conjunctival hemorrhage (13%), increased IOP (9%), blurred vision (8%) and neovascular age-related macular degeneration (7%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact IVERIC bio, Inc. at 1-800-707-4479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2023

FULL PRESCRIBING INFORM ATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

Ophthalmic Complement Inhibitors

Goal(s):

- To ensure appropriate use of complement inhibitors in patients with geographic atrophy (GA) due to age-related macular degeneration (AMD).

Length of Authorization:

Up to 6 months with total cumulative lifetime treatment period not to exceed 24 months per affected eye.

Requires PA:

- Pegcetacoplan (SYFOVRE); Avacincaptad Pegol (IZERVAY); (applies to both physician-administered and pharmacy claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Dosage and Administration per FDA Labeling.

	Pegcetacoplan (SYFOVRE)	**Avacincaptad pegol (IZERVAY)**
Dose (per single affected eye)	15 mg (0.1 mL of 150 mg/mL solution)	2 mg (0.1 mL of 20 mg/mL solution)
Route of Administration	Intravitreal Injection	Intravitreal Injection
Frequency	Once every 25 to 60 days	Once monthly (approximately 28 ± 7 days)
Maximum Lifetime Limit	Unknown	12 months

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the patient an adult with a diagnosis of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) supported by clinical documentation of appropriate testing (e.g. fundus autofluorescence (FAF), optical coherence tomography (OCT))?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have any of the following: • active intraocular inflammation? • active ocular or periocular infections? • history of intraocular surgery or laser therapy in the macular region?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for continuation of therapy for a patient who has received ≥ 6 months of initial therapy with the requested agent?	**Yes:** Go to **Renewal Criteria**.	**No:** Go to #5
5. Is the agent being prescribed and administered by or under the supervision of an ophthalmologist?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have a best corrected visual acuity (BCVA) in the affected eye of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent)?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there evidence that the patient is currently receiving therapy with a different ophthalmic complement inhibitor or medication for GA treatment?	**Yes:** Go to #8	**No:** Go to #9
8. Is this a switch in GA therapy due to intolerance, allergy or ineffectiveness and has therapy with the previous agent been discontinued?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have active choroidal neovascularization or wet age-related macular degeneration?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10

Approval Criteria		
10. Is the dose, route, and frequency consistent with the FDA-labeling for the requested agent?	**Yes**: Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this a request for avacincaptad pegol?	**Yes**: Go to #2	**No:** Go to #3
2. Has the patient already received 12 months of cumulative therapy in the affected eye(s)?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #3
3. Does the patient exhibit any evidence of the following: • Unacceptable toxicity or adverse events (e.g. endophthalmitis, retinal detachment, or conversion to wet AMD)? • Significant decline in visual acuity (loss of 10 or more letters on EDTRS chart)?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Has the prescriber documented a positive patient response to therapy such as disease stabilization or slowing in the growth rate of geographic atrophy lesions compared to pre-treatment baseline?	**Yes**: Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/24 (DE)
Implementation: TBD

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: Phosphate Binders

Date of Review: April 2024

Date of Last Review: August 2021
Dates of Literature Search: 05/19/2021 – 01/18/2024
Brand Name (Manufacturer): XPHOZAH® (Ardelyx)
Dossier Received: Not available

Generic Name: tenapanor

Current Status of Preferred Drug List (PDL) Class:
See **Appendix 1**.

Purpose for Class Update:
Review new evidence of efficacy and safety for the phosphate binder class, tenapanor (XPHOZAH), for the Oregon Health Plan (OHP) fee-for-service (FFS) program.

Plain Language Summary:
- People with kidney disease may experience increased levels of phosphate in the blood. High blood phosphate levels can decrease levels of calcium in the blood and lead to bone loss. High phosphate levels can also combine with calcium, leading to dangerous deposits in the blood vessels, lungs, eyes, and heart. Over time this can cause an increased risk for heart attack, stroke, or death.
- Phosphate binders are medicines that prevent phosphate in food from being absorbed into the body. Phosphate binders are all effective in lowering phosphate levels but have different side effects. Side effects include high calcium levels in the blood, nausea, constipation, and diarrhea.
- XPHOAZAH (tenapanor) is a new medication approved in 2023 that works differently than phosphate binders but can also lower phosphate levels when combined with a phosphate binder. Diarrhea is a common side effect of this medicine, but goes away after the first week of treatment.
- Two phosphate binders, calcium acetate and sevelamer, are preferred medications on the Oregon Health Plan fee-for-service Preferred Drug List. The other medications are not preferred and providers must receive prior authorization before the prescription is covered for the member.

Research Questions:
1. What is the comparative efficacy of phosphate binders (i.e., calcium acetate, calcium carbonate, sevelamer hydrochloride, sevelamer carbonate, lanthanum, sucroferric oxyhydroxide, and ferric citrate) to reduce serum phosphate?
2. What are the comparative harms of phosphate binders when used to reduce serum phosphate?
3. What is the evidence for the safety and efficacy of tenapanor when used as add-on therapy to reduce serum phosphate in patients with chronic kidney disease (CKD) on dialysis?
4. Do the phosphate binders differ in their effectiveness or harms based on age, race, ethnicity, gender, or patients with comorbidities?

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Conclusions:

- One guideline issued by the National Institute for Health and Care Excellence (NICE) was identified since the last P & T Committee review of this drug class.[1]
- In 2021, NICE updated guidance for assessment and management of people with CKD.[1]
    - Due to insufficient evidence, NICE recommendations for the use of phosphate binders in children and young people has not changed from the 2013 CKD guidance. Children and young people with CKD stage 4 or 5 and hyperphosphatemia should be offered a calcium-based phosphate binder to control serum phosphate levels.[1]
    - NICE recommendations for phosphate binders in adults are as follows:
        - Calcium acetate in adults with CKD stage 4 or 5 and hyperphosphatemia.[1]
        - Sevelamer carbonate if calcium acetate is not indicated (e.g., hypercalcemia or low serum parathyroid hormone [PTH] levels).[1]
        - If calcium acetate and sevelamer carbonate cannot be used, consider:
            - sucroferric oxyhydroxide for adults on dialysis if a calcium-based phosphate binder is not needed; or
            - calcium carbonate if a calcium-based phosphate binder is needed.[1]
        - Only consider lanthanum carbonate for adults with CKD stage 4 or 5 if other phosphate binders cannot be used.[1]
- Tenapanor (XPHOZAH) received FDA approval in October 2023 as an add-on therapy in adults with CKD on dialysis to reduce serum phosphate in patients who have had an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder.[2]
- The safety and efficacy of tenapanor was evaluated in three phase 3, randomized controlled trials (RCTs) conducted over 4 to 12 weeks.[2] In these trials, tenapanor combined with a phosphate binder was effective in reducing serum phosphate compared with placebo. The trials do not provide evidence for long-term safety and efficacy of tenapanor.
    - The first phase 3 (RCT) was conducted in 2 phases: an 8-week dose-finding phase (3 mg, 10 mg, and 30 mg twice daily) followed by a 4-week, withdrawal, placebo-controlled phase.[3] Enrolled participants were receiving hemodialysis and taking at least 3 doses of a phosphate binder per day.[3] In the 4-week withdrawal phase, the difference in serum phosphate change between the tenapanor plus phosphate binder group (n=82) and the placebo plus phosphate binder group (n=82) was statistically significant (mean increase ± standard deviation [SD] of 0.85 ± 1.68 mg/dL with placebo versus mean increase ± SD 0.02 ± 1.63 mg/dL with tenapanor; least squares mean difference [LSMD], −0.72 mg/dL; 95% confidence interval [CI], −1.19 to −0.25 mg/dL; p=0.003; moderate-quality evidence).[3]
    - The second phase 3 RCT (AMPLIFY) was a parallel-group, double-blind, placebo-controlled study that evaluated the effect of tenapanor on the change in serum phosphate when used as add-on therapy in adults maintained on hemodialysis or peritoneal dialysis and stable phosphate-binder therapy with serum phosphorus greater than or equal to 5.5 mg/dL.[4] Patients treated with tenapanor plus phosphate binder achieved a larger mean change in serum phosphate concentration from baseline to week 4 compared with placebo plus binder (−0.84 vs. −0.19 mg/dL; LSMD, -0.65; 95% CI -1.01 to -0.29; p<0.001; moderate-quality evidence).[4]
    - The final phase 3 RCT (PHREEDOM) had a complex study design conducted over 3 separate periods: a 26-week open-label randomized treatment period, a 12-week double-blind, placebo-controlled randomized withdrawal period, and a 14-week open-label safety extension period.[5] Forty weeks of this 52-week study were open-label. In the efficacy analysis set (n=131), the least square mean change in serum phosphate over 12 weeks was 0.4 mg/dL for the tenapanor group and 1.8 mg/dL for the placebo group (LSMD −1.37; 95% CI -1.92 to -0.82 mg/dL; p<0.001; moderate-quality evidence).[6]
    - In these trials, diarrhea was the most common adverse effect (AE) reported with tenapanor treatment.[4] Diarrhea was typically transient (less than 1 week in duration) and mild to moderate in severity.[4] Approximately two-thirds of cases occurred within 1 week of initiating treatment with tenapanor.[4]

- No evidence was identified to assess if the phosphate binders differ in their effectiveness or harms based on age, race, ethnicity, gender, or patients with comorbidities.

Recommendations:
- Revise name of the preferred drug list (PDL) class from “phosphate binders” to “phosphate binders and absorption inhibitors” due to unique mechanism of action for the newest product, tenapanor.
- Maintain tenapanor as nonpreferred and amend prior authorization (PA) criteria in **Appendix 4** to provide coverage for clinically appropriate use of tenapanor as add-on therapy in patients with hyperphosphatemia and CKD.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy
The phosphate binder drug class was last reviewed by the P & T Committee at the August 2021 meeting. There is no comparative evidence that one phosphate binder is more effective or safer than another; however, there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide and ferric citrate. The Committee recommended removal of the PA requirement for preferred products. Preferred phosphate binders include calcium acetate, sevelamer hydrochloride, and sevelamer carbonate tablets. Non-preferred phosphate binders are listed in **Appendix 1.** The current PA criteria for phosphate binders (with amendments for tenapanor) are presented in **Appendix 4**.

In the fourth quarter of 2023 (September 1, 2023 to December 31, 2023), approximately 90% of FFS phosphate binder claims were for 2 preferred agents, calcium acetate (48%) and sevelamer carbonate (42%). Non-preferred utilization of phosphate binders was due to sucroferric oxyhydroxide (8%) and lanthanum (2%).

Background:
Phosphorous is an abundant mineral in the body and is predominantly an intracellular anion.[7] Ninety percent of the daily phosphate load is excreted by the kidneys, while the gastrointestinal (GI) tract excretes the other 10%.[7] Phosphate homeostasis is influenced by calcitriol, parathyroid hormone (PTH), and fibroblast growth factor-23 (FGF-23).[7] Fibroblast growth factor-23 is the most potent hormone regulating phosphate homeostasis, increasing urinary excretion of phosphate by inhibiting phosphate reabsorption in the renal proximal tubule.[7] Phosphate is essential for cellular energy production and bone mineralization.[8] Hyperphosphatemia can occur with excessive phosphate load, decreased renal excretion, or transcellular shifting.[7] High intake of phosphate due to excessive use of phosphate-containing laxatives or vitamin D can result in hyperphosphatemia.[7] Tissue breakdown due to tumor lysis syndrome or rhabdomyolysis can lead to the release of intracellular phosphate into extracellular fluid.[7] Other reasons for hyperphosphatemia include hypoparathyroidism, acromegaly, thyrotoxicosis, metabolic acidosis, lactic acidosis, and diabetic ketoacidosis. Some medications such as penicillin, corticosteroids, furosemide and thiazide diuretics can also cause hyperphosphatemia.[7]

In adults, hyperphosphatemia is defined as serum phosphate concentration greater than 4.5 mg/dL.[7] In children, normal serum phosphate levels range from 4 to 7 mg/dL.[7] People with CKD are at high risk for hyperphosphatemia due to impaired renal excretion of phosphate. In patients with end-stage renal disease, the prevalence of hyperphosphatemia ranges from 50 to 74%.[9] Hyperphosphatemia is common in late stages of CKD (i.e., glomerular filtration rate (GFR) less than 30 mL/min).[10] Elevated serum phosphate can cause secondary hyperparathyroidism, impaired bone metabolism, endothelial damage, and calcification of the blood vessels, heart valves, and myocardium.[11] Persistent hyperphosphatemia in CKD patients is associated with increased mortality in this population.[11]

Hyperphosphatemia is managed by restricting dietary phosphate, removing phosphate with dialysis, or minimizing phosphate absorption in the GI tract using phosphate binders. Phosphate binders are classified according to their molecular composition as: calcium-containing (calcium carbonate, calcium acetate), non-calcium-based (sevelamer carbonate, sevelamer hydrochloride, lanthanum), aluminum-containing (aluminum hydroxide) or iron-containing (sucroferric oxyhydroxide, ferric citrate).[11] The phosphate binders are all effective in lowering serum phosphorus, but they differ in their safety profiles.[11]

The first phosphate binders used in clinical practice were aluminum hydroxide preparations. With continued use, it became evident that these agents are associated with serious adverse effects due to aluminum accumulation, including osteomalacia, neurotoxicity, cognitive disturbances, and anemia.[11] Due to the risks of toxicity, aluminum hydroxide capsules are no longer manufactured. As calcium-based phosphate binders replaced aluminum preparations, increased risks for vascular calcification and arterial stiffness associated with calcium administration were identifed.[11] Excess exposure to calcium with calcium-based binders may be harmful in patients with any stage of CKD.[12] The first non-calcium containing phosphate binder, sevelamer hydrochloride, was approved by the FDA in 2000.[11] Sevelamer hydrochloride was found to worsen metabolic acidosis, so sevelamer carbonate was developed as an alternative.[11] Lanthanum carbonate, approved in 2004, also reduces phosphorus levels without increasing calcium load, which decreases the risk of treatment-related hypercalcemia.[6] The prescribing information for lanthanum includes a precaution for the risk of GI obstruction, ileus, GI perforation, and fecal impaction.[13] Iron-based phosphate binders include sucroferric hydroxide and ferric citrate. Sucroferric hydroxide was approved in 2013 and ferric citrate was approved in 2014.[14] Iron-containing agents can cause GI side effects including nausea, vomiting, diarrhea, and constipation.[11] Phosphate binder therapy is associated with poor GI tolerability, dosing up to 3 times per day, and a high pill burden.[5] The recently approved phosphate absorption inhibitor, tenapanor, has a unique mechanism of action and will be discussed in more depth later in this review. A summary of medications that inhibit phosphate absorption and their associated serious adverse effects is presented in **Table 1**.

Table 1. FDA-Approved Medications Which Inhibit Phosphate Absorption[14]

Generic Name (BRAND NAME)	Year of FDA Approval	FDA Approved Age Range	Serious Adverse Effects
Aluminum-Based Binders			
Aluminum Hydroxide (discontinued)	1970	N/A	Neurotoxicity, Cognitive Disorders, Osteomalacia, Anemia
Calcium-Based Binders			
Calcium Acetate (PHOSLO)	1990	Adults	Hypercalcemia which could lead to Vascular and Soft Tissue Calcification
Calcium Carbonate (TUMS)		Over-the-counter labeling includes dosing for pediatric patients	
Non-Calcium Based Binders			
Sevelamer Hydrochloride (RENAGEL)	2000	Adults	Metabolic Acidosis, GI Obstruction
Sevelamer Carbonate (RENVELA)			Ileus, Fecal Impaction, Bowel Obstruction, Bowel Perforation
Lanthanum Carbonate (FOSRENOL)	2004		Ileus, GI Obstruction, GI perforation, Fecal Impaction

Iron-Based Binders			
Sucroferric Oxyhydroxide (VELPHORO)	2013	Adults	Potential for Iron Overload
Ferric Citrate (AURYXIA)	2014		Potential for Iron Overload
Sodium-Hydrogen Exchanger			
Tenapanor (XPHOZAH)	2023	Adults	Severe Diarrhea
Abbreviations: FDA = Food and Drug Administration; GI = gastrointestinal; N/A = not available			

The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) work group concluded there is insufficient evidence for efficacy and safety of phosphate binders among patients not receiving dialysis with CKD Grades 3A through 5D.[12] The KDIGO panel suggested restricting the dose of calcium-based phosphate binders and stressed tolerance of mild and asymptomatic hypocalcemia, in order to avoid exogenous calcium loading.[12] The utility of calcium-free phosphate binders in reducing clinical events in CKD, balanced against their cost and potential harms has been controversial due insufficient and conflicting evidence.[15] Use of phosphate binders should be limited to patients with progressive or persistent hyperphosphatemia and not to prevent hyperphosphatemia.[12] For patients with CKD Grade 3a through 5, elevated phosphate levels should be reduced toward the normal range rather than normalized, while avoiding hypercalcemia for adult patients.[12] Most studies showed increasing risk of all-cause mortality with increasing levels of serum phosphate in a consistent and direct fashion, with moderate risk of bias and low quality of evidence.[12] Clinical trial evidence that treatments that lower serum phosphate improve patient-centered outcomes are still lacking, and therefore the strength of this recommendation remains weak.[12]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),[16-20] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[21-23] or outcome studied (e.g., non-clinical).

New Guidelines:
National Institute for Health and Care Excellence: Assessment and Management of Chronic Kidney Disease
In 2021 NICE updated guidance for assessment and management of people with CKD.[1] There was a significant amount of evidence (of varying quality) for the use of phosphate binders in adults with stage 5 CKD who are on dialysis.[1] However, evidence was limited for adults with stage 4 or 5 CKD not on dialysis, and for

children and young people.[1] The committee agreed to extrapolate from the evidence for adults with stage 5 CKD on dialysis, so they could make recommendations for the other populations.[1]

Phosphate Binders In Children And Young People

The committee reviewed the recommendations from the 2013 NICE guideline in the light of limited new evidence for the use of phosphate binders in children and young adults.[1]

NICE Recommendations:

- Offer children and young people with stage 4 or 5 CKD and hyperphosphatemia a calcium-based phosphate binder to control serum phosphate levels.[1]
- If serum calcium increases towards, or above, the age-adjusted upper normal limit:
    - Investigate possible causes other than the phosphate binder and
    - Consider reducing the dose of the calcium-based phosphate binder and adding sevelamer carbonate or switching to sevelamer carbonate alone. [1]
- For all children and young people who are taking more than a single phosphate binder, titrate the dosage to achieve the best possible control of serum phosphate while keeping serum calcium levels below the upper normal limit.[1]

Phosphate Binders In Adults

The committee reviewed the evidence for phosphate binders both in adults on dialysis and adults not receiving dialysis.[1] The committee agreed that diet and dialysis (when appropriate) had a large impact on serum phosphate levels.[1] Therefore, before offering phosphate binders it is important to provide dietary advice and ensure people are on the dialysis regimen that works best for them.[1]

The evidence summarized to support the guideline development showed no differences between phosphate binders for the impact on serum phosphate levels at 3, 6, and 12 months in adults with stage 5 CKD receiving dialysis.[24] However, calcium carbonate showed an increase in levels of serum calcium at 3, 6, and 12 months compared with sevelamer hydrochloride, an increase in levels of serum calcium at 6 months compared with magnesium carbonate, and a higher risk of hypercalcemia compared with lanthanum carbonate and sevelamer carbonate at 6 months in patients receiving dialysis.[24] People taking calcium acetate had higher risk of hypercalcemia, but there was no clinical difference on serum calcium levels at any of the time points compared with other phosphate binders.[24] Therefore, the committee agreed to keep calcium acetate as a first-line phosphate binder as it showed a clinically significant effect compared with placebo for increasing the proportion of adults achieving target (<1.78 mmol/L) phosphate levels.[24] The committee also made a recommendation to consider calcium carbonate if a calcium-based agent is required in adults who do not tolerate calcium acetate.[24] This decision was based on the data showing that, even though it carried a risk of hypercalcemia, calcium carbonate was effective at increasing the proportion of adults achieving phosphate control compared with placebo and at reducing the risk of constipation compared with calcium acetate and sevelamer hydrochloride.[24]

Evidence for sevelamer carbonate showed a clinically significant effect increasing the proportion of adults achieving phosphate control compared with placebo and a clinically significant effect reducing the risk of hypercalcemia compared with calcium carbonate and calcium acetate.[24] Lanthanum carbonate showed a clinically significant effect for increasing the proportion of adults achieving phosphate control compared with placebo, a significant effect in reducing serum calcium levels at 6 months compared with calcium carbonate, a significant effect in reducing the risk of hypercalcemia compared with calcium carbonate and calcium acetate, and a significant effect for decreasing the risk of constipation compared with calcium acetate and sevelamer hydrochloride.[24] The evidence for sucroferric oxyhydroxide showed a clinically significant effect for increasing the proportion of adults achieving phosphate control compared with placebo and a significant effect in reducing the risk of constipation compared with calcium acetate and sevelamer carbonate, but there was a higher risk of diarrhea compared with sevelamer hydrochloride.[24]

In 4 placebo-controlled RCTs in adults with stage 4 or 5 CKD not on dialysis, the active comparator (calcium carbonate, calcium acetate, ferric citrate, and lanthanum) was more favorable in reducing serum phosphate levels over 2 to 4 months.[24] In the head-to-head comparisons, there was no meaningful difference between phosphate binders in reduction of serum phosphate levels for CKD patients not on dialysis.[24] For adverse effects, there was no difference between lanthanum and ferric citrate in incidence of constipation or diarrhea.[24] However, lanthanum caused more constipation than placebo.[24]

NICE Recommendations:

- Calcium acetate for adults with stage 4 or 5 CKD and hyperphosphatemia to control serum phosphate levels.[1]
- Sevelamer carbonate if calcium acetate is not indicated (e.g., hypercalcemia or low serum PTH levels) or not tolerated.[1]
- If calcium acetate and sevelamer carbonate cannot be used, consider:
    - Sucroferric oxyhydroxide for adults on dialysis if a calcium-based phosphate binder is not needed or
    - Calcium carbonate if a calcium-based phosphate binder is needed.[1]
- Only consider lanthanum carbonate for adults with stage 4 or 5 CKD if other phosphate binders cannot be used.[1]
- If hyperphosphatemia persists in adults with stage 4 or 5 CKD after taking the maximum recommended dose (or the maximum dose they can tolerate) of a calcium-based phosphate binder, check they are taking it as prescribed and
    - consider combining a calcium-based phosphate binder with a non-calcium-based phosphate binder.[1]
- For all adults who are taking more than a single phosphate binder, titrate the dosage to achieve the best possible control of serum phosphate while keeping serum calcium levels below the upper normal limit.[1]

At every routine clinical review for adults, children and young people, assess the person's serum phosphate control, taking into account: diet, whether they are taking the phosphate binders as prescribed and other relevant factors, such as vitamin D levels, serum PTH levels, alkaline phosphatase, serum calcium, and medications that might affect serum phosphate, or dialysis.[1]

Randomized Controlled Trials:

A total of 22 citations were manually reviewed from the initial literature search. After further review, 22 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Tenapanor (XPHOZAH)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Tenapanor oral tablets were initially approved in 2019 for management of constipation-predominant irritable bowel syndrome under the brand name IBSRELA.[25] In October 2023, another tenapanor branded formulation, XPHOZAH, received FDA approval for reduction of serum phosphate in adults with CKD on dialysis as add-on therapy in patients who have had an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.[2] Tenapanor is a locally acting inhibitor of the sodium-hydrogen exchanger-3 (NHE3) in the small intestine and colon.[2] Inhibition of NHE3 reduces paracellular phosphate transport by blocking phosphate intestinal absorption.[2] Tenapanor is unique because it does not bind phosphate in the GI tract; instead, it reduces intestinal phosphate absorption. The recommended dose is 30 mg orally twice daily before the morning and evening meals.[2]

The safety and efficacy of tenapanor to lower serum phosphate in adults with CKD on dialysis was evaluated in three phase 3 RCTs.[2] Across these trials, the mean age of tenapanor-treated patients was 56 years (range 24 to 88 years), 61% were males, 44% were White, 49% were Black/African American, 3% were Asian, and 3% were American Indian or Alaska Native.[2]

The first RCT was conducted in 2 phases: an 8-week dose-finding phase followed by a 4-week placebo-controlled phase.[3] The trial was originally designed as a double-blind, dose-ranging phase 2 study with the primary end point the change in serum phosphate from baseline to the end of the 8-week randomized treatment period.[3] After trial initiation, FDA informed the sponsor that a previous phase 2 study was sufficient for dose-range finding and proposed conversion to a phase 3 trial incorporating a 4-week, double-blind, placebo-controlled, randomized withdrawal period.[3] The primary end point was amended to the between-groups (pooled tenapanor versus placebo) difference in the mean change in serum phosphate from the end of the randomized treatment period to the end of the randomized withdrawal period.[3]

In the first 8 weeks, 3 oral dosing regimens of tenapanor were evaluated (3 mg twice daily, 10 mg twice daily, or 30 mg twice daily) in 219 adults with hyperphosphatemia (serum phosphate 6.0 to 10 mg/dL).[3] Enrolled participants were receiving maintenance hemodialysis and taking at least 3 doses of a phosphate binder per day.[3] The types of phosphate binders were not described in the study summary. Of the 219 patients included in the trial, 164 patients completed the 8-week dose-finding treatment period and were re-randomized 1:1 to receive tenapanor or placebo in the next 4-week phase of the trial.[3] At the end of 4-week withdrawal phase, the difference in serum phosphorous change between the tenapanor group (n=82) and the placebo group (n=82) was statistically significant (mean ± SD increase of 0.85 ± 1.68 mg/dL with placebo versus mean ± SD 0.02 ± 1.63 mg/dL with tenapanor; LSMD, −0.72 mg/dL; 95% CI, −1.19 to −0.25 mg/dL; p=0.003).[3]

The second RCT (AMPLIFY) was a parallel-group, double-blind, placebo-controlled study that evaluated the effect of tenapanor on the change in serum phosphate when used as add-on therapy in adults maintained on hemodialysis or peritoneal dialysis and stable phosphate-binder therapy with serum phosphate greater than or equal to 5.5 mg/dL.[4] Most patients were receiving sevelamer (49%) as the phosphate binder.[4] Other phosphate binders included: calcium acetate (20%), calcium carbonate (2%), ferric citrate (9%), lanthanum (2%), sucroferric oxyhydroxide (9%) and a combination of non-sevelamer products (8%).[4] A total of 236 patients were randomized to receive oral tenapanor 30 mg twice daily (n=117) or placebo twice daily (n=119) for 4 weeks.[4] The primary efficacy end point was the change in serum phosphate from baseline to week 4.[4] Patients treated with tenapanor plus phosphate binder achieved a larger mean change in serum phosphate concentration from baseline to week 4 compared with placebo plus binder (−0.84 vs. −0.19 mg/dL; LSMD, -0.65; 95% CI -1.01 to -0.29; p<0.001).[4]

A 52-week phase 3 RCT (PHREEDOM) had a complex study design as it was conducted in 3 separate periods: a 26-week open-label randomized treatment period, a 12-week double-blind, placebo-controlled, randomized withdrawal period, and a 14-week open-label safety extension period.[5] Patients with a serum phosphate 4.0–8.0 mg/dL at the screening visit were eligible to enter the phosphate binder washout period of 1 to 4 weeks in duration.[5] Patients whose serum phosphate had increased by 1.5 mg/dL or more during this period, and who had a measured serum phosphate 6.0 mg/dL or higher and less than 10.0 mg/dL at the end of the washout period, were randomly assigned (3:1) to receive either tenapanor at a starting dose of 30 mg orally, twice daily for 26 weeks (randomized treatment period), or sevelamer carbonate (on the basis of standard of care) for 52 weeks.[5] At the end of the randomized treatment period, participants were re-randomized (1:1) to either continue to receive tenapanor treatment at the same dose, or switch to placebo for 12 weeks (randomized withdrawal period).[5] On completion of, or discontinuation from, the randomized withdrawal period, all re-randomized participants were eligible to enter a 14-week safety extension period for tenapanor treatment.[5] To compare the rates of serious adverse events (SAEs) among the high-risk population enrolled in the study, participants taking open-label sevelamer for the 52-week study were followed as a control group for safety comparison only.[5] Efficacy data are not presented for this group,

because these participants received sevelamer as "standard of care."[5] The use of phosphate binders to treat hyperphosphatemia (other than sevelamer used in the safety control group) was prohibited.[5]

The primary efficacy end point was the difference in the change in serum phosphate from period-specific baseline to the end of the 12-week randomized withdrawal period between the pooled tenapanor group and placebo group.[5] A total of 310 participants completed the 12-week randomized withdrawal period (83% of the 372 participants who entered the period): 112 (96%) participants in the sevelamer group, 99 (78%) participants in the placebo group, and 99 (77%) participants in the tenapanor group.[5] For the efficacy analysis set, the fixed tenapanor dose administered during the randomized withdrawal period (and the final tenapanor dose of the randomized treatment period) was 30 mg twice daily for 75 (57%) participants, 20 mg twice daily for 39 (30%) participants, and 10 mg twice daily for 17 (13%) participants, with a mean value of 24.4 mg twice daily.[5] In the efficacy analysis set (n=131), the least squares mean change in serum phosphate from period-specific baseline to the end of the randomized withdrawal period was 0.4 mg/dL for the tenapanor group and 1.8 mg/dL for the placebo group (LSMD −1.37; 95% CI -1.92 to -0.82 mg/dL; p<0.001).[5]

Additional study details are described and evaluated below in **Table 5.** In 3 RCTs conducted over 4 to 12 weeks, tenapanor combined with a phosphate binder was efficacious in reducing serum phosphate compared with placebo. However, these relatively short-term trials do not provide evidence for the long-term safety and efficacy of tenapanor. A long-term RCT would provide additional evidence on the impact of tenapanor on CV events and fractures. Tenapanor was always studied in combination with phosphate binders. Currently, there is insufficient comparative evidence between tenapanor and phosphate binders on relevant outcomes such as serum phosphate reduction, mortality, bone metabolism, and CV events.

The 52-week phase 3 PHREEDOM trial randomized enrolled participants to sevelamer only for safety analysis; an active comparator efficacy assessment was not conducted. The trial was largely open-label (40 weeks), and only 12 weeks were conducted in double-blind, randomized fashion. Participants who discontinued tenapanor during the randomized treatment period were not included in subsequent study periods; thus, the randomized withdrawal and safety extension periods may have been enriched for individuals who were better able to tolerate tenapanor.[5] Another limitation was that insufficient data were collected on the change in dose of concomitant medications that are known to affect serum phosphate (e.g., active vitamin D analogs, calcimimetics).[5]

Clinical Safety:

In clinical trials, the most common AE was diarrhea, reported by 43% to 53% of patients.[2] Most diarrhea events were reported to be mild-to-moderate in severity and resolved over time or with dose reduction.[2] Severe diarrhea was reported in 5% of tenapanor-treated patients.[24] Tenapanor is contraindicated in patients with a known or suspected mechanical GI obstruction.[24] The safety and effectiveness of tenapanor in pediatric patients has not been established.[3]

Look-alike / Sound-alike Error Risk Potential: Tenapanor (IBSRELA) – FDA-approved for treat of adults with irritable bowel syndrome with constipation[25]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Surrogate endpoint: serum phosphate concentration
2) Serum calcium concentration
3) Overall mortality
4) Mortality related to cardiovascular events
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Serum phosphate concentration

Table 4. Pharmacology and Pharmacokinetic Properties.[2]

Parameter	
Mechanism of Action	Sodium hydrogen exchanger 3 (NHE3) inhibitor
Oral Bioavailability	Minimal systemic absorption
Distribution and Protein Binding	Plasma protein binding: 99%
Elimination	Primarily in feces 70-79% as unchanged drug; 9% renal excretion as metabolites
Half-Life	Not determined due to minimal systemic absorption
Metabolism	Metabolized by the CYP3A4/5 primarily to an inactive metabolite, M1

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Block GA, et al.[3] MC, DB, PC, Phase 3 RCT 8-week dose finding period followed by 4-week placebo-controlled withdrawal phase	1. Tenapanor 3 mg PO BID 2. Tenapanor 10 mg PO BID 3. Tenapanor 30 mg PO BID 4. Placebo PO BID	Demographics: -Mean age: 56 y -Male: 58% -Race White: 40% Black: 57% Asian: 2% -Baseline serum phosphate: 7.4 mg/dL Key Inclusion Criteria: -Age 18-80 y -ESRD on HD -3 doses PB daily -Serum phosphate 6 to 10 mg/dL Key Exclusion Criteria: - Serum PTH > 1200 pg/mL - Serum phosphate >10 mg/dL -History of IBD or IBS with diarrhea - Diarrhea/loose stool ≥3 stools/day	ITT: 1. 25 2. 23 3. 34 4. 82 PP: 1. 24 2. 22 3. 32 4. 74 Attrition: 1. 1 (4%) 2. 1 (4%) 3. 2 (6%) 4. 8 (10%)	Primary Endpoint: LSMD change in serum phosphate over 4 weeks. (Pooled 1+2+3): 0.02 ± 1.63 mg/dL 4. Placebo: 0.85 ± 1.68 mg/dL LSMD: -0.72 mg/dL 95% CI -1.19 to -0.25 mg/dL P=0.003 Secondary Endpoint: Percent of Patients Achieving serum phosphorus < 5.5 mg/dL at 8 weeks. 1. 24/70 (34.3%) 2. 22/69 (31.9%) 3. 18/65 (27.7%) 4. Not Assessed	NA	AEs after placebo-controlled 4-week phase 1. 4 (16%) 2. 7 (30%) 3. 12 (35%) 4. 21 (26%) Treatment-related AE after initial 8-week phase 1. 24 (32%) 2. 38 (52%) 3. 33 (47%) 4. Not Applicable Diarrhea after initial 8-week phase 1. 24 (32%) 2. 35 (48%) 3. 40 (56%) 4. Not Applicable 95% CI and p-values NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 to tenapanor (3 separate dosing regimens) or placebo using a computer-generated schedule. Baseline characteristics similar in all groups. Performance Bias: Unclear. Study staff and patients blinded to treatment assignment. Method of blinding not described. Adverse effect of diarrhea may have resulted in unblinding. Patients recorded daily bowel habits in an electronic diary every day. Elevated phosphate levels in placebo arm could also lead to unblinding. All tenapanor doses looked alike. No details provided regarding appearance of placebo tablets. Detection Bias: Low. Patients and investigators masked to treatment assignment. Attrition Bias: Low. Attrition rates were similar in all 4 arms. Reporting Bias: Unclear. Protocol available online. Study design and primary efficacy outcome modified twice as study progressed based on FDA feedback. Other Bias: High. Manufacturer funded the trial. Several investigators received financial support from the manufacturer. **Applicability**: Patient: Only adults with ESRD on dialysis were enrolled this study. Cannot extrapolate data to patients not receiving dialysis or children. Renal disease impacts a large proportion of Black patients and a higher percentage of Black patients over White patients were enrolled in this trial. Intervention: Tenapanor formulation and doses are approved by FDA and available in U.S. Comparator: Placebo is appropriate to assess efficacy as an add-on therapy. Outcomes: Reduction in serum phosphate is surrogate outcome for an inhibitor of phosphate absorption. Trial was not long enough to evaluate cardiovascular and mortality outcomes. Setting: 41 sites in the U.S.

2. Pergola PE, et al.[4] AMPLIFY DB, MC, Phase 3 RCT Conducted over a 4-week treatment period while continuing to receive daily PB	1. Tenapanor 30 mg PO BID 2. Placebo PO BID	Demographics: -Mean age: 54 y -Male: 59% -Race White: 50% Black: 43% Asian: 2.5% Other: 4.5% -Baseline serum phosphate: 6.8 mg/dL -Concomitant PB Sevelamer: 49% Non-sevelamer: 51% Key Inclusion Criteria: -Adults undergoing HD or PD -Hyperphosphatemia (5.5-10 mg/dL) despite taking 3 doses of a PB daily Key Exclusion Criteria: - Serum PTH > 1200 pg/mL - Serum phosphate > 10 mg/dL -History of IBD or IBS with diarrhea	ITT: 1. 117 2. 119 PP: 1. 112 2. 116 Attrition: 1. 5 (4%) 2. 3 (3%)	Primary Endpoint: LSMD change in serum phosphorous over 4 weeks. 1. -0.84 2. -0.19 LSMD: -0.65 95% CI -1.01 to -0.29 P<0.001 Secondary Endpoint: Percent of Patients Achieving serum phosphorus < 5.5 mg/dL at 4 weeks. 1.43 (37.1%) 2.26 (21.8%) OR 2.1; P=0.0097	 NA NA	AEs: 1. 60 (51%) 2. 33 (28%) Treatment-related AEs: 1 .51 (44%) 2. 15 (13%) SAE: 1. 3 (2.6%) 2. 5 (4.2%) Diarrhea: 1.50(43%) 2.8 (7%) Nausea: 1. 6 (5%) 2. 3 (2.5%) 95% CI and p-values NR	 NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized via IRT 1:1 to active drug or placebo. Stratified by type of PB (sevelamer, non-sevelamer) and baseline serum phosphorus (< 7.5 or ≥ 7.5 mg/dL). Baseline demographics balanced between groups. Performance Bias: Unclear. Study described as double-blind. Blinding methods not described. Not clear how placebo and tenapanor tablets were formulated to minimize unblinding. Detection Bias: Low. Patients and investigators masked to treatment assignment. Attrition Bias: Low. Attrition rates similar in both arms. Reporting Bias: Low. Protocol available online. All outcomes reported as prespecified. Other Bias: High. Manufacturer funded the trial. Several investigators received financial support from the manufacturer. **Applicability**: Patient: Only adults with ESRD on dialysis were enrolled this study. Cannot extrapolate data to patients not receiving dialysis or children. Intervention: Tenapanor formulation and doses are approved by FDA and available in U.S. However, short study duration limits applicability. Comparator: Placebo is appropriate to establish efficacy as an add-on therapy. Additional comparative evidence with other PBs would be useful. Outcomes: Reduction in serum phosphate is surrogate outcome for an inhibitor of phosphate absorption. Trial was not long enough to evaluate cardiovascular and mortality outcomes. Setting: 46 sites in the U.S.

3. Block G, et al.[5] PHREEDOM MC, Phase 3 RCT 52-week study design: a. 26-weeks OL b. 12 weeks DB, PC , randomized withdrawal period. c. 14 weeks OL safety extension period	1. Tenapanor 30 mg PO BID 2. Placebo PO BID	Demographics: -Mean age: 58 y -Male: 65% -Race White: 48% Black: 45% Other: 6% -Baseline serum phosphate: 7.3 mg/dL Key Inclusion Criteria: -Adults -HD -3 doses of PB daily -Serum phosphate 6-10 mg/dL Key Exclusion Criteria: Serum PTH > 1200 pg/mL - Serum phosphate > 10 mg/dL -History of IBD or IBS with diarrhea	12-week period ITT: 1. 128 2. 127 12-week period PP: 1. 99 2. 99 Attrition: 1. 29 (23%) 2. 28 (22%)	Primary Endpoint: LSMD change in serum phosphorous over 12 weeks: 1. 0.4 mg/dL 2. 1.8 mg/dL LMSD: -1.37 mg/dL 95% CI -1.92 to -0.82 P<0.001	NA	AEs after 12-week phase 1.58 (46%) 2.70 (56%) AEs leading to drug discontinuation during 12-week phase 1.11 (9%) 2.17 (13%) Diarrhea during 12 week-phase 1. 5 (4%) 2. 2 (2%) 95% CI and p-values NR		**Risk of Bias (low/high/unclear)**: Selection Bias: High. Patients randomized 1:1 to tenapanor or placebo. Method of randomization not described. Baseline characteristics balanced between groups. Performance Bias: Unclear. Study described as double-blind for 12 weeks during placebo-controlled phase. Blinding methods not described. Not clear how placebo and tenapanor tablets were formulated to minimize unblinding. Detection Bias: Unclear. 40 weeks of this study were open label. Attrition Bias: High. Extensive attrition in both arms. Reporting Bias: Low. Protocol available online. All outcomes reported as prespecified. Other Bias: High. Manufacturer funded the trial. Several investigators received financial support from the manufacturer. **Applicability**: Patient: Only adults with ESRD on dialysis were enrolled this study. Cannot extrapolate data to patients not receiving dialysis or children. Intervention: Tenapanor formulation and doses are approved by FDA and available in U.S. Comparator: Placebo is an appropriate to establish efficacy. Additional comparative evidence with other PBs would be useful. Sevelamer included as safety control only, comparative efficacy not evaluated. Outcomes: Reduction in serum phosphate is surrogate outcome for an inhibitor of phosphate absorption. Trial was not long enough to evaluate cardiovascular and mortality outcomes. Setting: 104 sites in the U.S.

Abbreviations: AE = adverse effect; ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; CKD = chronic kidney disease; DB = double-blind; dL = deciliter; ESRD = end stage renal disease; FDA = Food and Drug Administration; HD = hemodialysis; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; IRT = interactive response technology; ITT = intention to treat; mg = milligram; MC = multi-center; LSMD = least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open label; PB = phosphate binder; PC = placebo-controlled; PD = peritoneal dialysis; pg = picograms; PO = oral; PP = per protocol; PTH = parathyroid hormone; RCT = randomized controlled trial; SAE = serious adverse effect; U.S.=United States; y = years.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
calcium acetate	CALCIUM ACETATE	ORAL	CAPSULE	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	Y
calcium acetate	ACETICAL 170	ORAL	TABLET	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	Y
calcium acetate	CALPHRON	ORAL	TABLET	Y
sevelamer carbonate	RENVELA	ORAL	TABLET	Y
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	TABLET	Y
sevelamer HCl	RENAGEL	ORAL	TABLET	Y
sevelamer HCl	SEVELAMER HCL	ORAL	TABLET	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	N
calcium carbonate/mag carb	MAGNEBIND 300	ORAL	TABLET	N
calcium carbonate/mag carb	MAGNEBIND 400	ORAL	TABLET	N
ferric citrate	AURYXIA	ORAL	TABLET	N
lanthanum carbonate	FOSRENOL	ORAL	POWD PACK	N
lanthanum carbonate	FOSRENOL	ORAL	TAB CHEW	N
lanthanum carbonate	LANTHANUM CARBONATE	ORAL	TAB CHEW	N
sevelamer carbonate	RENVELA	ORAL	POWD PACK	N
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	POWD PACK	N
sucroferric oxyhydroxide	VELPHORO	ORAL	TAB CHEW	N
tenapanor HCl	XPHOZAH	ORAL	TABLET	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to January Week 2 2024; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to January 18, 2024

1	calcium acetate.mp.	397
2	exp Sevelamer/	707
3	sucroferric oxyhydroxide.mp.	90
4	ferric citrate.mp.	977
5	Lanthanum/	2807
6	tenapanor.mp.	72
7	Phosphorus Metabolism Disorders/ or Kidney Failure, Chronic/ or Hyperphosphatemia/	70875
8	1 or 2 or 3 or 4 or 5 or 6	4754
9	7 and 8	782
10	limit 9 to (humans and yr="2021 -Current" and (clinical trial, all or clinical trial, phase iii or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or evaluation study or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	22

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XPHOZAH® safely and effectively. See full prescribing information for XPHOZAH.

XPHOZAH (tenapanor) tablets, for oral use
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
XPHOZAH is a sodium hydrogen exchanger 3 (NHE3) inhibitor indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy (1).

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage: 30 mg orally twice daily before the morning and evening meals (2.1).
- Manage serum phosphorus levels and tolerability with dosage adjustments (2.1).
- Take just prior to the first and last meals of the day (2.2).
- Instruct patients not to take right before a hemodialysis session, and instead take right before the next meal following dialysis (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 10 mg, 20 mg, 30 mg (3).

----------CONTRAINDICATIONS----------
Pediatric patients under 6 years of age (4).
Patients with known or suspected mechanical gastrointestinal obstruction (4).

----------WARNINGS AND PRECAUTIONS----------
Patients may experience severe diarrhea (5.1).

----------ADVERSE REACTIONS----------
Most common adverse reaction in the combined clinical trials was diarrhea, reported by 43-53% of patients (6).

----------DRUG INTERACTIONS----------
- OATP2B1 Substrates: Potential for reduced exposure of the concomitant drug (e.g., enalapril). Monitor for signs related to loss of efficacy and adjust the dosage of the concomitantly administered drug as needed (7.1).
- Sodium Polystyrene Sulfonate (SPS): Separate administration by at least three hours (7.2).

To report SUSPECTED ADVERSE REACTIONS, contact Ardelyx at 1-844-974-6924 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2023

Phosphate Binders and Absorption Inhibitors

Goal(s):
- Promote use of preferred drugs for OHP-funded diagnoses.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred phosphate binders

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Go to #7
3. Is the request for an FDA-approved indication?	**Yes:** Go to #4	**No:** Go to #7
4. Is the request for tenapanor?	**Yes:** Go to #5	**No:** Go to #6
5. Is the request to use tenapanor as add-on therapy to a phosphate binder in an adult with chronic kidney disease receiving dialysis who has had an inadequate response to phosphate binders or who is intolerant of any dose of a phosphate binder?	**Yes:** Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Has the patient tried or have contraindications to a preferred phosphate binder (i.e., calcium acetate, sevelamer carbonate)?	**Yes:** Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred phosphate binder product.

7. RPh only: All other indications need to be evaluated as to whether use is for an OHP-funded diagnosis.
   - If funded and clinic provides supporting literature, approve for up to 12 months.
   - If not funded:
     - If current age < 21 years; Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)? AND
     - Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products?
       - Is yes, may approve for up to 12 months.
       - If No, Deny (medical necessity and appropriateness)
     - If current age ≥ 21 years, Deny; not funded by the OHP.

P&T Review: *4/24 (DM); 8/21 (DM); 1/16 (AG); 11/12; 9/12; 9/10*
Implementation: *TBD; 5/1/16; 2/21/13*