Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, June 4th, 2026 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. Mental Health Clinical Advisory Group Update	A. Gibler (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Inhalers for Asthma/COPD Literature Scan	
	B. Oncology Prior Authorization Updates	
	C. Orphan Drug Policy Updates	
	1. Public Comment	
1:25 PM	III. PDL OLD BUSINESS	S. Servid (OSU)
	A. Healthier Oregon Policy Update	
	1. Topical Antifungals	
	2. Antidiarrheals	
	3. Antacids, Proton Pump Inhibitors	
	4. Nasal Allergy Inhalers	
	5. Ophthalmic Medications for Allergies	
	6. Laxatives for Chronic Constipation	
1:30 PM	IV. DUR ACTIVITIES	
	A. Quarterly Utilization Report	R. Citron (OSU)
	B. P & T Methods	S. Servid (OSU)
	C. P & T Procedures	S. Servid (OSU)
	D. ProDUR Report	L. Starkweather (Gainwell)
	E. RetroDUR Report	D. Engen (OSU)
	F. Oregon State Drug Review	K. Sentena (OSU)
	1. Respiratory Syncytial Virus (RSV) Prevention Update	
	2. Evaluating the Quality of Evidence from Observational Studies: Lessons from Acetaminophen Use in Pregnancy	

V. NEW BUSINESS

1:55 PM	A. Topoisomerase II Inhibitors Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Nuzolvence (zoliflodacin) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:10 PM	B. Zycubo (Copper Histidinate) Orphan Drug Evaluation 1. Orphan Drug Evaluation 2. Prior Authorization Criteria 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
2:20 PM	C. Benzodiazepines Focused Scan for Catatonia 1. Literature Scan 2. Prior Authorization Update 3. Public Comment 4. Discussion and Clinical Recommendations	D. Engen (OSU)
2:35 PM	D. Cardamyst™ (etripamil) New Drug Evaluation 1. New Drug Evaluation 2. Prior Authorization Criteria 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:50 PM	BREAK	
3:05 PM	E. Spinal Muscular Atrophy Class Update 1. Class Update/Prior Authorization Criteria 2. Itvisma (onasemnogene abeparvovec) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:25 PM	F. Myasthenia Gravis DERP Report 1. DERP Report/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
3:40 PM	G. Loargys (pegzilarginase) Orphan Drug Evaluation 1. Orphan Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)

3:55 PM VI. EXECUTIVE SESSION

4:50 PM VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Bridget Bradley, PharmD, BCPP	Pharmacist	Kaiser Northwest Psychiatry	Beaverton	December 2026
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2026
Samara Stevens, ND	Public	Mental Health Naturopath	Portland	December 2026
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2027
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2027
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2027
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2027
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2028
Jennifer Henderson, DO	Physician	Asante Medical Director	Medford	December 2028
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2028
Bruce Leewiwatanakul, DO, MA	Physician	Child & Adolescent Psychiatry	Portland	December 2029

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, April 2nd, 2026
1:05 PM - 3:35 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: Samara Stevens, ND; Bridget Bradley, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Jennifer Henderson, DO; Russ Huffman, PMHNP; Tim Langford, PharmD; Eriko Onishi, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Lan Starkweather, PharmD; Brandon Wells; Dee Weston

Audience: Jessica Jay*, Vertex; Kathy Sapp*, American Chronic Pain Association; Barby Ingle*, International Pain Fund; Aimee Adelmann*, A2A Consulting; Jeff Martin*, Biocryst; Jessica Garrison, Gainwell; Erika Rosie, Vertex; Jeff Krueger, KalVista; Jenna Doerr, Artia Solutions; Lee Stout, Chiesi; Mike Donabedian, Sarepta; Herbert Starr, Acadia; Gary Parenteau, Dexcom; Lewis Backus, OHA; Sejal Upadhyaya, Novo Nordisk; Sergio Mayorga, Concis Labs; Lori Howarth, Bayer; Levi Smith, Vertex; April Grant, Vertex; Ann Nelson, Vertex; Holly Jo Hodges, EOCCO; Melissa Snyder, Gilead; Dan Yeager, Taiho Oncology; Rosalie Elliott, UHA; Tammi Ocumpaugh, Otsuka; Chris Ferrin, IHN; George Homsi; Rod Scott; Jill Carroll, BMS; Norm Navarro, Providence; Mark Kantor, AllCare; Brett Freund; Mark Harmon; Gloria Zepeda; Thomas Wolters, Gainwell; Shauna Wick, Leslie Ayhens, OHA

(*) Provided verbal testimony

I. CALL TO ORDER

A. Roll Call & Introductions
- Meeting 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. Approval of Agenda and February Minutes presented by Roger Citron, RPh
ACTION: Motion to approve, 2nd, all in favor

D. Department Update provided by Andrew Gibler, PharmD

E. Mental Health Clinical Advisory Group Update presented by Andrew Gibler, PharmD

OREGON HEALTH AUTHORITY

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Health Systems Division
500 Summer Street NE, E35; Salem, OR 97301-1079
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II. CONSENT AGENDA TOPICS

A. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Rybrevant Faspro (amivantamab and hyaluronidase-lpuj) to Table 1 in the Oncology Agents PA criteria

III. NEW BUSINESS

A. Analgesics Class Update: Sarah Servid, PharmD
Recommendation:
- Make no changes to the PDL based on review of the clinical evidence
- Update opioid, NSAID, and muscle relaxant PA criteria to align with current evidence for chronic pain conditions
- Evaluate costs in executive session

Public Comment: Jessica Jay, Vertex; Kathy Sapp, American Chronic Pain Association; Barby Ingle, International Pain Fund; Aimee Adelmann, A2A Consulting
ACTION: Motion to approve, 2nd, all in favor

B. Lynkuet® (elinzanetant) New Drug Evaluation: Deanna Moretz, PharmD
Recommendations:
- Create a "Neurokinin Receptor Antagonist" PDL class to include both fezolinetant and elinzanetant
- Designate elizanetant non-preferred and update the PA criteria as proposed

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

C. Hereditary Angioedema DERP Report: Sara Fletcher, PharmD
Recommendations:
- Update PA criteria as proposed to include new agents and step through preferred agents
- Evaluate comparative costs in executive session

Public Comment: Jeff Martin, Biocryst
ACTION: Motion to approve, 2nd, all in favor

D. GNRH Agonist and Antagonist Class Update Focused on Pelvic Pain and Dysmenorrhea: Deanna Moretz, PharmD
Recommendations:
- Make no changes to the PDL based on review of the clinical evidence
- Modify the GnRH Agonist and GnRH Antagonist PA criteria as proposed to align with HERC guidance
- Evaluate comparative costs in executive session

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

E. Waskyra™ (etuvetidigene autotemcel) Orphan Drug Evaluation: Sara Fletcher, PharmD
Recommendations:
- Implement proposed Etuvetidigene Autotemcel PA criteria
ACTION: Motion to approve, 2nd, all in favor

F. Myalept® (metreleptin) Orphan Drug Evaluation: Deanna Moretz, PharmD
Recommendations:
- Implement proposed Metreleptin PA criteria to ensure standard of care in patients diagnosed with lipodystrophy due to leptin deficiency
ACTION: Motion to approve, 2nd, all in favor

G. Cephalosporins Literature Scan: Kathy Sentena, PharmD
Recommendations:
- make cefaclor and cefpodoxime preferred based on guideline recommendations
- Evaluate comparative costs in executive session
ACTION: Motion to approve, 2nd, all in favor

H. Acne and Rosacea Class Update: Deanna Moretz, PharmD
Recommendations:
- Create a new PDL class for rosacea treatments
- Make at least one generic topical metronidazole product approved for management of rosacea preferred
- Make brimonidine non-preferred based on clinical evidence
- Maintain Twyneo and Cabtreo as non-preferred in the rosacea topical medication class
- Make Emrosi non-preferred in the oral tetracycline drug class
- Revise Acne PA criteria to include non-preferred topical agents for management of rosacea and add documentation of baseline assessment of disease severity
- Revise Oral Tetracycline PA criteria to include baseline assessments of acne and rosacea, when prescribed for these indications
- Add renewal criteria to topical acne/rosacea therapies and oral tetracyclines
- Evaluate comparative costs in executive session
ACTION: Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

Members Present: Samara Stevens, ND; Bridget Bradley, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Jennifer Henderson, DO; Russ Huffman, PMHNP; Tim Langford, PharmD; Eriko Onishi, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Lan Starkweather, PharmD; Brandon Wells; Kyle Hamilton

VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. Analgesics Class

Recommendation: Make tizanidine 2, 4, 6 mg capsules, piroxicam capsules, naproxen sodium capsules, indomethacin ER capsules, diclofenac ER 24H tablets, ketorolac tablets, tramadol ER 24H tablets, lidocaine ointment, capsaicin lotion, acetaminophen (all forms), aspirin-caffeine, acetaminophen-caffeine, and aspirin/acetaminophen/caffeine preferred; make ibuprofen 300 mg tablets, morphine sulfate solution, hydrocodone-acetaminophen solution, codeine sulfate tablet, butorphanol tartrate spray, hydromorphone suppository, opium-belladonna suppository, lidocaine 4% solution, lidocaine 4% cream, hydrocortisone-pramoxine lotion, hydrocortisone-pramoxine ointment, hydrocortisone-pramoxine cream, capsaicin 0.035% cream, and suzetrigine non-preferred. Make all other oral pain formulations containing acetaminophen or aspirin non-preferred

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

B. Hereditary Angioedema

Recommendation: Make generic icatibant preferred

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

C. GNRH Agonist and Antagonist

Recommendations: Make no changes to the PDL

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

D. Cephalosporins

Recommendations: Make cefaclor capsules, cefadroxil capsules, and cefpodoxime tablets preferred

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

E. Acne and Rosacea

Recommendations: Make topical generic metronidazole gel and cream preferred and make all other topical rosacea medications non-preferred; and make adapalene cream (brand and generic), benzoyl peroxide (Epsolay) cream, clindamycin phosphate foam, and tretinoin microspheres gel (brand and generic) non-preferred

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

VII. ADJOURN

Drug Use Research & Management Program
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Drug Class Literature Scan: Inhalers for Asthma/COPD

Date of Review: June 2026

Date of Last Review: June 2024
Literature Search: 12/01/2023 – 03/25/2026

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

Plain Language Summary:

- This review focuses on new information for inhalers in people who have asthma or chronic obstructive pulmonary disease (COPD).
- Inhaled medicines to treat asthma and COPD includes medicines called inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMAs), short-acting beta-agonists (SABA), short-acting muscarinic antagonists (SAMAs) and combinations of these medicines called ICS/LABA, LAMA/LABAs and ICS/LABA/LAMA.
- A review of studies in patients with COPD found that a combination LABA/LAMA inhaler called umeclidinium/vilanterol and a combination ICS/LABA/LAMA inhaler called umeclidinium/vilanterol/fluticasone furoate helped improve breathing problems, also known as exacerbations, compared to other similar inhaler therapy.
- A recent review that compiled data from many studies found that people who have moderate to severe COPD had fewer exacerbations when they added an ICS inhaler to their LAMA/LABA therapy.
- For people with COPD, the 2026 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends inhalers that align with fee-for-service (FFS) policy.
- For people with asthma, the Global Strategy for Asthma Management and Prevention (GINA), the British Thoracic Society (BTS), the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Veterans Administration and Department of Defense (VA/DOD) recommend inhalers that align with FFS policy.
- Two new studies showed that adding an ICS inhaler helps improve breathing in people with asthma who still have symptoms when using a LABA or SABA inhaler alone.
- The Drug Use Research and Management (DURM) group recommends continuing with the current policy for inhaler therapy offered to patients with asthma or COPD.

Conclusions:

- There were 2 systematic reviews and meta-analyses, 4 high quality guidelines and 2 randomized controlled trials (RCTs) included in this literature scan.
- A high-quality systematic review and meta-analysis found dual umeclidinium (UMEC)/vilanterol (VI) and triple UMEC/VI/fluticasone furoate (FF) therapy improved lung function and symptoms in patients with COPD, when compared to active treatment, or placebo.[1]

Author: Kathy Sentena, PharmD

- A Cochrane review evaluated addition of an inhaled corticosteroid (ICS) to a long-acting muscarinic antagonist (LAMA) and long-acting beta-agonist (LABA), known as triple therapy, in patients who have moderate to severe COPD.[2] Triple therapy decreased severe exacerbations compared to LAMA/LABA therapy based on low-quality evidence (relative risk [RR] 0.75; 95% confidence interval [CI], 0.67 to 0.84). The risk of pneumonia was increased with triple therapy compared to LAMA/LABA , 3.3% versus 1.9% (odds ratio [OR] 1.74; 95% CI, 1.39 to 2.18).[2]
- The GOLD guidance for management of COPD was updated in 2026.[3] Guideline recommendations for inhalers align with the current FFS policy.
- A collaborative guideline from the British Thoracic Society (BTS), National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) on the management of asthma for children and adults was published in 2024. Using anti-inflammatory therapy with reliever therapy is advocated as initial asthma management.[4] These recommendations align with other guidelines.[4]
- In 2025, GINA updated guidance for asthma management in individuals of all ages.[5] Recommendations for inhalers are consistent with the FFS policy and preferred drug list (PDL).
- The VA/DOD updated guidance on the management of asthma in primary care in 2025.[6] Updated guidance includes initiating therapy with an anti-inflammatory and rapid-acting LABA inhaler. Clinical guideline recommendations align with the current PDL.
- A RCT compared efficacy of FF/VI to FF monotherapy in patients 5 to 17 years. Patients were randomized to dual therapy or continuation of ICS (e.g., FF).[7] The combination of FF/VI was more effective at improving forced expiratory volume in one second (FEV_1) than FF monotherapy (treatment difference [TD] 0.083 L; 95% CI, 0.037 to 0.129; p<0.001), a difference that was both statistically and clinically significant.[7]
- A RCT evaluated combination therapy with albuterol/budesonide compared to albuterol alone in patients 12 years of age and older with mild asthma uncontrolled despite treatment with a SABA with or without low-dose inhaled glucocorticoid or leukotriene receptor antagonist.[8] The combination regimen was superior to albuterol alone for the outcome of first severe asthma exacerbation (hazard ratio [HR] 0.53; 95% CI, 0.39 to 0.73; P<0.001).[8] The trial was stopped early due to significant reduction in the risk of severe exacerbations with combination therapy.

Recommendations:
- No changes to the PDL are recommended based on the review of the clinical evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The inhaled therapies for asthma and COPD are comprised of 5 classes: SABAs, LABAs, SAMAs, LAMAs, and ICS. For ease of administration, these drug classes are combined into single combination 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.
- This class was last reviewed in June of 2024 and no changes were made to the PDL based on a review of the evidence.
- After evaluation of costs in executive session, beclomethasone dipropionate HFA (QVAR RediHaler) and mometasone HFA (ASMANEX) were made preferred on the PDL and fluticasone propionate HFA was made non-preferred.
- A complete list of preferred and nonpreferred products is available in **Appendix 1**.
- Specific prior authorization requirements are outlined in **Appendix 6** for the following:
    - Non-preferred ICS inhalers
    - Non-preferred LABA inhalers
    - Non-preferred LAMA/LABA and LAMA/LABA/ICS inhalers

- There were over 2,000 claims for inhalers for asthma and COPD, costing almost $200,000, in quarter 4 of 2025 (September 1 to December 31).

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, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) 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:

Zhu – Umeclidinium/Vilanterol for COPD
A systematic review and meta-analysis evaluated the efficacy of combination UMEC/VI and UMEC/VI/FF therapies compared to other active treatments or placebo in people with COPD.[1] Literature was searched up till June 30, 2024. Fifteen RCTs (n=31,184) met inclusion criteria. Individuals 18 years or older, average age of 64 years, with mild to moderate COPD were included. Trials lasted 8-52 weeks in duration. Eleven of the 15 RCTs evaluated UMEC/VI dual therapy effectiveness compared to other therapies, with the remaining 4 studies evaluating triple therapy.[1] Active treatment comparisons included: tiotropium, salmeterol, tiotropium/olodaterol, budesonide formoterol, salmeterol/fluticasone propionate, tiotropium/indacaterol, indacaterol/glycopyrrolate, glycopyrrolate/formoterol fumarate and fluticasone furoate/vilanterol. Evaluation of risk of bias by the authors determined that a majority of the studies had low risk.

Lung function, as measure by FEV_1, was significantly improve, compared to active treatment described above, with UMEC/VI (OR 1.98; 95% CI, 1.70 to 2.30) and transitional dyspnea index [TDI] values (OR 1.97; 95% CI, 1.72 to 2.26).[1] Quality of life scores, measured by St. George's Respiratory Questionnaire Total Score (SGRQTS), were reduced (OR 1.99; 95% CI, 1.71 to 2.32).[1] Triple therapy with UMEC/VI/FF also improved FEV_1 (OR, 1.93; 95% CI, 1.73 to 2.15) and TDI (OR 2.37; 95% CI, 2.15 to 2.61) with reduced SGRQ total scores (OR 1.83; 95% CI, 1.63 to 2.05).[1] Both treatments were well tolerated and associated with fewer adverse events compared to active treatment (described above). Overall, combination therapy with UMEC/VI and UMEC/VI/FF are effective treatment options for patients with COPD.[1]

Cochrane – Inhaled Corticosteroids with LABAs and LAMAs for COPD
A systematic review and meta-analysis evaluated the efficacy of adding an ICS to LAMA/LABA (triple therapy) for the treatment of COPD.[2] A total of 4 studies (n= 15,412) met inclusion criteria. Females represented 28% to 40% of the enrolled populations with the average age of all participants of 64.4 to 65.3 years. All participants had symptomatic air flow restriction (severe to very severe airflow limitation) with FEV_1 of <50% predicted.[2] Most participants had one or more moderate to severe COPD exacerbations in the last 12 months. Study duration was 24 weeks to 52 weeks.[2] The risk of bias was determined to be low in the

majority of studies. The primary outcomes were acute COPD exacerbations, respiratory health related quality of life, frequency of pneumonia and adverse events.

There was low-quality evidence that triple therapy (ICS/LAMA/LABA) reduced moderate-to-severe COPD exacerbations compared to LAMA/LABA inhalers (RR 0.74; 95% CI, 0.67 to 0.81; n=15,397).[2] Patients that had high blood eosinophil counts (150 -200 eosinophils/µL) may benefit more from triple therapy by a reduction in exacerbations (RR 0.67; 95% CI, 0.60 to 0.75) compared to those with low blood eosinophil counts (RR 0.87; 95% CI, 0.81 to 0.93); however, results were based on observational data.[2] Severe COPD exacerbations with triple therapy may be reduced more than LAMA/LABA therapy based on low-quality evidence (RR 0.75; 95% CI, 0.67 to 0.84).[2]

Quality of life was improved with triple therapy, as measured by a change of at least 4 points (which is the minimal clinically important difference [MCID]) in the SGRQ score (OR 1.35; 95% CI, 1.26 to 1.45) (high-quality evidence).[2] There is moderate-quality evidence that triple therapy may reduce symptoms, as measured by the TD (OR 1.33; 95% CI, 1.13 to 1.57). Changes in trough FEV_1 favored triple therapy although evidence was of low quality (mean difference [MD] 38.68 mL; 95% CI, 22.58 to 54.77).[2] Neither changes in TDI or trough FEV_1 were considered clinically meaningful.

When triple therapy is compared to LAMA/LABA there was an increased risk of pneumonia, 3.3% versus 1.9% (OR 1.74; 95% CI, 1.39 to 2.18) based on moderate-quality evidence.[2] There was low-quality evidence that serious adverse events and all-cause mortality were similar between the groups.

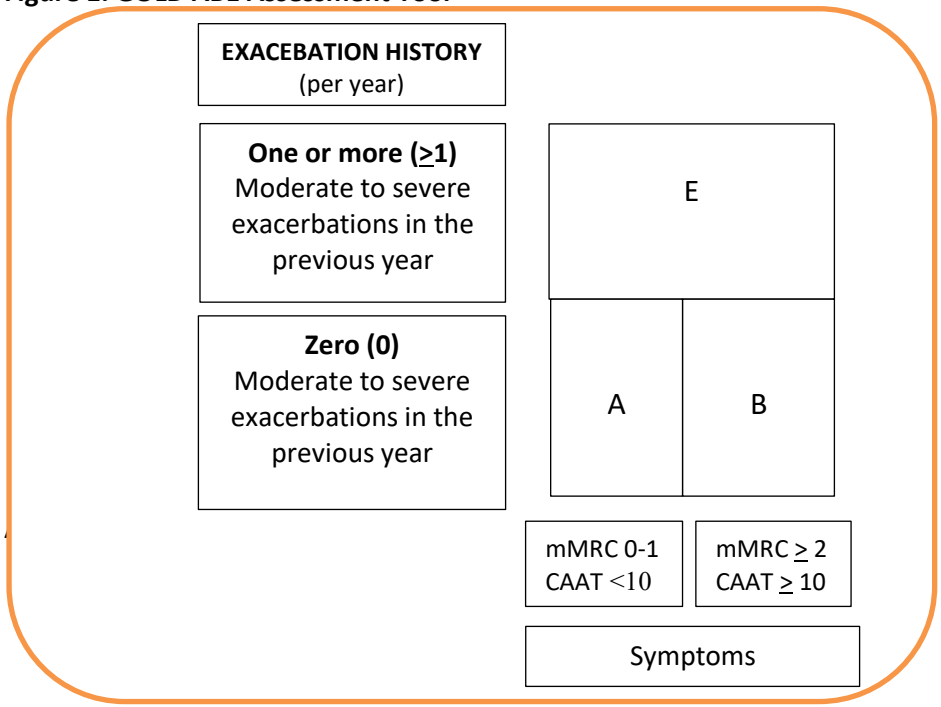
After review, 6 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[9–15]

New Guidelines:
High Quality Guidelines:

<u>GOLD Guidelines – Global Initiative for Chronic Obstructive Lung Disease</u>
In 2026, GOLD published their annual update of guidance for management of COPD.[3] The evidence was graded as A (high-quality evidence from RCTs without significant limitations), B (from RCTs with limitations), C (non-randomized trials and observational studies), and D (panel consensus). Important updates related to management and pharmacotherapy include: new definitions of GOLD A, B and E categories, revised management cycle and treatment algorithm to emphasize the distinction between initial pharmacotherapy and follow-up treatment, use of biologic therapy, and management of COPD exacerbations. For a full description of all the 2026 updates consult the GOLD report.[3]

One clarifications made in the 2026 recommendations are to the GOLD ABE Assessment Tool (**Figure 1**).[3] The recommendations are that the categories be adjusted to emphasize the importance that moderate to severe exacerbations play in predicting subsequent events.[3] If exacerbations are more frequent or severe, the risk of additional exacerbations is even higher.[3] The threshold has been reduced so that even one moderate exacerbation may be cause for treatment escalation.

Figure 1. GOLD ABE Assessment Tool[3]



The guideline also updated its management of COPD recommendations.[3] Patients who smoke are strongly encouraged to quit (Evidence A).[3] Guideline recommended vaccines for people with COPD are: COVID-19 vaccination, influenza, pneumococcal, and RSV (Evidence B for all but RSV which has Evidence level A).[3] Tetanus, diphtheria, and acellular pertussis vaccine (Tdap) vaccination and the shingles vaccine are also recommended (Evidence B). In additional to pharmacotherapy interventions, non-pharmacological measures should be considered (i.e., pulmonary rehabilitation, exercise training, COPD education) which has been shown to improve exercise capacity and quality of life in patients with COPD.[3] Long-term oxygen therapy may improve survival in patients with severe resting chronic hypoxemia, but otherwise should not be prescribed for patients with stable COPD and those with resting or exercise-induced moderate desaturation.[3] Surgical or bronchoscopic interventions may be beneficial in select patients with advanced emphysema refractory to optimized medical care.

Pharmacological Maintenance Treatment of COPD:[3]

- Initial pharmacotherapy should be selected based on the severity of symptoms, exacerbation risk, adverse reactions, patient comorbidities, drug availability, cost and the patient's preference and ability to use drug delivery devices (**Table 1**).[3]
- Attainment and barriers to treatment goals should be reviewed at intervals dependent upon disease severity.
- LABA + LAMA + ICS is the only pharmacotherapy with evidence of a mortality reduction in COPD patients with symptoms and history of frequent and/or severe exacerbations.

Table 1. Pharmacological Management for the Treatment of COPD[3]

Initial Treatment		
Group	**Treatment**	**Notes**
E	LABA + LAMA*	Consider LABA + LAMA + ICS if blood eos ≥ 300 cells/µL
A	Bronchodilator (no specific treatment recommended)	Short or long-acting bronchodilators, but long-acting are preferred
B	LABA + LAMA*	Combination with LABA + LAMA is the preferred therapy If combination therapy is not appropriate then there is no comparative evidence suggesting one class of long-acting bronchodilator over another (LABA or LAMA) Treat comorbidities if present
Follow-up Treatment if Dyspnea or Exacerbation		
Symptom	**Treatment**	**Notes**
Persistent dyspnea	LABA or LAMA ↓ LABA + LAMA	• Consider switching inhaler device or molecules • Implement or escalate non-pharmacological treatment(s) • Consider adding ensifentrine • Evaluate for other causes of dyspnea and treat if indicated
One or more moderate or severe exacerbation	LABA or LAMA ↓ LABA + LAMA – if blood eos < 300 cells/µL **OR** LABA + LAMA + ICS – if blood eos ≥ 300 cells/µL	• If patient continues to have symptoms move to next row
Ongoing symptoms and taking LABA + LAMA therapy	LABA + LAMA + ICS – if blood eos ≥ 100 cells/µL **OR** - If blood eos < 100 cells/µL > Roflumilast **OR** Azithromycin	• Roflumilast is preferred if FEV_1 < 50% & chronic bronchitis • Azithromycin preferentially in former smokers
Ongoing symptoms and taking LABA + LAMA + ICS therapy	Roflumilast **OR** Azithromycin	• Roflumilast is preferred if FEV_1 < 50% & chronic bronchitis • Azithromycin preferentially in former smokers
Ongoing symptoms and taking LABA + LAMA + ICS therapy **AND** Two moderate or one severe exacerbation **AND** blood eos ≥ 300 cells/µL	Biologic Therapy	• Dupilumab (with chronic bronchitis) • Mepolizumab (with or without chronic bronchitis)
Patients taking LABA + ICS		
LABA + ICS and no relevant exacerbation history	Consider changing to LABA + LAMA	• NA

LABA + ICS with no relevant exacerbation history and high symptoms	Consider LABA + LAMA + ICS	• If the patient has no current exacerbations and previous positive response to treatment and low symptoms then continue LABA + ICS treatment
LABA + ICS and current exacerbations with blood eos < 100 cells/µL	Consider changing to LABA + LAMA	• Blood eosinophils dictate best treatment path
LABA + ICS and current exacerbations with blood eos ≥ 100 cells/µL	Consider escalating to LABA + LAMA + ICS	• NA

Key: * Single combination inhaler may be more convenient and improve adherence to treatment
Abbreviations: eos = eosinophil count; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic receptor antagonist; NA = not applicable.

If a patient has asthma and COPD, they should be considered different diseases and pharmacotherapy should primarily follow asthma guidelines.[3] The use of ICS with long-acting bronchodilators in patients with COPD should be considered in patients with history of hospitalization for COPD exacerbations, 2 or more moderate exacerbations of COPD per year, blood eosinophils of 300 cells/µL or higher, or history of asthma, as these characteristics strongly favor ICS use. For patients with 1 or more moderate exacerbation of COPD annually or blood eosinophils 100 to <300 cells/µL, the use of ICS is favored. For patients with repeat pneumonia, blood eosinophils < 100 cells/µL, or history of mycobacterial infection, the use of ICS is not recommended.[3] De-escalation of ICS is recommended for patients that develop pneumonia or other adverse reactions.[3]

The GOLD guidelines also offer recommendations for the management of COPD exacerbations. Recommendations include:
- Initiation of SABAs with or without short-acting anticholinergics as the initial bronchodilators to treat an acute exacerbation (Evidence C).[3]
- Systemic corticosteroids for 5 days can be considered to improve lung function (FEV_1), oxygenation, and shorten recovery time and hospitalization time (Evidence A).[3]
- Antibiotics are recommended in patients with purulent sputum, prior positive sputum bacteria culture, or requiring mechanical ventilation (invasive or noninvasive) (Evidence A). When given for 5 days they have been shown to shorten recovery time, reduce risk of relapse, reduce treatment failure, and shorten hospitalizations (Evidence B).[3]
- Consider appropriate regimens to decrease frequency of COPD exacerbations

<u>SIGN Guidelines – Asthma: Diagnosing, Monitoring and Chronic Asthma Management (SIGN 245)</u>
A collaboration between the BTS, NICE and SIGN published recommendations for the management of chronic asthma in 2024, with a minor update in November 2025.[4] The guideline includes diagnosis and assessment of asthma in adults and children, pharmacological treatment, and monitoring. This review will focus on recommendations for pharmacotherapy in asthma.

Assessment of uncontrolled asthma should be done prior to initiating medications or adjusting asthma medications.[5] Adherence, inhaler technique, alternative diagnoses or comorbidities, smoking, and occupation exposure, psychosocial factors, seasonal factors and environmental factors should be considered. Determine fractional exhale nitric oxide (FeNO) level if possible.[4] If levels are high, there may be adherence issues or need for an increased dose of corticosteroid. Recommendations for asthma medication management in those 12 and older are included in **Table 3,** for those 5 to 11 years in **Table 4** and for

those under 5 in **Table 5.** Response to treatment should be reviewed 8-12 weeks after starting or adjusting treatment.[4] If considering step-down treatment for people aged 12 and over who are using low-dose maintenance ICS plus a SABA as needed or low-dose MART (maintenance and reliever therapy), step down to low-dose ICS/formoterol combination inhaler as needed (as-needed anti-inflammatory reliever [AIR] therapy).[4] The use of MART allows for individuals to use the same inhaler for maintenance and rescue therapy because it contains an ICS and a fast-acting beta-agonist, such as formoterol. Anti-inflammatory Reliever therapy, known as AIR therapy, uses a single inhaler containing a fast-acting bronchodilator, such as formoterol, and an ICS to use as needed, in place of traditional SABA therapy.

Table 3. SIGN Pharmacotherapy Recommendations for Asthma Management in People Aged 12 and Over[4]

Recommendation
Do not prescribe a SABA to people of any age with asthma without a concomitant prescription of an ICS.
Initial Management
Offer low-dose ICS/formoterol combination inhaler for as needed symptom relief (AIR therapy).*
Highly symptomatic patients or those with severe exacerbations: start with low-dose MART therapy in addition to treating acute symptoms. Consider step-down therapy to AIR therapy.
Offer low-dose MART to people aged 12 and over with asthma that is not controlled with an as needed low-dose ICS/formoterol combination inhaler.
Offer moderate-dose MART to people aged 12 and over with asthma that is not controlled on low-dose MART.
For people not controlled on moderate-dose MART despite good adherence, check the FeNO level and blood eosinophil count if available. If neither level is raised, consider trial of LTRA or LAMA.
Uncontrolled Asthma
If using a SABA only, change treatment to low-dose ICS/formoterol combination inhaler used as needed (as-needed AIR therapy).
Consider changing treatment to low-dose MART for people with asthma that is not controlled on: • Regular low-dose ICS plus SABA as needed • Regular low-dose ICS/LABA combination inhaler plus SABA as needed • Regular low-dose ICS and supplementary therapy (LTRA) plus SABA as needed • Regular low-dose ICS/LABA combination inhaler and supplementary therapy (LTRA) plus SABA as needed
Consider changing treatment to moderate-dose MART for people with asthma that is not controlled on: • Regular moderate-dose ICS plus SABA as needed • Regular moderate-dose ICS/LABA combination inhaler plus SABA as needed • Regular moderate-dose ICS and supplementary therapy (LTRA or LAMA, or both) plus SABA as needed • Regular moderate-dose ICS/LABA combination inhaler and supplementary therapy (LTRA or LAMA, or both) plus SABA as needed
When changing from low- or moderate-dose ICS (or ICS/LABA combination inhaler) plus supplementary therapy to MART, consider whether to stop or continue the supplementary therapy based on the degree of benefit achieved when first introduced.
Key: * Only certain budesonide/formoterol inhalers are approved for as-needed AIR therapy in mild asthma Abbreviations: AIR – anti-inflammatory reliever; FeNO – fractional exhaled nitric oxide (FeNO); ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; LAMA – long-acting muscarinic receptor antagonist; LTRA – leukotriene receptor antagonist; MART – maintenance and reliever therapy; SABA – short-acting beta-agonist.

Table 4. SIGN Pharmacotherapy Recommendations for Asthma Management in People Aged 5 to 11 years[4]

Recommendation
Initial Management
Offer a twice-daily pediatric low-dose ICS with SABA as needed.
Consider pediatric low-dose MART for children with asthma that is not controlled on low-dose ICS plus SABA as needed, as long as they are assessed to have the ability to manage a MART regimen*.
Uncontrolled Asthma Management
Consider increasing to pediatric moderate-dose MART if asthma is not controlled on pediatric low-dose MART.
Consider adding a LTRA to twice daily pediatric low-dose ICS plus SABA as needed when a child has uncontrolled asthma and is assessed as unable to manage the MART regimen.
Offer a twice daily pediatric low-dose ICS/LABA combination inhaler plus SABA as needed to children assessed as unable to manage the MART regimen if their asthma is not controlled on pediatric low-dose ICS plus SABA as needed (with or without a LTRA depending on previous response).
Offer a twice daily pediatric moderate-dose ICS/LABA inhaler plus SABA as needed to children with asthma that is not controlled on pediatric low-dose ICS/LABA plus SABA as needed (with or without an LTRA depending on previous response).
Key: * only one budesonide/formoterol dry powder inhaler (100 micrograms/6 micrograms per inhalation) is licensed for MART in children aged 6 to 11 years. Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; LAMA – long-acting muscarinic receptor antagonist; LTRA – leukotriene receptor antagonist; MART – maintenance and reliever therapy; SABA – short-acting beta-agonist.

Table 5. SIGN Pharmacotherapy Recommendations for Asthma Management in Children under 5 years[4]

Recommendation
Newly Suspected Asthma, Confirmed Asthma, or Uncontrolled on Current Treatment
Consider an 8 to 12 week trial of twice-daily pediatric ICS as maintenance therapy (with SABA for reliever therapy) in children under 5 with suspected asthma and: • symptoms at presentation that indicate the need for maintenance therapy (for example, interval symptoms in children with another atopic disorder), **or** • severe acute episodes of difficulty breathing and wheeze (for example, requiring hospital admission, or needing 2 or more courses of oral corticosteroids)
If symptoms resolve during the trial period, but then recur by the 3-month review or the child has an acute episode requiring systemic corticosteroids or hospitalization: • restart regular ICS (begin at a pediatric low dose and titrate up to a pediatric moderate dose if needed) with SABA as needed and consider a further trial without treatment after reviewing the child within 12 months
If suspected asthma is uncontrolled in children under 5 on a pediatric moderate dose of ICS as maintenance therapy (with SABA as needed), consider a LTRA in addition to the ICS. Give the LTRA for a trial period of 8 to 12 weeks (unless there are side effects), then stop it if it is ineffective.
If suspected asthma is uncontrolled in children under 5 on a pediatric moderate dose of ICS as maintenance therapy and a trial of an LTRA has been unsuccessful or not tolerated, stop the LTRA and refer the child to a specialist in asthma care for further investigation and management.
Abbreviations: ICS – inhaled corticosteroid; LTRA – leukotriene receptor antagonist; SABA – short-acting beta-agonist.

In April 2025, a reminder was issued of the risk of severe asthma attacks and increased mortality with the overuse of SABA with or without an ICS.[4]

GINA – Global Strategy for Asthma Management and Prevention

In 2025, GINA updated asthma diagnosis and management guidance for adults and children.[5] The focus of this update will be on pharmacotherapy recommendations for asthma.

The goal of asthma management is to control symptoms, prevent exacerbations, airway damage and medication side-effects. Pharmacotherapy recommendations are presented in **Table 6**.[5]

Table 6. GINA General Asthma Pharmacotherapy Recommendations[5]

Recommendation	Notes
1. Makes sure every patient has an ICS (or combination that contains an ICS)	- This recommendation applies even if symptoms are infrequent. - ICS medication should be started as soon as possible after diagnosis. - Any patient can have a severe exacerbation, even if asthma is mild. - ICS products decrease risk of asthma hospitalization and death. - Early ICS treatment with low-dose ICS is associated with better lung function. - Patients who have a severe exacerbation when not using an ICS have worse long-term lung function compared to those that use an ICS.
2. Every patient needs a reliever inhaler containing a rapid-acting bronchodilator to use for symptom management	- Options include ICS-formoterol, ICS-SABA or SABA. - Low-dose ICS-formoterol is the preferred option in adolescents and adults compared to regimens containing SABAs.
3. Treatment containing only as-needed SABAs are not recommended.	- The use of SABA-only treatments has been shown to increase risk of exacerbations, worsen lung function and increase risk of death due to asthma.
Abbreviations: ICS = inhaled corticosteroid; SABA= Short-acting beta-agonist	

Specific, step-based treatment recommendations are included below in **Table 7**. The table refers to anti-inflammatory reliever (AIR) therapy, which is the use of ICS-formoterol combination inhaler as needed for asthma symptoms.[5] The table also describes the use of maintenance-and-reliever therapy (MART), which is the combination ICS-formoterol is taken as a daily maintenance treatment and an extra dose is used of the same medication when there are asthma symptoms. Once good asthma control has been achieved and maintained for 2-3 months, consider stepping down therapy to the lowest treatment dose to control both symptoms and exacerbations.[5] In adults and adolescents with severe asthma, assessment for asthma inflammatory phenotype and sputum eosinophil count is recommended, if available, to guide treatment. Maintenance oral corticosteroids should only be used as a last resort.[5]

Table 7. Pharmacotherapy Recommendations by GINA for Adults and Adolescents 12 Years and Older[5]

Track 1 – Preferred Controller and Reliever Therapy				
Step 1–2	**Step 3**	**Step 4**	**Step 5**	
AIR-only: low-dose ICS-formoterol as needed	MART with low-dose maintenance ICS-formoterol	MART with medium-dose maintenance ICS-formoterol	Add-on LAMA. Refer for assessment of phenotype. Consider high-dose maintenance ICS-formoterol. Consider biologics: anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP*	
Reliever therapy for all steps: As-needed low-dose ICS-formoterol				
Track 2 – Alternative Controller and Reliever				
Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Reliever only; if SABA used, take ICS with each dose	Low-dose maintenance ICS	Low-dose maintenance ICS–LABA	Medium-dose maintenance ICS–LABA.	Add-on LAMA. Refer for phenotype assessment. Consider biologics: anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP*
Reliever therapy for all steps: As-needed ICS–SABA or as-needed SABA				

Abbreviations: AIR = Anti-inflammatory reliever; ICS = Inhaled corticosteroids; IL = interleukin; LABA = Long-acting beta2-agonist; LAMA = Long-acting muscarinic antagonist; LTRA leukotriene receptor antagonist; MART = maintenance-and-reliever therapy with ICS-formoterol; SABA= Short-acting beta2-agonist; TSLP = Thymic stromal lymphopoietin.
Key: * Anti-IgE (anti-immunoglobulin E) like omalizumab for severe allergic asthma; Anti-IL5/5R (anti-interleukin 5 or anti-interleukin 5 receptor alpha for severe eosinophilic asthma) like reslizumab, mepolizumab, benralizumab; Anti-IL4Rα (anti-interleukin 4 receptor alpha) like dupilumab for severe eosinophilic asthma/asthma Type 2 airway inflammation or for patients requiring maintenance oral corticosteroids; anti-TSLP (anti-thymic stromal lymphopoietin) like tezepelumab.

Treatment recommendations for children 6-11 years with asthma are described in **Table 8**.[5]

Table 8. Pharmacotherapy Recommendations by GINA for Children 6-11 years[5]

Preferred Controller				
Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Low-dose ICS taken whenever SABA taken	Daily low-dose inhaled corticosteroid (ICS)	Low-dose ICS-LABA OR medium-dose ICS OR very-low-dose ICS-formoterol maintenance and reliever (MART)	Medium-dose ICS-LABA OR low-dose ICS-formoterol MART OR refer for expert advice	Refer for phenotypic assessment ± higher-dose ICS-LABA or add-on therapy (e.g., LAMA, anti-IgE, anti-IL4Rα, anti-IL5)
Other Controller Options				
Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Low-dose ICS taken whenever SABA taken	Daily LTRA OR low-dose ICS whenever SABA taken	Low-dose ICS + LTRA	Add tiotropium OR add LTRA	As last resort, consider low-dose OCS but monitor for side effects
Reliever therapy for all steps: As-needed SABA (or ICS-formoterol reliever in MART Steps 3 and 4)				
Abbreviations: anti-IgE = anti-immunoglobulin E; anti-IL4Rα = anti-interleukin 4 receptor alpha; anti-IL5 = anti-interleukin 5; ICS = Inhaled corticosteroids; Ig = immunoglobulin; LABA = Long-acting beta2-agonist; LAMA = Long acting muscarinic antagonist; LTRA = Leukotriene receptor antagonist; MART = maintenance-and-reliever therapy with ICS-formoterol; OCS = oral corticosteroid; SABA= Short-acting beta2-agonist.				

The pharmacotherapy recommendations for asthma treatment for those 5 years and younger by GINA are outlined in **Table 9**.[5] Updated acute exacerbation recommendations include a new oxygen saturation target of 94% or greater with supportive intravenous magnesium in severe cases (if the child is 2 or older).[5] Prompt use of SABA with a spacer (4-6 puffs or 2.5 mg by nebulizer every 20 minutes) is recommended as initial management.

Table 9. Pharmacotherapy Recommendations by GINA for Children 5 years and younger[5]

Preferred Controller			
Step 1	**Step 2**	**Step 3**	**Step 4**
Insufficient evidence for daily controller	Daily low-dose ICS	Double low-dose ICS	Continue controller & refer for specialist assessment
Other Controller Options (limited evidence, or less evidence for efficacy or safety)			
Step 1	**Step 2**	**Step 3**	**Step 4**
Consider intermittent short course ICS at onset of viral illness	Daily LTRA or intermittent short course ICS at onset of respiratory illness	Consider specialist referral	NA
Reliever therapy for all steps: As-needed SABA			
Consider the Steps Above For Children With:			
Infrequent acute wheezing episodes (e.g., viral-induced) and no interval asthma symptoms	Asthma symptoms not well controlled or ≥1 severe exacerbation in past year	Asthma not well controlled on low-dose ICS	Asthma not well controlled on double ICS
		Before stepping up, check for alternative diagnosis and inhaler skills, review adherence and exposures	
Abbreviations: ICS = Inhaled corticosteroids; LTRA = Leukotriene receptor antagonist; NA = not applicable			

VA/DOD – Primary Care Management of Asthma

The 2019 guidance on managing asthma was updated in 2025 by the VA/DOD. Evidence is current from May of 2024.[6] There were 14 new, reviewed or amended recommendations included in the guideline.

New pharmacotherapy recommendations include[6]:

- For individuals 12 years and older, ICS combined with rapid-onset LABA (e.g., formoterol) is suggested for control and relief. (Weak recommendation for treatment)
- For individuals with uncontrolled asthma on ICS and LABA who use SABA for relief, it is suggested that ICS and rapid-acting LABA as both for controller and reliever. (Weak recommendation for treatment)
- For individuals with asthma that are 12 years and older that are not controlled by medium and high dose ICS and LABA, it is suggested to add a LAMA. (Weak recommendation for treatment)
- For individuals with exercise-induced bronchoconstriction, the VA suggests pre-exertional SABA. (Weak recommendation for treatment)

In patients with confirmed asthma, the VA/DOD recommends starting or continuing therapy with an ICS and rapid-onset LABA as a reliever and to initiate asthma education and care management.[6] If the patient has more than mild symptoms, a ICS and rapid-onset LABA as controller and reliever is recommended. If the patient still has symptoms, verify adherence and proper inhaler technique and/or dose escalation. If the patient's symptoms are controlled, recommend reassessment in 3 months.[6] If symptoms are stable for 90 days or more, consider step-down therapy. If the patient continues to have symptoms with on ICS/rapid-onset LABA therapy, consider increasing to moderate dose ICS and rapid-onset LABA as controller and reliever. If a patient continues to have symptoms on moderate ICS/rapid-onset LABA therapy, add LAMA and consider specialist referral.[6]

New Formulations:

None identified.

New FDA Safety Alerts:

None identified.

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Appendix 1: Current Preferred Drug List

Corticosteroids, Inhaled

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

Corticosteroids/Beta-agonist Combination, Inhalers

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

Beta-agonists, Inhaled Long-acting

Generic	Brand	Form	PDL
salmeterol xinafoate	SEREVENT DISKUS	BLST W/DEV	Y
arformoterol tartrate	ARFORMOTEROL TARTRATE	VIAL-NEB	N
arformoterol tartrate	BROVANA	VIAL-NEB	N

formoterol fumarate	FORMOTEROL FUMARATE	VIAL-NEB	N
formoterol fumarate	PERFOROMIST	VIAL-NEB	N
olodaterol HCl	STRIVERDI RESPIMAT	MIST INHAL	N

Beta-agonists, Inhaled Short-acting

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

LAMA/LABA Combination, Inhalers

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

Muscarinic Agonists, Inhaled

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

Appendix 2: New Comparative Clinical Trials

A total of 131 citations were manually reviewed from the initial literature search. After further review, 129 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 3**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Bareille, et al[7] DB, Phase 3, RCT	Fluticasone furoate (FF)/vilanterol (VI) (50/25 µg once daily for children and 100/25 µg once daily for adolescents) Versus Fluticasone furoate (FF) (50 µg once daily in children and 100 µg once daily in adolescents) Treatment duration: 24-week	Participants 5-17 years with 6 months or more asthma history that was uncontrolled on ICS monotherapy N = 902	Week 12 weighted mean FEV_1; 0-4 hours in those 5-17 years (US requirement) and change from baseline pre-dose morning peak expiratory flow (change AM PEF) averaged over weeks 1-12 in participants 5-11 years (European regulatory requirements)	Weighted mean FEV_1 (0-4 hours) FF/VI: 0.406 L FF: 0.323 L TD 0.083 L (95% CI, 0.037 to 0.129); P<0.001 Change AM PEF: FF/VI: 12.0 L FF: 8.8 L TD 3.2 L/min (95% CI, -2.0 to 8.4); P = 0.228	- Patients had a 4-week open-label run in period with fluticasone propionate (100 µg twice daily) - Baseline FEV_1 2.04 L - Most patients had asthma more than 1 and less than 10 years - Changes in FEV_1 were clinically (increase of 10% or more) and statistically significant - No new safety concerns
LaForce, et al[8] BATURA DB, Phase 3b, RCT	Albuterol 180 µg + budesonide 160 µg as needed Vs. Albuterol 180 µg as needed Treatment duration: up to 52 weeks	Participants 12 years and older with mild asthma that was uncontrolled despite treatment with a SABA with or without low-dose inhaled glucocorticoid or leukotriene receptor antagonist N = 2516	First severe asthma exacerbation (assessed in a time-to-event analysis)	Severe asthma exacerbation: Albuterol/budesonide: 62 (5.1%) Albuterol: 110 (9.1%) HR 0.53 (95% CI, 0.39 to 0.73) P<0.001	- Mean age was 42.7 years, 68% female, White 70% - Adverse events were similar between groups - Trial stopped early due to significantly lower risk of severe exacerbations with combination treatment

Abbreviations: CI = confidence interval; DB = double blind; FEV_1 = forced expiratory flow volume in 1 second; HR = hazard ratio; ICS = inhaled corticosteroid; PEF = peak expiratory flow; RCT = randomized clinical trial; SABA = short-acting beta agonist; TD = treatment difference.

Appendix 3: Abstracts of Comparative Clinical Trials

Once-daily fluticasone furoate/vilanterol vs once-daily fluticasone furoate in patients with asthma aged 5 to 17 years

Bareille P, Forth R, Imber V, et al

Background: Limited data exist comparing inhaled corticosteroid (ICS) plus adjunctive therapy vs ICS alone in pediatric asthma patients.

Objective: To evaluate the efficacy and safety of fluticasone furoate/vilanterol (FF/VI) vs FF in children and adolescents with asthma.

Methods: This phase 3, randomized, double-blind, multicenter study (NCT03248128) included participants aged 5 to 17 years with six months or more asthma history uncontrolled on ICS monotherapy. Participants received 4-week open-label fluticasone propionate(100 µg) twice daily before 1:1 randomization to 24-week double-blind FF (50 µg:100 µg) or FF/VI (50/25 µg:100/25 µg) once daily. Two populations with different primary endpoints were analyzed to meet United States (week 12 weighted mean forced expiratory volume in 1 second [FEV_1; 0-4 hours]; participants aged 5–17 years) and European (change from baseline pre-dose morning peak expiratory flow[ΔAM PEF] averaged over weeks 1-12; participants aged 5-11 years) regulatory requirements.

Results: Overall, 902 participants, including 673 children aged 5 to 11 years, were randomized and treated. In participants aged 5 to 17, week 12 weighted mean FEV_1(0-4 hours) was greater with FF/VI vs FF (difference: 0.083 L; $P < .001$). In participants aged 5 to 11, ΔAM PEF over weeks 1 to 12 showed numerical improvement with FF/VI vs FF but was not statistically significant (difference: 3.2 L/min; $P = .228$). No drug-related serious adverse events or deaths were reported.

Conclusion: FF/VI significantly improved weighted mean FEV_1 (0-4 hours; participants aged 5-17 years), but not ΔAM PEF (participants aged 5-11 years) vs FF. No new safety concerns were apparent.

As-Needed Albuterol–Budesonide in Mild Asthma

Craig LaForce, M.D., Frank Albers, M.D., PhD, Anna Danilewicz, B.Sc., et al

As-needed use of albuterol–budesonide has been shown to result in a significantly lower risk of severe asthma exacerbation than as-needed use of albuterol alone among patients with moderate-to-severe asthma. Data on albuterol–budesonide in mild asthma are needed.

We conducted a fully virtual, decentralized, phase 3b, multicenter, double-blind, event-driven trial involving persons 12 years of age or older with disease that was uncontrolled despite treatment for mild asthma with a short-acting β_2-agonist (SABA) with or without a low-dose inhaled glucocorticoid or leukotriene-receptor antagonist. Participants were randomly assigned in a 1:1 ratio to a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide (with each dose consisting of two inhaler actuations of 90 µg and 80 µg, respectively) or 180 µg of albuterol (with each dose consisting of two inhaler actuations of 90 µg) on an as-needed basis for up to 52 weeks. The primary end point was the first severe asthma exacerbation, assessed in a time-to-event analysis, in the on-treatment efficacy population, and the key secondary end point was the first severe exacerbation in the intention-to-treat population. Secondary end points included the annualized rate of severe asthma exacerbations and exposure to systemic glucocorticoids.

A total of 2516 participants underwent randomization; 1797 (71.4%) completed the trial. Of 2421 participants in the full analysis population (1209 assigned to the albuterol–budesonide group and 1212 to the albuterol group), 97.2% were 18 years of age or older; 74.4% used a SABA alone at baseline. The trial was stopped for efficacy at a prespecified interim analysis. A severe exacerbation occurred in 5.1% of the participants in the albuterol–budesonide group and in 9.1% of those in the albuterol group in the on-treatment efficacy population (hazard ratio, 0.53; 95% confidence interval [CI], 0.39 to 0.73) and in 5.3% and 9.4%, respectively, in the intention-to-treat population (hazard ratio, 0.54; 95% CI, 0.40 to 0.73) (P<0.001 for both comparisons). The annualized rate of severe asthma exacerbations was lower with albuterol–budesonide than with albuterol (0.15 vs. 0.32; rate

ratio, 0.47; 95% CI, 0.34 to 0.64), as was the mean annualized total dose of systemic glucocorticoids (23.2 vs. 61.9 mg per year). Adverse events were similar in the two treatment groups.

As-needed use of albuterol–budesonide resulted in a lower risk of a severe asthma exacerbation than as-needed use of albuterol alone among participants with disease that was uncontrolled despite treatment for mild asthma.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 23, 2026

Search Strategy:

#	Searches	Results
1	Tiotropium Bromide/ or tiotropium.mp.	2117
2	umeclidinium.mp.	452
3	aclidinium.mp.	269
4	budesonide.mp. or Budesonide/	8039
5	Glycopyrrolate/ or glycopyrrolate.mp.	1914
6	olodaterol.mp.	284
7	vilanterol.mp.	660
8	Formoterol Fumarate/ or formoterol.mp.	3334
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	13951
10	limit 9 to (english language and humans and yr="2024 -Current")	626
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	76

Database(s): **Ovid MEDLINE(R) ALL** 1946 to March 03, 2026

Search Strategy:

#	Searches	Results
1	ipratropium.mp. or Ipratropium/	2776
2	revefenacin.mp.	53

3	mometasone.mp.	1559
4	Albuterol/ or albuterol.mp.	11569
5	Salmeterol Xinafoate/ or salmeterol.mp.	3290
6	vilanterol.mp.	659
7	aformoterol.mp.	1
8	olodaterol.mp.	284
9	levalbuterol.mp. or Levalbuterol/	176
10	fluticasone.mp. or Fluticasone/	5536
11	beclomethasone dipropionate.mp. or Beclomethasone/	3615
12	budesonide.mp. or Budesonide/	8043
13	ciclesonide.mp.	511
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	29345
15	limit 14 to (english language and humans and yr="2023 -Current")	1281
16	limit 15 to yr="2023 -Current"	1281
17	limit 16 to (clinical trial, phase iii or guideline or meta-analysis or practice guideline or "systematic review")	131

Appendix 5: Key Inclusion Criteria

Population	Patients with asthma or COPD
Intervention	Inhalers used to treat asthma and/or COPD (e.g., ICS, LABA, LAMA, SABA, muscarinic agonists, ICS/LABA, ICS/LABA/LAMA, LABA/LAMA)
Comparator	Placebo or active treatment
Outcomes	Change in exacerbations, lung function, hospitalizations, mortality
Setting	Outpatient

Long-acting Beta-agonists (LABA)

Goals:
- To optimize the safe and effective use of LABA therapy in patients with asthma and chronic obstructive pulmonary disease (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. Has the patient tried and failed, have contraindications or documented inability to use the preferred products?	**Yes:** Go to #3	**No:** Deny; Medical appropriateness. Inform prescriber of preferred LABA therapies.
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.

Approval Criteria		
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: *6/26 (KS), 2/24 (DM); 10/23 (SF); 10/22 (KS), 10/20, 5/19; 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 chronic obstructive pulmonary disease (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

Approval Criteria		
2. Has the patient tried and failed, have contraindications or documented inability to use the preferred products?	**Yes:** Go to #3	**No:** Deny; Medical appropriateness. Inform prescriber of preferred product in class.
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Go to #8	**No:** Go to #4
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.
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: *6/26 (KS),2/24 (DM); 10/23(SF); 10/22(KS), 10/21; 12/20, 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*

Inhaled Corticosteroids (ICS)

Goals:
- To optimize the safe and effective use of ICS therapy in patients with asthma and chronic obstructive pulmonary disease (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. Has the patient tried and failed, have contraindications or documented inability to use the preferred products?	**Yes:** Go to #3	**No:** Deny; Medical appropriateness. Inform prescriber of preferred alternatives in class.

Approval Criteria		
3. Is the request for treatment of asthma or reactive airway disease?	**Yes:** Go to #6	**No:** Go to #4
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.
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: *6/26 (KS), 2/24 (DM); 10/23 (SF); 10/22(KS), 10/20, 5/19, 1/18; 9/16; 9/15*
Implementation: *3/1/18; 10/13/16; 10/9/15*

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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
carfilzomib	KITPROZY
dasatinib anhydrous	PHYRAGO
mitomycin	ZUSDURI
relacorilant	LIFYORLI
selumetinib	KOSELUGO

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.
- Incorporate 2-step review process for drugs on the high-cost drug carve-out list.

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Populations:

- Elzonris (tatagraxofusp-erzs): FFS and CCO populations beginning 1/1/26
- All others: FFS only

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: National Comprehensive Cancer Network (NCCN) Categories for Recommendations

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
For the 'Uniformed NCCN consensus' defined in Category 1 and 2A, a majority Panel vote of at least 85% is required. For the 'NCCN consensus' defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Strong Panel disagreement regardless of the quality of evidence is a vote of at least 25%.	

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 (if specified) or 12 months, (if duration is unspecified).	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy (if specified) or 12 months (if duration is unspecified).	**No**: Go to #4

4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No: If not eligible for EPSDT review:** Pass to RPh. Deny; not funded by the OHP **If eligible for EPSDT review:** 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.
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**: Go to #8	**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:** Go to #8	**No:** Go to #9
8. Are there equally or higher recommended alternative agents based on NCCN categories of evidence (Table 1) for the requested indication and place in therapy? Note: When efficacy is similar, the choice of agent should be determined by safety, and then cost. In the absence of a safety concern, the prescriber is expected to use the least costly alternative.	**Yes:** HCDCO list: Pass to RPh. Pend; Refer to DMAP for secondary review. All other requests: Approve for length of therapy (if specified) or 12 months (if duration is unspecified).	**No:** HCDCO list: Pass to RPh. Pend; Refer to DMAP for secondary review. All other requests: Approve for length of therapy (if specified) or 12 months (if duration is unspecified).
9. Is there documentation based on chart notes that the patient is enrolled in a	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10

clinical trial to evaluate efficacy or safety of the requested drug?	Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	
10. 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 #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. 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 5/4/2026)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting.
Biosimilars for drugs on this list are included in the policy but may not be specifically listed.

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
afamitresgene autoleucel	TECELRA
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVANT
amivantamab/ hyaluronidase-lpuj	RYBREVANT FASPRO
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
avutometinib and defactinib	AVMAPKI FAKZYNJA CO-PACK
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, KITPROZY
cemiplimab-rwlc	LIBTAYO

Generic Name	Brand Name
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
cosibelimab-ipdl	UNLOXCYT
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
dasatinib anhydrous	PHYRAGO
datopotamab deruxtecan-dlnk	DATROWAY
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
denileukin diftitox-cxdl	LYMPHIR
dordaviprone	MODEYSO
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
ensartinib	ENSACOVE
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

Generic Name	Brand Name
idelalisib	ZYDELIG
imetelstat	RYTELO
Imlunestrant tosylate	INLURIYO
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lazertinib	LAZCLUZE
lenvatinib mesylate	LENVIMA
lifileucel	AMTAGVI
linvoseltamab-gcpt	LYNOZYFIC
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
mitomycin	ZUSDURI
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 and hyaluronidase-nvhy	OPDIVO QVANTIG
nivolumab; relatlimab-rmbw	OPDUALAG
nogapendekin alfa inbakicept-pmln	ANKTIVA
obecabtagene autoleucel	AUCATZYL
obinutuzumab	GAZYVA
ofatumumab	ARZERRA

Generic Name	Brand Name
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
pembrolizumab;berahyaluronidase alfa-pmph	KEYTRUDA QLEX
pemigatinib	PEMAZYRE
penpulimab-kcqx	none
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
relacorilant	LIFYORLI
relugolix	ORGOVYX
repotrectinib	AUGTYRO
retifanlimab-dlwr	ZYNYZ
revumenib	REVUFORJ
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
selumetinib	KOSELUGO
sevabertinib	HYRNUO

Generic Name	Brand Name
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
sunvozertinib	ZEGFROVY
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
taletrectinib	IBTROZI
talimogene laherparepvec	IMLYGIC
talquetamab-tgvs	TALVEY
tarlatamab-dlle	IMDELLTRA
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
telisotuzumab vedotin-tllv	EMRELIS
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tislelizumab-jsgr	TEVIMBRA
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
toripalimab-tpzi	LOQTORZI
tovorafenib	OJEMDA
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
trastuzumab-strf	HERCESSI
tremlimumab	IMJUDO
treosulfan	GRAFAPEX
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vimseltinib	ROMVIMZA
vismodegib	ERIVEDGE
vorasidenib	VORANIGO
zanidatamab-hrii	ZIIHERA
zanubrutinib	BRUKINSA
zenocutuzumab-Zbco	BIZENGRI
ziftomenib	KOMZIFTI
ziv-aflibercept	ZALTRAP
zongertinib	HERNEXEOS

P&T/DUR Review: 6/2020 (JP)
Implementation: 10/1/20

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. Updated orphan drugs

Generic	Brand	High Cost Drug Carve-out
doxecitine and doxribtimine	KYGEVVI	Yes (5/1/26)
linerixibat	LYNAVOY	No
lunsotogene parvec	OTARMENI	No
marnetegragene autotemcel	KRESLADI	Yes (5/1/26)
tividenofusp alfa	AVLAYAH	Yes (5/1/26)

Recommendation:

- Modify PA criteria to include new orphan drugs and carve-out status.
- Update renewal criteria to accommodate longer approvals for chronic therapy.

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 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/

Table 1. Included orphan drugs

Drug	Covered Population
ADAMTS13, recombinant-krhn (ADZYNMA)	FFS
Aficamten (MYQORZO)	FFS
Allogeneic processed thymus tissue-agdc (RETHYMIC)	FFS and CCO populations beginning 1/1/26
Alpelisib (VIJOICE)	FFS
Asfotase alfa (STRENSIQ)	FFS and CCO populations beginning 1/1/26
Atidarsagene autotemcel (LENMELDY)	FFS and CCO populations beginning 1/1/26
Avacopan (TAVNEOS)	FFS
Axatilimab-csfr (NIKTIMVO)	FFS
Belumosudil (REZUROCK)	FFS
Burosumab-twza (CRYSVITA)	FFS
Cerliponase alfa (BRINEURA)	FFS
Chenodiol (CTEXLI)	FFS and CCO populations beginning 1/1/26
Crinecefont (CRENESSITY)	FFS
Crovalimab-akkz (PIASKY)	FFS
Danicopan (VOYDEYA)	FFS
doxecitine and doxribtimine (KYGEVVI)	FFS and CCO populations beginning 5/1/26
Eculizumab (SOLIRIS)	FFS
Eculizumab-aagh (EPYSQLI)	FFS
Eculizumab-aeeb (BKEMV)	FFS

Eladocagene exuparvovec-tneq (KEBILDI)	FFS and CCO populations beginning 1/1/26
Elafibranor (IQIRVO)	FFS
Elapegademase-lvlr (REVCOVI)	FFS and CCO populations beginning 1/1/26
Elivaldogene autotemcel (SKYSONA)	FFS and CCO populations beginning 1/1/26
Elosulfase alfa (VIMIZIM)	FFS and CCO populations beginning 1/1/26
Fosdenopterin (NULIBRY)	FFS
Galsulfase (NAGLAZYME)	FFS and CCO populations beginning 1/1/26
Givosiran (GIVLAARI)	FFS
Idursulfase (ELAPRASE)	FFS and CCO populations beginning 1/1/26
Inebilizumab-cdon (UPLIZNA)	FFS
Iptacopan (FABHALTA)	FFS
Leniolisib (JOENJA)	FFS and CCO populations beginning 5/1/26
Levoketoconazole (RECORLEV)	FFS
linerixibat (LYNAVOY)	FFS
Lonafarnib (ZOKINVY)	FFS and CCO populations beginning 1/1/26
Lumasiran (OXLUMO)	FFS and CCO populations beginning 1/1/26
lunsotogene parvec (OTARMENI)	FFS
Luspatercept (REBLOZYL)	FFS
Maralixibat (LIVMARLI)	FFS and CCO populations beginning 1/1/26
marnetegragene autotemcel (KRESLADI)	FFS and CCO populations beginning 5/1/26
Mavacamten (CAMZYOS)	FFS
Mavorixafor (XOLREMDI)	FFS
Mirdametinib (GOMEKLI)	FFS
Mitapivat (PYRUKYND)	FFS
Nedosiran (RIVFLOZA)	FFS
Nerandomilast (JASCAYD)	FFS
Nipocalimab-aahu (IMAAVY)	FFS
Odevixibat (BYLVAY)	FFS and CCO populations beginning 1/1/26
Olipudase alfa-rpcp (XENPOZYME)	FFS and CCO populations beginning 1/1/26
Palopegteriparatide (YORVIPATH)	FFS
Paltusotine (PALSONIFY)	FFS
Pegcetacoplan (EMPAVELI)	FFS
Plasminogen, human-tvmh (RYPLAZIM)	FFS
Pozelimab-bbfg (VEOPOZ)	FFS and CCO populations beginning 1/1/26
Ravulizumab-cwvz (ULTOMIRIS)	FFS
Remestemcel-L-rknd (RYONCIL)	FFS
Rezafungin (REZZAYO)	FFS
Rozanolixizumab-noli (RYSTIGGO)	FFS

Satralizumab-mwge (ENSPRYNG)	FFS
Seladelpar (LIVDELZI)	FFS
Sodium thiosulfate (PEDMARK)	FFS
Sutimlimab-jome (ENJAYMO)	FFS
tividenofusp alfa (AVLAYAH)	FFS and CCO populations beginning 5/1/26
Tofersen (QALSODY)	FFS
Trientine tetrahydrochloride (CUVRIOR)	FFS
Velmanase alfa-tycv (LAMZEDE)	FFS and CCO populations beginning 1/1/26
Vestronidase alfa-vjbk (MEPSEVII)	FFS and CCO populations beginning 1/1/26
Zilucoplan (ZILBRYSQ)	FFS

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3
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 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.

Approval Criteria		
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.
8. Have other therapies been tried and failed? Note: drugs carved-out of CCOs require secondary review by DMAP before approval.	**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

Renewal Criteria		
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? Note: drugs carved-out of CCOs require secondary review by DMAP before approval.	**Yes:** 1st renewal: Approve for up to 6 months. Subsequent renewals: Approve up to 12 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)? Note: drugs carved-out of CCOs require secondary review by DMAP before approval.	**Yes**: 1st renewal: Approve for up to 6 months. Subsequent renewals: Approve up to 12 months. Document benefit and provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/26; 8/25; 6/25; 4/25; 2/25; 12/24; 10/24; 8/24; 4/24; 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: 3/1/26; 9/15/25; 5/12/25; 3/10/25; 1/1/25; 9/1/24; 5/1/24; 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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Policy Update: Healthier Oregon Program

Program Updates and Changes:

Healthier Oregon is a program that offers free health coverage through the Oregon Health Plan (OHP) for people of any immigration status who live in Oregon and meet income and other eligibility requirements for OHP. Unlike traditional Medicaid, non-emergency services (including most drug coverage) for members enrolled through Healthier Oregon are funded by the state and are not eligible for federal matching funds or Medicaid drug rebates.

In April 2026, about 99,400 members in Healthier Oregon were enrolled in coordinated care organizations (CCOs). However, beginning in January 2027, these members will move to OHP Open Card (also called the fee-for-service program). This will double the current OHP Open Card population which enrolls about 98,700 members through the Medicaid program.

As a result of these changes and because of the differences in funding between the Healthier Oregon and Medicaid populations, the Pharmacy and Therapeutics (P&T) Committee will need to re-evaluate choice of products on the preferred drug list (PDL). The P&T Committee is charged with evaluating comparative efficacy and safety of prescription drugs to inform PDL decisions. In the absence of differences in efficacy or safety, the P&T committee evaluates comparative drug costs. With such a large proportion of members enrolled through Healthier Oregon who are not eligible for Medicaid rebates, the most cost effective products for the state may be those with the lowest upfront costs.

PDL classes for which the P&T Committee has recently reviewed evidence of efficacy and safety will be brought back to the P&T committee as old business to evaluate utilization for Healthier Oregon members and pricing. The following classes have been recently reviewed by the Pharmacy and Therapeutics Committee. Included drugs, PDL status, and prior authorization criteria are referenced in the previous P&T documents.

PDL Class	Last P&T Review Date
Antifungals, Topical	December 2025
Antidiarrheals	February 2025
Antacids, Proton Pump Inhibitors	October 2024
Nasal Allergy Inhalers	February 2026
Ophthalmic Medications for Allergies	February 2026
Laxatives for Chronic Constipation	February 2025

Recommendation:

- Evaluate comparative costs in executive session.

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: October 2024 - September 2025

Eligibility	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
Total Members (FFS & Encounter)	1,247,678	1,254,503	1,257,986	1,241,274	1,243,854	1,234,473	1,242,572	1,246,331	1,249,863	1,242,513	1,233,644	1,231,323	1,243,835
FFS Members	99,056	99,856	98,868	99,039	93,047	91,577	91,602	90,100	89,262	90,257	88,300	87,978	93,245
OHP Basic with Medicare	8,222	7,915	7,437	7,659	7,451	7,022	6,746	6,382	6,097	6,372	6,183	6,002	6,957
OHP Basic without Medicare	9,278	9,034	8,899	8,472	8,170	8,072	8,028	8,016	7,876	7,937	7,856	7,841	8,290
ACA	81,556	82,907	82,532	82,908	77,426	76,483	76,828	75,702	75,289	75,948	74,261	74,135	77,998
Encounter Members	1,148,622	1,154,647	1,159,118	1,142,235	1,150,807	1,142,896	1,150,970	1,156,231	1,160,601	1,152,256	1,145,344	1,143,345	1,150,589
OHP Basic with Medicare	103,103	98,130	90,342	82,625	80,472	75,440	76,700	77,380	77,913	77,511	77,694	77,785	82,925
OHP Basic without Medicare	66,469	66,271	65,605	64,002	63,793	62,866	62,847	62,790	62,724	62,691	62,765	62,703	63,794
ACA	979,050	990,246	1,003,171	995,608	1,006,542	1,004,590	1,011,423	1,016,061	1,019,964	1,012,054	1,004,885	1,002,857	1,003,871

Gross Cost Figures for Drugs	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	YTD Sum
Total Amount Paid (FFS & Encounter)	$141,769,154	$127,028,705	$139,522,968	$147,069,205	$133,458,549	$149,173,460	$151,547,617	$148,165,761	$148,455,155	$154,639,364	$145,102,232	$151,383,475	$1,737,315,645
Mental Health Carve-Out Drugs	$13,455,745	$11,702,277	$14,415,823	$14,619,079	$13,503,540	$14,845,426	$15,636,427	$15,273,342	$15,644,776	$15,970,250	$16,005,096	$16,149,979	$177,221,759
OHP Basic with Medicare	$10,098	$9,432	$1,264	$6,525	$5,748	$2,268	$5,567	$8,358	$10,675	$8,753	$10,307	$9,941	$88,936
OHP Basic without Medicare	$4,500,352	$3,944,281	$4,745,104	$4,549,707	$4,595,534	$5,042,973	$4,923,294	$4,720,030	$4,594,550	$4,688,172	$4,901,068	$4,663,165	$55,868,228
ACA	$7,633,987	$6,801,867	$8,420,881	$8,560,562	$7,554,853	$8,510,744	$9,056,320	$8,754,890	$8,794,514	$9,092,422	$8,994,010	$9,228,700	$101,403,751
FFS Physical Health Drugs	$2,160,681	$1,777,406	$2,155,894	$2,388,406	$2,251,048	$2,215,126	$2,259,784	$2,258,310	$2,124,672	$2,178,576	$1,975,332	$1,956,453	$25,701,688
OHP Basic with Medicare	$30,120	$27,308	$28,640	$29,730	$28,798	$27,238	$26,075	$24,680	$23,216	$24,981	$23,738	$22,336	$316,859
OHP Basic without Medicare	$660,620	$540,646	$641,289	$678,897	$705,078	$664,971	$718,207	$654,319	$596,726	$608,494	$476,549	$507,274	$7,453,070
ACA	$1,327,872	$1,066,047	$1,282,663	$1,372,569	$1,218,184	$1,281,340	$1,245,308	$1,306,048	$1,193,995	$1,240,745	$1,139,089	$1,160,733	$14,834,593
FFS Physician Administered Drugs	$1,371,126	$1,616,427	$1,256,300	$1,817,399	$1,688,126	$1,542,654	$1,750,105	$1,144,954	$962,197	$1,752,669	$1,285,578	$1,274,873	$17,462,406
OHP Basic with Medicare	$132,502	$84,411	$123,545	$143,936	$85,996	$121,094	$113,354	$60,542	$73,183	$119,966	$99,057	$97,356	$1,254,944
OHP Basic without Medicare	$314,379	$432,207	$191,592	$236,232	$104,317	$346,878	$293,345	$167,275	$106,091	$188,091	$151,283	$72,150	$2,603,840
ACA	$511,128	$621,056	$537,583	$766,120	$592,780	$436,177	$626,748	$348,726	$337,108	$516,344	$621,512	$455,902	$6,371,183
Encounter Physical Health Drugs	$93,154,944	$84,759,384	$90,905,287	$93,008,839	$86,203,368	$95,478,746	$97,736,510	$96,169,753	$93,541,990	$98,110,731	$93,990,343	$98,784,557	$1,121,844,453
OHP Basic with Medicare	$429,773	$352,804	$334,681	$368,077	$337,593	$355,263	$382,574	$373,285	$346,645	$350,686	$361,317	$330,780	$4,323,480
OHP Basic without Medicare	$19,633,981	$17,567,030	$18,915,101	$19,324,380	$17,084,750	$18,639,235	$19,002,030	$18,041,542	$17,690,217	$18,190,675	$18,166,141	$18,740,873	$220,995,954
ACA	$61,318,437	$56,101,557	$60,507,183	$60,647,350	$56,578,259	$62,622,194	$64,424,806	$63,625,867	$61,206,614	$64,863,930	$61,279,265	$64,540,153	$737,715,617
Encounter Physician Administered Drugs	$31,626,658	$27,173,210	$30,789,665	$35,235,483	$29,812,467	$35,091,507	$34,164,791	$33,319,402	$36,181,521	$36,627,139	$31,845,883	$33,217,613	$395,085,340
OHP Basic with Medicare	$1,133,635	$802,160	$801,687	$1,178,608	$875,046	$797,451	$894,201	$826,563	$780,194	$828,021	$679,082	$756,821	$10,353,469
OHP Basic without Medicare	$6,384,872	$5,327,648	$5,780,536	$5,738,280	$5,968,709	$9,498,713	$6,084,282	$6,181,766	$5,977,686	$6,521,627	$5,634,800	$6,332,889	$75,431,808
ACA	$20,031,484	$17,806,304	$19,845,362	$23,672,579	$18,102,738	$19,752,875	$21,265,940	$20,506,903	$23,755,911	$22,410,686	$19,996,734	$20,352,584	$247,500,101

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: April 24, 2026

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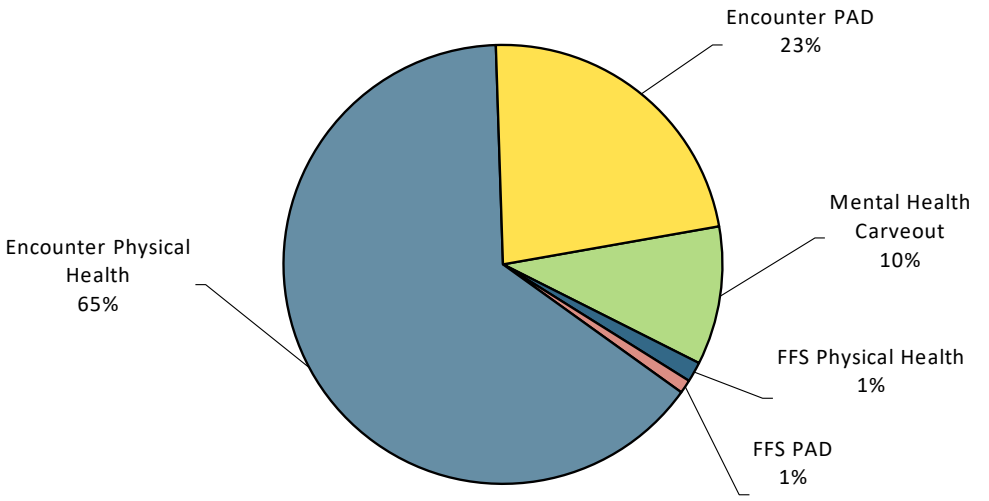
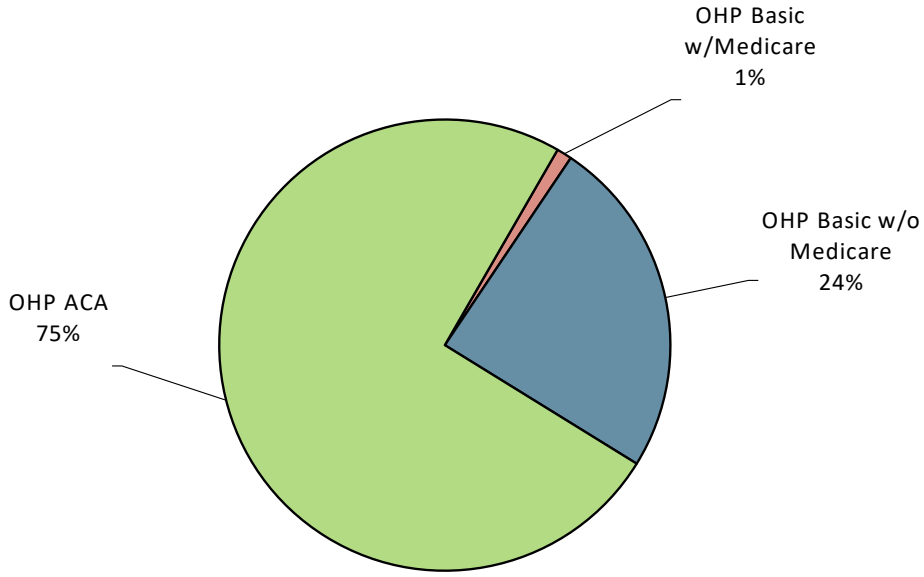
Pharmacy Utilization Summary Report: October 2024 - September 2025

YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee.
If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

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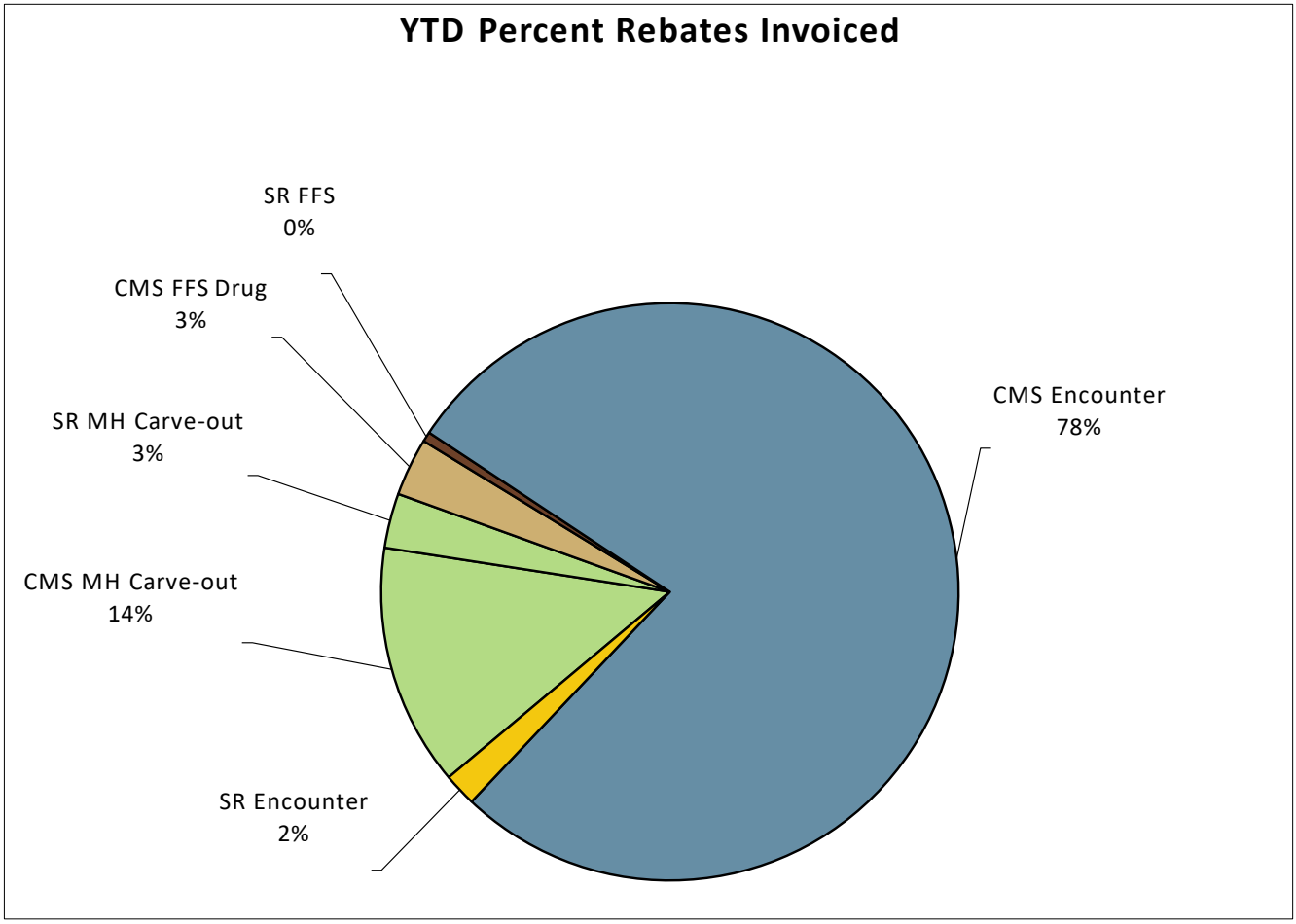
Pharmacy Utilization Summary Report: October 2024 - September 2025

Quarterly Rebates Invoiced	2024-Q4	2025-Q1	2025-Q2	2025-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$119,353,767	$63,503,670	$138,781,198	$121,855,581	$443,494,215
CMS MH Carve-out	$13,561,282	$15,437,788	$15,508,845	$15,634,284	$60,142,199
SR MH Carve-out	$3,353,582	$3,054,466	$3,496,840	$3,652,698	$13,557,587
CMS FFS Drug	$3,278,483	$4,222,380	$3,755,428	$3,134,987	$14,391,279
SR FFS	$481,787	$651,850	$737,025	$569,654	$2,440,316
CMS Encounter	$95,621,692	$38,602,257	$113,423,769	$97,144,925	$344,792,643
SR Encounter	$3,056,941	$1,534,929	$1,859,289	$1,719,033	$8,170,192

Quaterly Net Drug Costs	2024-Q4	2025-Q1	2025-Q2	2025-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$288,967,061	$366,197,544	$309,387,335	$329,269,490	$1,293,821,430
Mental Health Carve-Out Drugs	$22,658,980	$24,475,792	$27,548,859	$28,838,342	$103,521,973
FFS Phys Health + PAD	$6,577,564	$7,028,528	$6,007,566	$6,718,840	$26,332,499
Encounter Phys Health + PAD	$259,730,517	$334,693,224	$275,830,910	$293,712,307	$1,163,966,958



SR = Supplemental Rebate
CMS = Center for Medicaid Services
PAD = Physician-administered drugs
MH = Mental Health

Last Updated: April 24, 2026

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: October 2024 - September 2025

Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$113.63	$101.26	$110.91	$118.48	$107.29	$120.84	$121.96	$118.88	$118.78	$124.46	$117.62	$122.94	$116.42
Mental Health Carve-Out Drugs	$10.78	$9.33	$11.46	$11.78	$10.86	$12.03	$12.58	$12.25	$12.52	$12.85	$12.97	$13.12	$11.88
FFS Physical Health Drugs	$21.81	$17.80	$21.81	$24.12	$24.19	$24.19	$24.67	$25.06	$23.80	$24.14	$22.37	$22.24	$23.02
FFS Physician Administered Drugs	$13.84	$16.19	$12.71	$18.35	$18.14	$16.85	$19.11	$12.71	$10.78	$19.42	$14.56	$14.49	$15.59
Encounter Physical Health Drugs	$81.10	$73.41	$78.43	$81.43	$74.91	$83.54	$84.92	$83.18	$80.60	$85.15	$82.06	$86.40	$81.26
Encounter Physician Administered Drugs	$27.53	$23.53	$26.56	$30.85	$25.91	$30.70	$29.68	$28.82	$31.17	$31.79	$27.80	$29.05	$28.62

Claim Counts	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
Total Claim Count (FFS & Encounter)	1,341,258	1,235,127	1,320,422	1,372,984	1,245,826	1,358,392	1,384,468	1,370,079	1,325,158	1,357,432	1,297,286	1,330,225	1,328,221
Mental Health Carve-Out Drugs	222,240	204,478	221,204	229,233	209,570	228,400	230,361	227,804	224,446	232,525	224,310	227,462	223,503
FFS Physical Health Drugs	26,882	24,300	26,406	29,485	26,290	27,633	27,281	25,874	24,617	25,464	23,975	24,029	26,020
FFS Physician Administered Drugs	8,464	7,352	7,894	10,126	8,980	9,085	9,131	8,824	8,456	9,218	8,679	9,403	8,801
Encounter Physical Health Drugs	941,600	866,199	926,618	955,275	863,266	947,028	963,849	951,667	916,656	938,301	893,367	920,976	923,734
Encounter Physician Administered Drugs	142,072	132,798	138,300	148,865	137,720	146,246	153,846	155,910	150,983	151,924	146,955	148,355	146,165

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$105.70	$102.85	$105.67	$107.12	$107.12	$109.82	$109.46	$108.14	$112.03	$113.92	$111.85	$113.80	$108.96
Mental Health Carve-Out Drugs	$60.55	$57.23	$65.17	$63.77	$64.43	$65.00	$67.88	$67.05	$69.70	$68.68	$71.35	$71.00	$65.98
FFS Physical Health Drugs	$80.38	$73.14	$81.64	$81.00	$85.62	$80.16	$82.83	$87.28	$86.31	$85.56	$82.39	$81.42	$82.31
FFS Physician Administered Drugs	$162.00	$219.86	$159.15	$179.48	$187.99	$169.80	$191.67	$129.75	$113.79	$190.14	$148.13	$135.58	$165.61
Encounter Physical Health Drugs	$98.93	$97.85	$98.10	$97.36	$99.86	$100.82	$101.40	$101.05	$102.05	$104.56	$105.21	$107.26	$101.21
Encounter Physician Administered Drugs	$222.61	$204.62	$222.63	$236.69	$216.47	$239.95	$222.07	$213.71	$239.64	$241.09	$216.70	$223.91	$225.01

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.56	$22.11	$22.30	$22.21	$22.29	$22.65	$22.89	$22.70	$23.12	$23.60	$24.22	$24.37	$22.92
Mental Health Carve-Out Drugs	$14.34	$14.19	$15.29	$15.76	$16.27	$15.73	$16.79	$15.54	$15.61	$15.65	$15.50	$15.38	$15.51
FFS Physical Health Drugs	$21.60	$21.63	$20.80	$22.43	$22.70	$23.23	$22.46	$23.82	$24.08	$25.17	$26.61	$24.58	$23.26
Encounter Physical Health Drugs	$24.71	$24.16	$24.15	$23.87	$23.85	$24.43	$24.46	$24.51	$25.07	$25.67	$26.51	$26.77	$24.85

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$725.91	$751.79	$816.42	$829.26	$868.23	$869.26	$874.25	$882.67	$882.08	$892.86	$893.29	$820.87	$842.24
Mental Health Carve-Out Drugs	$1,689.62	$1,594.32	$1,780.08	$1,733.06	$1,722.19	$1,725.93	$1,771.91	$1,750.69	$1,802.28	$1,743.95	$1,779.45	$1,737.20	$1,735.89
FFS Physical Health Drugs	$437.53	$401.30	$479.57	$476.58	$506.38	$473.23	$496.27	$507.61	$504.90	$487.65	$456.33	$454.20	$473.46
Encounter Physical Health Drugs	$680.75	$713.60	$764.10	$781.24	$821.83	$822.36	$823.55	$831.73	$824.83	$840.82	$836.45	$765.40	$792.22

Generic Drug Use Percentage	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
Generic Drug Use Percentage	90.2%	90.7%	91.3%	91.5%	91.7%	91.6%	91.6%	91.7%	91.6%	91.5%	91.5%	90.5%	91.3%
Mental Health Carve-Out Drugs	97.2%	97.3%	97.2%	97.2%	97.2%	97.1%	97.1%	97.0%	97.0%	96.9%	96.8%	96.8%	97.1%
FFS Physical Health Drugs	85.9%	86.4%	86.7%	87.1%	87.0%	87.3%	87.3%	86.9%	87.1%	86.9%	87.0%	86.8%	86.9%
Encounter Physical Health Drugs	88.7%	89.3%	90.0%	90.3%	90.5%	90.4%	90.4%	90.5%	90.4%	90.3%	90.3%	89.1%	90.0%

Preferred Drug Use Percentage	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Avg Monthly
Preferred Drug Use Percentage	88.47%	88.41%	88.34%	88.44%	88.42%	88.46%	88.49%	88.48%	88.51%	89.28%	89.34%	89.35%	88.7%
Mental Health Carve-Out Drugs	86.48%	86.52%	86.35%	86.28%	86.35%	86.27%	86.30%	86.29%	86.37%	86.24%	86.23%	86.20%	86.3%
FFS Physical Health Drugs	94.49%	94.67%	94.57%	94.41%	93.68%	94.21%	94.38%	93.95%	94.09%	94.85%	95.05%	95.01%	94.4%
Encounter Physical Health Drugs	88.81%	88.72%	88.67%	88.81%	88.80%	88.86%	88.88%	88.89%	88.92%	89.93%	90.02%	90.03%	89.1%

Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: April 24, 2026

Drug Use Research & Management Program
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Top 40 Mental Health Carve-out Drugs by Gross Amount Paid (FFS Only) - First Quarter 2026

Rank	PDL Class	Drug	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Antipsychotics, 2nd Gen	VRAYLAR *	$7,729,010	16.6%	5,142	$1,503	Y
2	Antipsychotics, Parenteral	INVEGA SUSTENNA	$5,997,325	12.9%	2,142	$2,800	Y
3	Antipsychotics, 2nd Gen	REXULTI *	$3,678,814	7.9%	2,575	$1,429	V
4	Antipsychotics, Parenteral	ABILIFY MAINTENA	$3,068,163	6.6%	1,217	$2,521	Y
5	Antipsychotics, 2nd Gen	CAPLYTA *	$2,731,947	5.9%	1,718	$1,590	V
6	Antidepressants	SPRAVATO *	$2,487,878	5.3%	1,665	$1,494	V
7	Antipsychotics, Parenteral	INVEGA TRINZA	$1,594,281	3.4%	190	$8,391	Y
8	Antidepressants	AUVELITY	$1,422,333	3.1%	1,372	$1,037	V
9	Antidepressants	TRINTELLIX	$1,244,251	2.7%	2,513	$495	V
10	Antipsychotics, Parenteral	ARISTADA	$1,216,833	2.6%	471	$2,584	Y
11	Antipsychotics, 2nd Gen	LYBALVI *	$957,616	2.1%	613	$1,562	V
12	Antipsychotics, Parenteral	ABILIFY ASIMTUFII	$868,807	1.9%	161	$5,396	Y
13	Antidepressants	BUPROPION XL	$826,520	1.8%	58,546	$14	Y
14	ADHD Drugs	QELBREE *	$797,355	1.7%	1,572	$507	Y
15	Antidepressants	SERTRALINE HCL	$724,249	1.6%	60,055	$12	Y
16	Antidepressants	TRAZODONE HCL	$720,983	1.5%	56,340	$13	V
17	Antidepressants	FLUOXETINE HCL	$640,282	1.4%	47,368	$14	Y
18	Antidepressants	DULOXETINE HCL	$618,840	1.3%	37,153	$17	Y
19	Antidepressants	ESCITALOPRAM OXALATE	$616,331	1.3%	47,217	$13	Y
20	Antipsychotics, Parenteral	INVEGA HAFYERA	$454,427	1.0%	24	$18,934	Y
21	Antiepileptics, Outpatient	LAMOTRIGINE	$450,796	1.0%	33,773	$13	Y
22	Antidepressants	BUSPIRONE HCL	$446,547	1.0%	32,977	$14	
23	Antipsychotics, 2nd Gen	ARIPIPRAZOLE *	$327,338	0.7%	23,070	$14	Y
24	Antipsychotics, 2nd Gen	QUETIAPINE FUMARATE *	$295,069	0.6%	22,071	$13	Y
25	Antipsychotics, Parenteral	UZEDY	$261,481	0.6%	96	$2,724	Y
26	ADHD Drugs	ATOMOXETINE HCL *	$254,329	0.5%	10,889	$23	Y
27	Antidepressants	VENLAFAXINE HCL ER	$239,051	0.5%	16,675	$14	Y
28	Antidepressants	SERTRALINE HCL	$237,163	0.5%	1,580	$150	V
29	Antipsychotics, 2nd Gen	COBENFY *	$234,928	0.5%	145	$1,620	V
30	Antidepressants	MIRTAZAPINE	$223,814	0.5%	14,835	$15	Y
31	ADHD Drugs	GUANFACINE HCL ER	$222,283	0.5%	15,016	$15	Y
32	Antipsychotics, 2nd Gen	OLANZAPINE *	$200,790	0.4%	14,357	$14	Y
33	Antiepileptics, Outpatient	LAMOTRIGINE ER	$188,864	0.4%	5,317	$36	V
34	Antidepressants	CITALOPRAM HBR	$176,998	0.4%	14,138	$13	Y
35	Antipsychotics, Parenteral	RISPERDAL CONSTA *	$165,503	0.4%	140	$1,182	Y
36	Antidepressants	AMITRIPTYLINE HCL *	$160,246	0.3%	12,462	$13	Y
37	Antidepressants	DESVENLAFAXINE SUCCINATE ER	$155,296	0.3%	7,205	$22	Y
38	Antidepressants	BUPROPION XL	$136,350	0.3%	853	$160	V
39	Antipsychotics, 2nd Gen	RISPERIDONE *	$133,495	0.3%	9,664	$14	Y
40	Antidepressants	BUPROPION HCL SR	$127,530	0.3%	9,045	$14	Y
		Top 40 Aggregate:	**$43,034,117**		**572,362**	**$75**	
		All Mental Health Carveout Drugs Totals:	**$46,551,101**		**673,931**	**$69**	
		All FFS Drug Totals:	**$65,079,146**		**788,044**	**$83**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: April 26, 2026

Drug Use Research & Management Program
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Top 40 Physical Health Carve-out Drugs by Gross Amount Paid (FFS Only) - First Quarter 2026

Rank	PDL Class	Drug	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Niemann-Pick Type C	MIPLYFFA *	$1,075,163	13.8%	12	$89,597	N
2	Epidermolysis Bullosa	VYJUVEK *	$951,815	12.2%	16	$59,488	N
3	Duchenne Muscular Dystrophy	AMONDYS-45 *	$699,260	9.0%	6	$116,543	N
4	Niemann-Pick Type C	AQNEURSA *	$601,354	7.7%	12	$50,113	N
5	Physican Administered Drug	Inj, Lovotibeglogene Autotem *	$535,681	6.9%	1	$535,681	
6	Bile Therapy	CHOLBAM *	$473,894	6.1%	5	$94,779	N
7	STC 99 - Miscellaneous	DAYBUE *	$384,133	4.9%	13	$29,549	N
8	STC 99 - Miscellaneous	VYKAT XR *	$376,037	4.8%	12	$31,336	N
9	Lysosomal Storage Disorders	YARGESA *	$361,758	4.6%	9	$40,195	N
10	Duchenne Muscular Dystrophy	VYONDYS-53 *	$320,020	4.1%	2	$160,010	N
11	Duchenne Muscular Dystrophy	DUVYZAT *	$309,484	4.0%	8	$38,685	N
12	Duchenne Muscular Dystrophy	VILTEPSO *	$304,644	3.9%	5	$60,929	N
13	STC 99 - Miscellaneous	DAYBUE STIX *	$212,690	2.7%	5	$42,538	N
14	STC 99 - Miscellaneous	SOHONOS *	$203,226	2.6%	4	$50,807	N
15	Orphan Drug	LIVMARLI *	$186,577	2.4%	1	$186,577	
16	Orphan Drug	BYLVAY *	$182,468	2.3%	2	$91,234	
17	Orphan Drug	CTEXLI *	$175,920	2.3%	3	$58,640	
18	Orphan Drug	STRENSIQ *	$175,072	2.3%	4	$43,768	
19	Orphan Drug	ELAPRASE *	$99,349	1.3%	3	$33,116	
20	Lysosomal Storage Disorders	MIGLUSTAT *	$71,584	0.9%	7	$10,226	N
21	Epidermolysis Bullosa	FILSUVEZ *	$61,711	0.8%	1	$61,711	N
22	Physican Administered Drug	Elosulfase Alfa, Injection *	$18,716	0.2%	4	$4,679	
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		Top 40 Aggregate:	**$7,780,555**		**135**	**$57,634**	
		All Physical Health Carveout Drugs Totals:	**$7,780,555**		**135**	**$57,634**	
		All FFS Drug Totals:	**$65,079,146**		**788,044**	**$83**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: April 26, 2026

Drug Use Research & Management Program
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Top 40 Physical Health Drugs Not Carved-out by Gross Amount Paid (FFS Only) - First Quarter 2026

Rank	PDL Class	Drug	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	HIV	BIKTARVY	$354,655	3.3%	102	$3,477	Y
2	Physican Administered Drug	Inj, Nusinersen, 0.1mg *	$255,229	2.4%	1	$255,229	
3	Diabetes, GLP-1 Receptor Agonists and GIP Therapies	OZEMPIC *	$226,664	2.1%	448	$506	N
4	Hepatitis C, Direct-Acting Antivirals	MAVYRET *	$214,509	2.0%	20	$10,725	Y
5	Substance Use Disorders, Opioid & Alcohol	SUBLOCADE	$213,222	2.0%	107	$1,993	Y
6	Physican Administered Drug	Etonogestrel Implant System	$202,497	1.9%	341	$594	
7	Physican Administered Drug	Inj Pembrolizumab *	$167,861	1.6%	70	$2,398	
8	Diabetes, GLP-1 Receptor Agonists and GIP Therapies	MOUNJARO *	$159,024	1.5%	290	$548	N
9	Antiepileptics, Outpatient	EPIDIOLEX *	$155,272	1.4%	103	$1,507	N
10	Antiepileptics, Outpatient	FINTEPLA *	$147,153	1.4%	14	$10,511	N
11	Targeted Immune Modulators	HUMIRA(CF) PEN *	$139,717	1.3%	25	$5,589	Y
12	Cystic Fibrosis	TRIKAFTA *	$134,038	1.2%	25	$5,362	N
13	Physican Administered Drug	Inj., Emicizumab-Kxwh 0.5 Mg	$129,592	1.2%	9	$14,399	
14	Weight Management Drugs	IMCIVREE *	$128,782	1.2%	6	$21,464	
15	Physican Administered Drug	Inj Fam-Trastu Deru-Nxki 1mg *	$125,186	1.2%	12	$10,432	
16	Physican Administered Drug	Mirena, 52 Mg	$120,863	1.1%	293	$413	
17	Antineoplastics, Newer	KISQALI *	$120,607	1.1%	8	$15,076	
18	Physican Administered Drug	Injection, Nivolumab *	$115,845	1.1%	39	$2,970	
19	Anticoagulants, Oral and SQ	ELIQUIS	$104,611	1.0%	395	$265	Y
20	Diabetes, GLP-1 Receptor Agonists and GIP Therapies	TRULICITY *	$101,675	0.9%	155	$656	Y
21	Antineoplastics, Newer	EVEROLIMUS *	$98,982	0.9%	14	$7,070	
22	Spinal Muscular Atrophy	EVRYSDI *	$95,650	0.9%	19	$5,034	N
23	Diabetes, SGLT-2 Inhibitors	JARDIANCE	$93,171	0.9%	412	$226	Y
24	Substance Use Disorders, Opioid & Alcohol	BRIXADI	$92,423	0.9%	62	$1,491	Y
25	Targeted Immune Modulators	RINVOQ *	$86,941	0.8%	33	$2,635	N
26	Diabetic Supplies, CGM	DEXCOM G7 SENSOR *	$80,909	0.8%	347	$233	Y
27	Contraceptives	SLYND	$76,457	0.7%	245	$312	
28	Physican Administered Drug	Contraceptive Pills For Bc *	$75,911	0.7%	1,625	$47	
29	ADHD Drugs	LISDEXAMFETAMINE DIMESYLATE *	$73,613	0.7%	1,093	$67	Y
30	Targeted Immune Modulators for Asthma and Atopic Der	DUPIXENT PEN *	$73,000	0.7%	35	$2,086	N
31	STC 58 - Diabetic Therapy	MIFEPRISTONE	$71,735	0.7%	2	$35,868	
32	Antiepileptics, Outpatient	XCOPRI	$71,063	0.7%	95	$748	N
33	Physican Administered Drug	Inj., Durvalumab, 10 Mg *	$68,639	0.6%	28	$2,451	
34	Pulmonary Arterial Hypertension Oral and Inhaled Drugs	OPSUMIT *	$66,639	0.6%	5	$13,328	N
35	Beta-Agonists, Inhaled Short-Acting	ALBUTEROL SULFATE HFA	$65,938	0.6%	2,402	$27	Y
36	Substance Use Disorders, Opioid & Alcohol	BUPRENORPHINE-NALOXONE *	$65,419	0.6%	1,032	$63	Y
37	Thrombocytopenia Drugs	ELTROMBOPAG OLAMINE	$64,622	0.6%	10	$6,462	Y
38	Growth Hormones	NORDITROPIN FLEXPRO *	$64,564	0.6%	49	$1,318	Y
39	Physican Administered Drug	Contraceptive Hormone Patch	$64,004	0.6%	112	$571	
40	Targeted Immune Modulators	TALTZ AUTOINJECTOR *	$62,549	0.6%	10	$6,255	Y
		Top 40 Aggregate:	**$4,829,230**		**10,093**	**$478**	
		All Physical Health Drugs Not Carved-out Totals:	**$10,747,491**		**113,978**	**$94**	
		All FFS Drug Totals:	**$65,079,146**		**788,044**	**$83**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

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Review Standards and Methods for Quality Assessment of Evidence
Updated: ~~August 2025~~ June 2026

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drugs, drug classes, and select non-drug item reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the preferred drug list (PDL), preferred non-drug items, and clinical prior authorization (PA) criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices.

2. The types of reviews may include, but are not limited to, the following:

Type of Review	Rationale for Review
~~Abbreviated Drug Review~~	~~New drug with evidence only for non-funded condition(s)~~
Class Literature Scan	Used when limited literature is found which would affect clinical changes in PDL status or PA criteria based on efficacy or safety data (may include new drug formulations or expanded indications if available; literature would not change PDL status or PA criteria). Identifies new or newly available literature, ~~Provides a summary of new or available literature, and~~ outcomes are not evaluated via the GRADE methodology listed in **Appendix** D and full quality assessment is not performed for identified literature.
New Drug Evaluation (NDE)	Single new drug identified and the PDL class was recently reviewed, or the drug is not assigned to a PDL drug class.
Class Review	New PDL class
Class Update	New systematic review(s) and clinical trials ~~identified that may~~ that inform change in PDL status or clinical PA criteria in an established PDL class.
Class Update with New Drug Evaluation	New drugs(s) or indication(s) also identified (excludes new formulations, expanded indications, biosimilars, or drugs for unfunded indications)
DERP Summary Report	New DERP report which evaluates comparative evidence
Drug Use Evaluation	Analysis of utilization trends in FFS population in order to identify safety issues or inform future policy decisions
Policy Evaluation	Evaluate ~~ion~~ safety, efficacy, and utilization trends after implementation of a policy to identify areas for improvement

Prior Authorization Update	To evaluate targeted updates to PA criteria based on current policy guidance from the Health Evidence Review Commission, recommendations from the Mental Health Clinical Advisory Group, or expanded labeling from the FDA
Non-Drug Item Review (Specific non-drug items billed through pharmacy [e.g., non-durable medical equipment] as requested by Oregon Health Authority (OHA)	Assessment of products identified by OHA where pharmacy point-of-sale dispensing is considered necessary.
High Cost Orphan Drug Evaluation	Streamlined review of single new drug identified as an orphan drug and planned for addition to High Cost Drug Carve Out.

3. The P&T Committee will rely primarily on high quality systematic reviews and randomized controlled trials in making its evidence summary recommendations. High quality clinical practice guidelines and relevant clinical trials are also used as supplementary evidence.

4. Emphasis will be placed on the highest quality evidence available. Poor quality trials, systematic reviews or guidelines are excluded if higher quality literature is available and results offer no additional value. Unless the trial evaluates an outcome or comparison of high clinical importance, individual RCTs with the following study types will be excluded from class updates, class reviews, and literature scans:
    a. Non-comparative, placebo-controlled trials
    b. Non-inferiority trials
    c. Extension studies
    d. Poor quality studies (as assessed in **Appendix A**)

5. Individual drug evaluations rely primarily on high quality RCTs or clinical trials used for FDA approval. Evidence from poor quality or non-comparative RCTs may be included if there is no higher quality evidence available.

6. Phase 2 trials may be considered if there is a compelling reason to include, such as use for FDA approval. Preference will be given for inclusion of applicable phase 3 and 4 trials over earlier phase studies. If fully published, of adequate duration, and with appropriate clinical outcome measures, authors may include phase 2 studies if phase 3 or 4 trials are inadequate or when direct comparative evidence and/or dose response are reported in a comparable population to available phase 3 or 4 studies.

7. The following are preferred sources that provide high quality evidence at this time:

    a. Drug Effectiveness Review Project at Oregon Health & Science University (OHSU)
    b. U.S. Department of Veterans Affairs/Department of Defense
    c. Agency for Healthcare Research and Quality (AHRQ)
    d. Canadian Agency for Drugs and Technologies in Health (CADTH)
    e. National Institute for Clinical Excellence (NICE)
    f. Scottish Intercollegiate Guidelines Network (SIGN)

g. Oregon Mental Health Clinical Advisory Group (MHCAG)

8. The following types of evidence are preferred and will be considered only if they are of high methodological quality as evaluated by the quality assessment criteria below:

    a. Systematic reviews of randomized controlled trials
    b. Direct comparative randomized controlled trials (RCTs) evaluating clinically relevant outcomes; placebo-controlled studies not related to initial FDA-drug approval or new indications may be considered if likely to impact current policy
    c. FDA review documents
    d. Clinical Practice Guidelines developed using explicit evidence evaluation processes

9. The following types of literature are considered unreliable sources of evidence and will rarely be reviewed by the P&T Committee:

    a. Observational studies, case reports, case series
        i. However, observational studies and systematic reviews of observational studies will be included to evaluate significant safety data beyond the FDA labeling information. Observational studies will only be included when there is not adequate data from higher quality literature.
    b. Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles) that do not include sufficient methodological details for quality evaluation, with the exception of FDA review documents
    c. Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality compared to other relevant literature, or duplicate information in other materials under review.
    d. Studies not designed to investigate clinically relevant outcomes
    e. Systematic reviews identified with the following characteristics:
        i. Evidence is of poor or very poor quality
        ii. Evidence is of limited applicability to a US population
        iii. Systematic review does not meet defined applicability criteria (PICOTS criteria) for the topic
        iv. Systematic review is of poor methodological quality as evaluated by AMSTAR II criteria (see **Appendix B**)
        v. Evidence is based on indirect comparisons from network meta-analyses
        vi. Conflicts of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)
    f. Guidelines identified with the following characteristics:
        i. There is no systematic guideline development method described
        ii. Strength of evidence for guideline recommendations are not provided
        iii. Recommendations are largely based on expert opinion
        iv. Poor methodological quality as assessed in **Appendix C** (AGREE II score is less than 113 points OR modified AGREE II-GRS score is less than 30 points)
        v. Conflict of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)

10. When assessing efficacy and safety of non-drug items (e.g., devices, digital health technologies), primary emphasis will be on studies that compare the new technology or device to currently available health and social care system technologies or the current standard of care. Included literature for medical technologies and non-drug items will focus on clinical efficacy and safety outcomes measured by relevant outcome indicators. Because the

efficacy and safety of medical technologies and non-drug items may be dependent on the training and experience of the user, may be influenced by organizational factors, and may be influenced by changes in the technology over time, pragmatic usability details (e.g., user experience) will also be included.

QUALITY ASSESSMENT

1. The standard methods used by the DURM faculty to assess quality of evidence incorporated into the evidence summaries for the OHP Pharmacy and Therapeutics Committee are described in detail in **Appendix A-C**.

2. The Cochrane Risk of Bias tool (modified) described in **Appendix A** is used to assess risk of bias (i.e., internal validity) of randomized controlled trials. The quality of non-inferiority trials will be also assessed using the additional criteria for non-inferiority trials in **Appendix A**. Internal validity of clinical trials are graded as poor, fair, or good quality.

3. The AMSTAR II measurement tool is used to assess for methodological quality of systematic reviews and is provided in **Appendix B**. Systematic reviews, meta-analyses or guidance identified from 'best sources' listed in **Appendix B** undergo methodological rigor and are considered to be high quality and are not scored for quality using the AMSTAR II tool.

4. Clinical practice guidelines are considered for inclusion after assessment of methodological quality using the AGREE II global rating scale provided in **Appendix C**. If there are concerns regarding applicability of guidelines to the Medicaid population, the AGREE-REX tool is available for use (https://www.agreetrust.org/resource-centre/agree-rex-recommendation-excellence/).

5. The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability, or directness, of randomized controlled trials to the OHP population. Detailed guidance is provided in **Appendix A**. Only randomized controlled trials with applicability to the OHP population, as assessed by the PICOS framework, are included in evidence summaries.

6. Emphasis of the review will be on clinically relevant outcomes. The following clinically relevant outcomes are graded for quality: mortality, morbidity outcomes, symptom relief, quality of life, functioning (physical, mental, or emotional), early discontinuation due to adverse events, and severe adverse effects. Surrogate outcomes are considered if directly linked to mortality or a morbidity outcome. Clinically meaningful changes in these outcomes are emphasized.

7. The overall quality of evidence is graded for clinically relevant outcomes of efficacy and harm using the GRADE methodology listed in **Appendix D**. Evaluation of evidence for each outcome of interest is graded as **high**, **moderate**, **low**, or **insufficient**. Final evidence summary recommendations account for the availability and quality of evidence for relevant outcomes and perceived clinical impact on the OHP population.

    a. Evidence grades are defined as follows:
        i. High quality evidence: High confidence that the estimated effects produced in the studies reflect the true effect. Further research is very unlikely to change the estimated effect.
        ii. Moderate quality evidence: Moderate confidence that the estimated effects produced in the studies reflect the true effect. Further research may change the estimated effect.

iii. Low quality evidence: Limited confidence that the estimated effects produced in the studies reflect the true effect. Further research is likely to change the estimated effect.
iv. Insufficient evidence: Evidence is not available or too limited to permit any level of confidence in the estimated effect.

8. Conflict of Interest
    a. Conflict of interest is a critical component of quality assessment. A conflict of interest is "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a second interest." Conflict of interest includes any relationships or activities that could be perceived to have influenced or give the appearance of potentially influencing the literature.
        i. Reference: IOM (Institute of Medicine). 2009. *Conflict of Interest in Medical Research, Education, and Practice*. Washington, DC: The National Academies Press.

    b. Conflict of interest analysis for DURM reviews:
        1. Sources will be excluded due to conflict of interest concerns if they contain one of the "fatal flaws" in **Table 1** below.
        2. If no "fatal flaws" exist, an analysis of the conflicts of interest will be completed and any limitations (examples in **Table 1** below) will be first and foremost discussed in the evidence review.
        3. Conflict of interest is also assessed through the Cochrane risk of bias, AMSTAR II, and AGREE tools (**Appendix A, B, and C**).

Table 1. DURM Conflict of Interest Analysis

Type of literature	"Fatal flaws"	If no "fatal flaws" exist, potential limitations to discuss when including the piece of literature	Other considerations- specific to the type of literature
Randomized controlled trial	• Conflict of interest not documented	• Authors or committee members have significant conflicts of interest • Concerning high dollar amounts of conflicts of interest are documented	• Higher risk of bias when the study sponsor is the pharmaceutical manufacturer and is included in data analysis and manuscript writing
Systematic review	• Conflict of interest not documented • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* persons with potential conflicts of interest are excluded from the assessment or review process, independent second review of articles		• May consider funding sources or conflicts of interest for both the systematic review and the included studies

	considered for inclusion in SR that are reviewed first by their own author who is on the SR team	• Mitigation strategies (described in the article or journal/organization policies) are documented but could be more robust	
Guideline	• Conflict of interest not documented • Chair has a conflict of interest • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* excluding persons with significant conflict of interest from the review process, recusing members with significant conflict of interest from voting on recommendations or having them leave the room during the discussion		• Guidelines with "fatal flaws" which are commonly used in practice may be included for clinical context but will not be considered when creating conclusions or recommendations

APPENDIX A. Methods to Assess Quality of Studies.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	Selection bias refers to **systematic differences** between **baseline characteristics of the groups** that were compared. The unique strength of proper ***randomization*** is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants. Successful randomization depends on fulfilling several interrelated processes. A rule for allocating patients to groups must be specified, based on some chance (random) process. Furthermore, steps must be taken to secure strict implementation of that schedule of random assignments by preventing foreknowledge of the forthcoming allocations. This process if often termed ***allocation concealment***.
Performance Bias	Performance bias refers to **systematic differences** between groups in the **care provided**, or in exposure to factors other than the interventions of interest. After enrolment, ***blinding participants and investigators/care givers*** will reduce the risk that knowledge of which intervention was received affected the outcomes, rather than the intervention itself. Effective blinding ensures that all groups receive a similar amount of attention, ancillary treatment and diagnostic investigations. Therefore, risk of differences in intervention design and execution, care experiences, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations and study duration between study groups are minimized.
Detection Bias	Detection bias refers to **systematic differences** between groups in how **outcomes were assessed**. ***Blinding of outcome assessors*** will reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affected outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes (eg, degree of post-operative pain).
Attrition Bias	Attrition bias refers to **systematic differences** between groups in **withdrawals** (exclusions and attrition) from a study. ***Withdrawals*** from the study lead to incomplete outcome data. There are two reasons for withdrawals or incomplete outcome data in clinical trials. ***Exclusions*** refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to assessors. ***Attrition*** refers to situations in which outcome data are not available.
Reporting Bias	Reporting bias refers to the **selective reporting of pre-specified outcomes**, on the basis of the results. Of particular concern is that statistically non-significant (negative) primary endpoints might be selectively reported while select positive secondary endpoints are over-emphasized. Selective reporting of outcomes may arise in several ways: 1) there can be selective omission of pre-specified outcomes (ie, only some of the pre-specified outcomes are reported); 2) there can also be selection of choice data for an outcome that differs from what was pre-specified (eg, there may be different time points chosen to be reported for an outcome, or different methods used to measure an outcome at the same time point); and 3) there can be selective analyses of the same data that differs from what was pre-specified (eg, use of continuous vs. dichotomous outcomes for A1c lowering, selection from multiple cut-points, or analysis of between endpoint scores vs. change from baseline).
Other Bias	Other sources of bias may be present depending on conflict of interests and funding sources, trial design, or other specific circumstances not covered in the categories above. Of particular concern is how conflicts of interest and funding sources may potentially bias results. Inappropriate influence of funders (or, more generally, of people with a vested interest in the results) is often regarded as an important risk of bias. Information about vested interests should be collected and presented when relevant, with specific regard for methodology that might be been influenced by vested interests and which may lead directly to a risk of bias. Additional sources of bias may result from trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster-randomized trials); some can be found across a broad spectrum of trials, but only for specific circumstances (e.g. contamination, whereby the experimental and control interventions get 'mixed', for example if participants pool their drugs).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials; therefore, it is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Assess each domain separately to determine if risk of each bias is likely **LOW**, **HIGH** or **UNCLEAR** (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix D**).

Conflicts of interest should also be assessed when determining risk of bias. This may be considered part of risk of reporting bias. Funding sources for the trial, conflicts of interest of the authors, and role the study sponsor played in the trial should be considered in this domain.

The quality of each trial will be graded as **good, fair,** or **poor** based on the following thresholds for converting the Cochrane Risk of Bias Tool to AHRQ Standards. A good quality trial will have low risk of bias for all domains. A fair quality trial will have one domain with high risk of bias or 2 domains with unclear bias, with the assessment that the one or more biases are unlikely to influence the outcome, and there are no known limitations which could invalidate results. A poor quality trial will have high risk of bias for one or more domains or have 2 criteria with unknown bias for which there may be important limitations which could invalidate the results or likely bias the outcome. Trials of poor quality will be excluded from review if higher quality sources of evidence are available.

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table • Coin toss	Sequence generated by: • Odd or even date of birth • Rule based on date or admission date • Hospital or clinic number • Alternating numbers	Method of randomization not described or sequence generation process not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Participants or investigators could not foresee assignment because: • Central allocation (telephone, web-based, pharmacy-controlled) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Participants or investigators could possibly foresee assignment because: • Open random allocation • Envelopes without appropriate safeguards (eg, unsealed or not opaque) • Allocation based on date of birth or case record number • Alternating allocation	Method of concealment not described or not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate sequence generation, allocation concealment, or failed randomization. *Statistical tests of baseline imbalance are not helpful for randomized trials.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, other medications, medical/surgical history, etc.)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Systematic differences in how care was provided between groups due to un-blinding of participants or investigators/care providers or because of standard of care was not consistent across all sites.	• Study participants could not identify study assignment because blinding of participants was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • Protocol standardized across all sites and followed consistently	• Study participants could possibly identify study assignment because there was no blinding or incomplete blinding • Blinding potentially broken, which likely influenced effect estimate (eg, differences easily observed in appearance, taste/smell or adverse effects between groups) • Some sites had a different standard of care or varied from protocol which likely influenced effect estimate	Not described or insufficient information to permit definitive judgment

DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Outcome assessors un-blinded	Outcome assessors could not identify study assignment because: • Blinding of assessors was ensured and unlikely broken • No blinding or incomplete blinding, but effect estimate not likely influenced by lack of blinding (ie, objective outcomes)	• Outcome data assessors could possibly identify study assignment because no blinding or incomplete blinding, which likely influenced effect estimate • Blinding potentially broken, which likely influenced effect estimate (eg, large differences in efficacy or safety outcomes between groups)	Not described or insufficient information to permit definitive judgment
ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High Drop-out rate or loss to follow-up (eg, >10% for short-term studies; >20% for longer-term studies) • Differential drop-out or loss to follow-up >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed where appropriate (eg, superiority trials) • Intention-to-treat and per-protocol analyses performed and compared where appropriate (eg, non-inferiority trials) • Reasons for missing outcome data unlikely to influence effect estimates • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.)	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of selective outcome reporting	• Study protocol is available and was followed and all pre-specified primary and secondary outcomes are reported • Study protocol is not available, but it is clear that all expected outcomes are reported	• Not all pre-specified primary and secondary outcomes reported • Primary outcome(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary outcome(s) not pre-specified (unless clear justification provided) • Failure or incomplete reporting of other outcomes of interest • Inappropriate over-emphasis of positive secondary outcomes in study with negative primary outcome	Insufficient information to make determination
OTHER BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**

Evidence of other biases not described in the categories above	• No conflicts of interest present or study sponsor was not involved in trial design, data analysis or publication • No other potential sources of bias identified	• Conflicts of interest are present based on funding source or conflicting interests of authors • Study sponsor is involved in trial design, data analysis, and publication of data • There is a run-in period with pre-randomization administration of an intervention that could enhance or diminish the effect of a subsequent, randomized, intervention • Recruitment bias in cluster-randomized trials with differential participant recruitment in clusters for different interventions • Cross-over trials in which the crossover design is not suitable, there is significant carry-over effects, or incompletely reported data (data reported only for first period) • Conduct of the study is affected by interim results ((e.g. recruiting additional participants from a subgroup showing more benefit) • Deviation from the study protocol in a way that does not reflect clinical practice (e.g. post hoc stepping-up of doses to exaggerated levels).	• Conflicts of interest for authors or funding sources are not reported or not described • Insufficient information regarding other trial methodology and design to make a determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (ie, directness) of the evidence to the OHP population (**Table 3**).

Table 3. PICOS Domains that Affect Applicability.

PICOS Domain	Conditions that Limit Applicability
Patient	• Narrow eligibility criteria and broad exclusion criteria of those with comorbidities • Large differences between the demographic characteristics between the study population and patients in the OHP • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in OHP population
Intervention	• Doses, frequency schedule, formulations or duration of intervention used in study not reflective of clinical practice • Intensity/delivery of behavioral interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparator	• Inadequate dose or frequency schedule of comparator • Use of inferior or substandard comparator relative to alternative comparators that could be used
Outcomes	• Short-term or surrogate outcomes assessed • Composite outcomes used that mix outcomes of different significance
Setting	• Standards of care in study setting differ markedly from clinical practice • Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care from highly trained/proficient practitioners in trial not reflective of typical clinical practice where intervention likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Non-inferiority (NI) trials are designed to prove a new treatment is not worse than the control treatment by a pre-determined difference, with a given degree of confidence. The pre-determined margin of difference in non-inferiority trials is defined as delta. Correctly determining this margin is a challenge in the design and interpretation of NI trials. The greatest challenge in use of NI trials is recognizing inappropriate use.

Non-inferiority trials will only be included in evidence summaries when there is a compelling reason to include them, and higher quality evidence is not available. The compelling reason for inclusion will be clearly stated as an introduction to the reporting of the NI trial.

The following template was developed using CONSORT and FDA guidance[1,2] and will be used as a guideline to evaluate non-inferiority studies included in DURM evidence summaries. Unless the trial evaluates an outcome or comparison of high clinical importance, individual non-inferiority trials will be excluded from class updates, class reviews, and literature scans. Evidence from poor quality RCTs may be included in individual drug evaluations if there is no higher quality evidence available. Items in bold (#1-5) are essential to conducting a non-inferiority trial with good methodological rigor. In general, a non-inferiority trial with high quality methods will score a "yes" on most of the components listed below.

Table 4. Non-inferiority Trial Quality Scoring Template

Developed using CONSORT and FDA guidance[1,2] Use Template to evaluate trials supporting New Drug Evaluations and Class Update Reports A high-quality trial will meet all bolded assessments below	
1. Rationale for choosing comparator with historical study results confirming efficacy (or safety) of this comparator is provided.	□ **Yes** □ **No** □ **Can't answer**
2. Active control (or comparator) represents current standard of care.	□ **Yes** □ **No** □ **Can't answer**
3. Non-inferiority margin was specified a priori and based on statistical reasoning and clinical considerations regarding benefit, risk, and cost.	□ **Yes** □ **No** □ **Can't answer**
4. Noninferiority margin is not larger than the expected difference between active control (or comparator) and placebo.	□ **Yes** □ **No** □ **Can't answer**
5. If a superiority conclusion is drawn for outcome(s) for which noninferiority was hypothesized, the justification for switching is provided and superiority analysis was defined a priori.	□ **Yes** □ **No** □ **Can't answer**
6. Investigator reported both ITT and per-protocol analysis in detail and the results of both analyses demonstrate noninferiority. (If only one analysis is provided, per protocol is subject to less bias than ITT analysis in noninferiority trials.)	□ **Yes** □ **No** □ **Can't answer**
7. Rationale for using a noninferiority design is included (or why it would likely be unethical to conduct a placebo-controlled superiority trial of the new therapy).	□ Yes □ No □ Can't answer
8. Study hypothesis is stated in terms of noninferiority.	□ Yes □ No □ Can't answer
9.Eligibility criteria for participants and the settings in which the data were collected are similar to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
10. Trial is designed to be consistent with historical placebo-controlled trials.	□ Yes □ No □ Can't answer
11. The reference treatment in the noninferiority trial is identical (or very similar) to that in any trial(s) that established efficacy (or safety).	□ Yes □ No □ Can't answer
12. The outcomes in the noninferiority trial are identical (or very similar) to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
13. The lower bound of that CI is clinically significant.	□ Yes □ No □ Can't answer
14. For the outcome(s) for which noninferiority was hypothesized, a figure showing confidence intervals and the noninferiority margin is included.	□ Yes □ No □ Can't answer
15. Results are interpreted in relation to the noninferiority hypothesis.	□ Yes □ No □ Can't answer

References:
1. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *Jama.* 2012;308(24):2594-2604.
2. FDA Industry Guidance for Noninferiority Trials. November 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.

APPENDIX B. Methods to Assess Methodological Quality of Systematic Reviews.

A measurement tool for the "assessment of multiple systematic reviews" (AMSTAR II) was developed and shown to be a validated and reliable measurement tool to assess the methodological quality of systematic reviews. There are 16 components addressed in the measurement tool below, and questions can be scored in one of four ways: "Yes", "Partial Yes", "No", or "Not Applicable". The AMSTAR II is used as a guideline to identify high quality systematic reviews eligible for inclusion in DURM evidence summaries. High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#4); characteristics of studies not provided (#8); quality of studies were not assessed or considered when conclusions were formulated (#9 and #13)). Other areas identified as important domains in the AMSTAR II criteria include registration of a protocol (#2); justification for excluding individual studies (#7); appropriateness of meta-analysis methods (#11); and assessment of publication bias (#15). In general, a high quality systematic review will score a "yes" on most components presented in the AMSTAR II tool.

Ref. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Systematic reviews or guidance identified from 'best sources' undergo methodological rigor considered to be of high quality and are not scored for quality. 'Best sources' include, but are not limited to: Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center; Agency for Healthcare Research and Quality (AHRQ); National Institute for Health and Care Excellence (NICE); U.S. Department of Veterans Affairs (VA); and Canadian Agency for Drugs and Technologies in Health (CADTH); and BMJ Clinical Evidence.

AMSTAR II Quality Scoring Template

1) Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)

- ☐ Timeframe for follow-up

☐ Yes
☐ No

2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:

- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes: As for partial yes, plus the protocol should be registered and should also have specified:

- ☐ a meta-analysis/synthesis plan, if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

3) Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☐ OR Explanation for including both RCTs and NRSI

☐ Yes
☐ No

4) Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes
- Partial Yes
- No

5) Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- No

6) Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- No

7) Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- Justified the exclusion from the review of each potentially relevant study

- Yes
- Partial Yes
- No

8) Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:
- described population in detail
- described intervention in detail (including doses where relevant)
- described comparator in detail (including doses where relevant)
- described study's setting
- timeframe for follow-up

- Yes
- Partial Yes
- No

9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from:
- unconcealed allocation, and
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- allocation sequence that was not truly random, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- from confounding, and
- from selection bias

For Yes, must also have assessed RoB:
- methods used to ascertain exposures and outcomes, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only RCTs

10) Did the review authors report on the sources of funding for the studies included in the review?

For Yes: Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- Yes
- No

11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:
- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- AND investigated the causes of any heterogeneity

- Yes
- No
- No meta-analysis conducted

NRSI	**For Yes:** □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	□ Yes □ No □ No meta-analysis conducted
12)	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** **For Yes:** □ included only low risk of bias RCTs □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	□ Yes □ No □ No meta-analysis conducted
13)	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?** **For Yes:** □ included only low risk of bias RCTs □ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	□ Yes □ No
14)	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** **For Yes:** □ There was no significant heterogeneity in the results □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	□ Yes □ No
15)	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** **For Yes:** □ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	□ Yes □ No □ No meta-analysis conducted
16)	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** **For Yes:** □ The authors reported no competing interests OR □ The authors described their funding sources and how they managed potential conflicts of interest	□ Yes □ No

APPENDIX C. Methods to Assess Methodological Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument (www.agreetrust.org) assesses the methodologic rigor in which a guideline is developed and used. The AGREE II is an updated instrument that has been validated. It consists of 23 items in 6 domains (scope, stakeholder involvement, rigor of development, clarity, applicability, and editorial independence) to rate (**Table 1**). Because it is time-consuming to administer, a consolidated global rating scale (GRS) was developed, and is generally a reasonable alternative to AGREE II if resources are limited. The AGREE II-GRS instrument consists of only 4 items (**Table 2**). As the AGREE II-GRS does not take into account conflicts of interest, questions 22 and 23 regarding "Editorial Independence" will also be evaluated in conjunction with the AGREE II-GRS. With both instruments, each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. High quality clinical practice guidelines are eligible for inclusion in DURM evidence summaries. These guidelines will score 6-7 points for each component on rigor of development. In general, a high quality clinical practice guideline will score 5-7 points on most components presented in the AGREE II and each component of the AGREE II-GRS.

Table 1. AGREE II Instrument.

	ITEM	DESCRIPTION
SCOPE AND PURPOSE		
1	The overall objective(s) of the guideline is (are) specifically described.	The overall objective(s) of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem or health topic. **[SCORE:]**
2	The health question(s) covered by the guideline is (are) specifically described.	A detailed description of the health questions covered by the guideline should be provided, particularly for key recommendations, although they need not be phrased as questions. **[SCORE:]**
3	The population to whom the guideline is meant to apply is specifically described.	A clear description of the population (ie, patients, public, etc.) covered by a guideline should be provided. The age range, sex, clinical description, and comorbidities may be provided. **[SCORE:]**
STAKEHOLDER INVOLVEMENT		
4	The guideline development group includes individuals from all relevant professional groups.	This may include members of the steering group, the research team involved in selection and review of the evidence and individuals involved in formulation of the final recommendations. **[SCORE:]**
5	The views and preferences of the target population have been sought.	Information about target population experiences and expectations of health care should inform the development of guidelines. There should be evidence that some process has taken place and that stakeholders' views have been considered. For example, the public was formally consulted to determine priority topics, participation of these stakeholders on the guideline development group, or external review by these stakeholders on draft documents. Alternatively, information could be obtained from interviews of these stakeholders or from literature reviews of patient/public values, preferences or experiences. **[SCORE:]**
6	The target users of the guideline are clearly defined.	The target users should be clearly defined in the guideline so the reader can immediately determine if the guideline is relevant to them. For example, the target users for a guideline on low back pain may include general practitioners, neurologists, orthopedic surgeons, rheumatologists, and physiotherapists. **[SCORE:]**
RIGOR OF DEVELOPMENT		
7	Systematic methods were used to search for evidence.	Details of the strategy used to search for evidence should be provided, which include search terms used, sources consulted, and dates of the literature covered. The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated. **[SCORE:]**
8	The criteria for selecting the evidence are clearly described.	Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. **[SCORE:]**

9	The strengths and limitations of the body of evidence are clearly described.	Statements that highlight the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions, using informal or formal tools/methods, to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. **[SCORE:]**
10	The methods for formulating the recommendations are clearly described.	A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, or formal consensus techniques (eg, Delphi, Glaser techniques). **[SCORE:]**
11	The health benefits, adverse effects, and risks have been considered in formulating the recommendations.	The guideline should consider both effectiveness/efficacy and safety when recommendations are formulated. **[SCORE:]**
12	There is an explicit link between the recommendations and the supporting evidence.	An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. **[SCORE:]**
13	The guideline has been externally reviewed by experts prior to its publication.	A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include both clinical and methodological experts. **[SCORE:]**
14	A procedure for updating the guideline is provided.	A clear statement about the procedure for updating the guideline should be provided. **[SCORE:]**
CLARITY OF PRESENTATION		
15	The recommendations are specific and unambiguous.	A recommendation should provide a precise description of which option is appropriate in which situation and in what population. It is important to note that in some instances, evidence is not always clear and there may be uncertainty about the best practice. In this case, the uncertainty should be stated in the guideline. **[SCORE:]**
16	The different options for management of the condition or health issue are clearly presented.	A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. **[SCORE:]**
17	Key recommendations are easily identifiable	Users should be able to find the most relevant recommendations easily. **[SCORE:]**
APPLICABILITY		
18	The guideline describes facilitators and barriers to its application.	There may be existing facilitators and barriers that will impact the application of guideline recommendations. **[SCORE:]**
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	For a guideline to be effective, it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer/online support. **[SCORE:]**
20	The potential resource implications of applying the recommendations have been considered.	The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff or expensive drug treatment. These may have cost implications on health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources. **[SCORE:]**
21	The guideline presents monitoring and/or auditing criteria	Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline (eg, HbA1c <7%, DBP <95 mm Hg). **[SCORE:]**
EDITORIAL INDEPENDENCE		
22	The views of the funding body have not influenced the content of the guideline.	Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations. **[SCORE:]**
23	Competing interests of guideline development group members have been recorded and addressed	There should be an explicit statement that all group members have declared whether they have any competing interests. **[SCORE:]**

Table 2. AGREE II Global Rating Scale (modified).

	ITEM	DESCRIPTION
1	Rate the guideline development methods. **[SCORE:]**	• Appropriate stakeholders were involved in the development of the guideline. • The evidentiary base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs was made.
2	Rate the guideline presentation. **[SCORE:]**	• The guideline was well organized. • The recommendations were easy to find.
3	Rate the guideline recommendations. **[SCORE:]**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
4	Rate the completeness of reporting, editorial independence. **[SCORE:]**	• The information is complete to inform decision making. • The guideline development process is transparent and reproducible.
5	The views of the funding body have not influenced the content of the guideline. **[SCORE:]**	• Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.
6	Competing interests of guideline development group members have been recorded and addressed. **[SCORE:]**	• There should be an explicit statement that all group members have declared whether they have any competing interests. • All competing interests should be listed • There should be no significant competing interests

APPENDIX D. GRADE Quality of Evidence.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) provides a framework to assess quality of evidence for an *outcome* that emphasizes transparency of how evidence judgments are made, though it does not necessarily guarantee consistency in assessment. Quality assessment in GRADE is 'outcome-centric' and distinct from quality assessment of an individual study. Information on risk of bias (internal validity), indirectness (applicability), imprecision, inconsistency, and publication bias is necessary to assess quality of evidence and overall confidence in the estimated effect size. The GRADE framework provides an assessment for each outcome.

DURM evidence summaries, unless a single drug is evaluated, depend on the whole body of available evidence. Evidence from high quality systematic reviews is the primary basis for recommendations in the evidence summaries. High quality evidence-based clinical practice guidelines and relevant randomized controlled trials are used to supplement the whole body of evidence.

High quality systematic reviews and clinical practice guidelines often use the GRADE framework to assess overall quality of evidence for a given outcome. In such cases, the grade of evidence provided in the respective report can be directly transferred to the DURM evidence summary. When an evidence summary includes relevant clinical trials, or when high quality systematic reviews or clinical practice guidelines that did not use the GRADE framework were identified, quality of evidence will be graded based on hierarchy of available evidence, homogeneity of results for a given outcome, and methodological flaws identified in the available evidence (**Table 1**).

Table 1. Evidence Grades for Benefit and Harm Outcomes When a Body of Evidence is Evaluated.

GRADE	TYPE OF EVIDENCE
High	• Evidence is based on data derived from multiple randomized controlled trials with homogeneity with regard to the direction of effect between studies AND • Evidence is based on multiple, well-done randomized controlled trials that involved large numbers of patients.
Moderate	• Evidence is based on data derived from randomized controlled trials with some conflicting conclusions with regard to the direction of effect between studies OR • Evidence is based on data derived from randomized controlled trials that involved small numbers of patients but showed homogeneity with regard to the direction of effect between studies OR • Some evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.)
Low	• Most evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.) OR • Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with homogeneity with regard to the direction of effect between studies
Insufficient	• Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with some conflicting conclusions with regard to direction of effect between studies OR • Evidence is based on data derived from expert opinion/panel consensus, case reports or case series OR • Evidence is not available

New Drug Evaluations cannot depend on evidence from systematic reviews and clinical practice guidelines. A body of evidence that solely consists of one or more clinical trials is initially assigned 4 points. For every relevant limitation, points are deducted; but points are added for consistently large effect sizes between studies or for a consistent dose-response observed in the studies (**Table 2**). The quality of evidence is subsequently graded as shown:

QUALITY OF EVIDENCE GRADES:

- ≥4 points = **HIGH**
- 3 points = **MODERATE**
- 2 points = **LOW**
- ≤1 point = **INSUFFICIENT**

Table 2. Domains to Grade Evidence for Benefit and Harm Outcomes from Clinical Trials: Cochrane Evidence Grades (modified).

DOMAIN	DESCRIPTION	SCORE DEMOTION/PROMOTION (start with 4 points)
Risk of Bias (internal validity)	Risk of bias is the likelihood to which the included studies for a given comparison and outcome has an inadequate protection against bias that affects the internal validity of the study. • *Did any studies have important limitations that degrade your confidence in estimates of effectiveness or safety?*	• No serious limitation: all studies have low risk of bias: **(0)** • Serious limitations: ≥1 trial has high or unclear risk of bias: **(-1)** • Very serious limitations: most studies have high risk of bias: **(-2)**
Indirectness (applicability)	Directness (applicability) relates to evidence that adequately compares 2 or more reasonable interventions that can be directly linked to a clinically relevant outcome in a population of interest. • *Do studies directly compare interventions of interest in populations of interest using outcomes of interest (use of clinically relevant outcomes)?*	• Direct: clinically relevant outcomes of important comparisons in relevant populations studied: **(0)** • Indirect: important comparisons missing; surrogate outcome(s) used; or population not relevant: **(-1)**
Inconsistency	Inconsistency (heterogeneity) is the degree to which reported effect sizes from included studies appear to differ in direction of effect. Effect sizes have the same sign (ie, are on the same side of ''no effect'') and the range of effect sizes is narrow. • *Did trials have similar or widely varying results? Can heterogeneity be explained by differences in trial design and execution?*	• Large magnitude of effect consistent between studies: **(+1)** • Dose-response observed: **(+1)** • Small magnitude of effect consistent between studies: **(0)** • 1 study with large magnitude of effect: **(0)** • 1 study with small magnitude of effect: **(-1)** • Inconsistent direction of effect across studies that cannot be explained: **(-1)**
Imprecision	Imprecision is the degree of uncertainty surrounding an effect estimate with respect to a given outcome (ie, the confidence interval for each outcome is too wide to rule out no effect). • *Are confidence intervals for treatment effect sufficiently narrow to rule out no effect?*	• Precise: all studies have 95% confidence intervals that rule out no effect: **(0)** • Imprecise: ≥1 study demonstrated 95% confidence interval fails to rule out no effect: **(-1)**
Publication Bias	Publication bias is the degree in which completed trials are not published or represented. Unpublished studies may have negative outcomes that would otherwise change our confidence in the body of evidence for a particular comparison and outcome. • *Is there evidence that important trials are not represented?*	• No publication bias: all important trials published or represented: **(0)** • Serious publication bias: ≥1 important trial(s) completed but not published: **(-1)**

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: June 2026 ~~August 2025~~

MISSION:

To encourage safe, effective, and innovative drug policies that promote high value medications for patients served by the Oregon Health Plan (OHP) and other health care programs under the Oregon Health Authority (OHA) by evidence-based committee review of drug use research, clinical guidance and education.

DUTIES:

As defined by Oregon Revised Statutes (Chapter 414) the Pharmacy and Therapeutics (P&T) Committee was established to perform functions previously fulfilled by the Drug Use Review Board and Health Resources Commission. Responsibilities of the P&T committee include:

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the OHA for drugs to be included on the preferred drug list (PDL).
    a. The P&T Committee may direct a Subcommittee to prepare these reviews.
2. Advise the OHA on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
3. Advise the OHA on coverage of select non-drug items (e.g., devices, digital health technologies) billed through pharmacy which includes recommending preferred products, utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
4. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs or select non-drug items, as well as the ability of Oregonians to access products that are appropriate for their clinical conditions.
5. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs. Meeting materials including written public comments, recordings, documents, and minutes remain publicly available online after the meeting. Comments are subject to Oregon public records law and should not disclose identifiable, personal health information.
6. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.
7. Consider input from Mental Health Clinical Advisory Group (MHCAG) on topics involving mental health. The Mental Health Clinical Advisory Group can make recommendations to both the Oregon Health Authority and the Pharmacy and Therapeutics Committee for:
    a. Implementation of evidence-based algorithms.
    b. Any changes needed to any preferred drug list used by the authority.
    c. Practice guidelines for the treatment of mental health disorders with mental health drugs.

d. Coordinating the work of the group with an entity that offers a psychiatric advice hotline.

8. Guide and approve meeting agendas.

9. Periodically review and update operating procedures and evidence grading methods as needed.

AD HOC SUBJECT MATTER EXPERT INVOLVEMENT:

1. The Director shall appoint an ad hoc expert to the P&T Committee when:
    a. The P&T Committee determines it lacks current clinical or treatment expertise with respect to a particular therapeutic class; or
    b. An interested outside party requests appointment and demonstrates to the satisfaction of Oregon Health Authority that the P&T Committee lacks necessary clinical knowledge or subject matter expertise with respect to a particular therapeutic class. All such requests must be made at least 21 calendar days before the P&T Committee meeting at which the class will be discussed.
    c. Requests for consideration of subject matter expert appointment may be sent by email to OHA.pharmacy@odhsoha.oregon.gov. Requests must identify the clinical topic under review and rational for why an ad hoc subject matter expert would be necessary to add to the P&T Committee.
    d. Ad hoc subject matter experts will have the same requirements, duties, and responsibilities as current P&T Committee members.
    e. Subject matter experts must be licensed and actively practicing in Oregon.

2. The subject matter experts shall have full voting rights with respect to the PDL drugs for which they have been selected and appointed including all utilization controls, prior authorization requirements, review of confidential pricing information or other conditions for the inclusion of a drug on the PDL. The subject matter experts may participate but may not vote in any other activities of the committee during the meeting.

3. P&T Committee staff also may engage relevant health care professionals with clinical specialty to review evidence summary documents prepared for the P&T Committee, in addition to the ad hoc subject matter experts, if needed.

CONDUCT OF MEETINGS:

1. All meetings and notice of meetings will be held in compliance with the Oregon Public Meetings Law.

2. The P&T Committee will elect a Chairperson and Vice Chairperson to conduct the meetings. Elections shall be held the first meeting of the calendar year.

3. Quorum consists of 6 permanent members of the P&T Committee. Quorum is required for any official vote or action to take place throughout a meeting.

4. All official actions must be taken by a public vote. Any recommendation from the Committee requires an affirmative vote of a majority of the Committee members.

5. The committee shall meet in executive session for purposes of reviewing the prescribing or dispensing practices of individual prescribers or pharmacists; reviewing profiles of individual patients; and reviewing confidential drug or select non-drug items pricing information to inform the recommendations regarding inclusion of drugs on the Practitioner-Managed Prescription Drug Plan (PMPDP) or any preferred drug or select non-drug items lists adopted by the OHA.

6. Meetings will be held at least quarterly but the Committee may be asked to convene up to monthly by the call of the OHA Director or a majority of the members of the Committee. DUR programs will be the focus of the meeting quarterly.

7. Agenda items for which there are no recommended changes based on the clinical evidence may be included in a consent agenda.

    a. Items listed under the consent agenda will be approved by a single motion without separate discussion. If separate discussion is desired, that item will be removed from the consent agenda and placed on the regular business agenda.
    b. Consent agenda items may include (but are not limited to) meeting minutes, drug class literature scans, and abbreviated drug reviews for unfunded conditions.

8. The Oregon Health Authority and P&T Committee are committed to creating a public meeting environment that is inclusive, welcoming, and respectful for all P&T Committee members, staff, and public attendees. Some general guidance and expectations for respectful meeting conduct include:
    a. Attendees of any P&T Committee meeting are expected to behave in a professional, honest, and ethical manner.
    b. Abusive, aggressive, and disrespectful language or behavior is not welcome at meetings. Staff have the authority to mute meeting participants or remove them from the meeting if they engage in this behavior.
    c. If you have a concern regarding your experience during a meeting, please help staff create an inclusive environment by sharing your experience, concerns, and feedback. Feedback can be submitted to osupharm.di@oregonstate.edu.

CONFLICT OF INTEREST POLICY:

The P&T Committee will function in a way that ensures the objectivity and credibility of its recommendations.

1. All potential initial committee members, staff members and consultants, future applicants, expert or peer reviewers, and ad-hoc subject matter experts selected for individual P&T Committee meetings are subject to the Conflict of Interest disclosure requirements in ORS Chapter 244 and are required to submit a completed disclosure form as part of the appointment process and annually during their appointment. Any changes in status must be updated promptly.

2. Staff members are required to have no financial conflicts related to any pharmaceutical industry business for duration of work on P&T projects.

3. All disclosed conflicts will be considered before an offer of appointment is made.

4. If any material conflict of interest is not disclosed by a member of the P&T Committee on his or her application or prior to participation in consideration of an affected drug or drug class or other action of the Committee, that person will not be able to participate in voting decisions of the affected drug or drug class and may be subject to dismissal. Circumstances in which conflicts of interest not fully disclosed for peer reviewers, ad-hoc experts, or persons providing public comment will be addressed on a case by case basis.

5. Any person providing public testimony are also requested to disclose all conflicts of interest including, but not limited to, industry funded research prior to any testimony pertaining to issues before the P&T Committee. This includes any relationships or activities which could be perceived to have influenced, or that would give the appearance of potentially influencing testimony.

PUBLIC COMMENT:

1. The P&T Committee meetings will be open to the public.

2. The P&T Committee shall provide appropriate opportunity for public testimony at each meeting.

    a. Testimony can be submitted in writing or provided in-person. Persons planning to provide oral testimony during the meeting are requested to sign up and submit a conflict of interest form no later than 24 hours prior to the start of the meeting.

    b. Maximum of 3 minutes per speaker/institution per agenda item

        i. Information that is most helpful to the Committee is evidence-based and comparative research, limited to new information not already being reviewed by the Committee.
        ii. Oral presentation of information from FDA-approved labeling (i.e., Prescribing Information or "package insert") is not helpful to the Committee.

    c. Please address written testimony related to final posted documents to the P&T Committee. Interested parties may submit written testimony on agenda items being considered by the P&T committee through the public comment link found on the P&T Committee website: (https://pharmacy.oregonstate.edu/research/drug-use-research-management/oregon-pt-committee/public-comment). Written testimony that includes clinical information should be submitted at least 2 weeks prior to the scheduled meeting to allow staff and Committee members time to review the information.

    d. Written documents provided during scheduled public testimony time of P&T Committee meetings will be limited to 2 pages of new information that was not included in previous reviews. Prescribing Information is not considered new information; only clinically relevant changes made to Prescribing Information should be submitted.

    e. If committee members have additional questions or request input from public members during deliberations after the public comment period, members of the public may be recognized at the discretion of the committee chair to answer questions of the committee or provide additional commentary.

3. Written public comment is welcome from all interested parties on draft documents posted prior to the meeting.
    a. Written public comments submitted during the draft comment period are only considered by staff in order to prepare final documents. Only written public comment submitted based on final documents will be submitted to the P&T Committee for consideration.
    b. Interested parties may submit written testimony on posted draft documents through the public comment link found on the P&T Committee website: (https://pharmacy.oregonstate.edu/drug-policy/meetings).

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug and drug class reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the PDL and clinical prior authorization criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices. For detailed description of review standards, preferred sources of evidence, and evidence grading methods, see Quality Assessment Tool and Evidence Grading Methods.

2. Final documents as outlined in Chapter 414 of the Oregon Revised Statutes shall be made publicly available at least 30 days prior to review by the P&T Committee. Posted documents will include the agenda for the meeting, a list of drug classes to be considered, and background materials and supporting documentation which have been provided to committee members with respect to drugs and drug classes that are before the committee for review.

DRUG AND DRUG CLASS REVIEWS:

1. Drug Class Reviews, ~~and~~ New Drug Evaluations, and Orphan Drug Evaluations:
    a. The P&T Committee will review drugs and drug classes that have not been previously reviewed for PDL inclusion or for clinical PA criteria and will be prioritized based on:
        i. Potential benefit or risk
        ii. Use or potential use in covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.
    b. The P&T Committee will make a reasonable effort to perform a timely review of new FDA-approved drug products following their market release, when they are a new molecular entity and are candidates for coverage under the pharmacy benefit.
        i. Until new drugs are reviewed by the P&T Committee, drugs meeting the following criteria will be reviewed to ensure they are used appropriately for an FDA-approved or compendia-supported indication, with FDA-approved dosing, and that the indication is funded by the OHP:
            a. A new drug in a drug class with clinical prior authorization criteria.
            b. A new drug used for a non-funded condition on the HERC Prioritized List of Health Services.
            c. A new drug not in a PDL class with existing PA criteria identified by the reviewing pharmacist during the weekly claim processing drug file load costing more than $5,000 per claim or $5,000 per month.
    c. Line Extension and Combination Product Policy for existing drugs or active ingredients
        i. Line extensions include new strengths or new formulations of an existing drug.
            1. When a new strength or formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply until the new strength or formulation is presented to the P&T Committee for review.
            2. If a new strength or formulation becomes available for an existing preferred drug and the new product significantly differs from the existing medication in clinical uses or cost, the drug will not be preferred until the drug is reviewed by the P&T Committee.
        ii. When a new combination product becomes available that is a formulation of one or more drugs that have been reviewed for the PDL, the product will be designated a non-preferred drug until the P&T Committee reviews the combination product.
        iii. When a product becomes available that is a biosimilar for one or more drugs that have been reviewed for the PDL, where applicable, the product will be designated a non-preferred drug until the P&T Committee reviews the product. A complete list of biological products and biosimilar products can be accessed at the FDA's Purple Book website.

iv. Over-the-counter (OTC) formulations:
    1. When a product becomes available that is an over-the-counter formulation, the product will be added to the fee-for-service (FFS) benefit if it falls within an existing PDL class previously reviewed by P&T. The policy outlined above for line extensions will apply. Exceptions to the standard rebate process will be determined by the Oregon Health Authority on a case-by-case basis based on access, availability, and affordability.
    2. If OTC formulations that are not in an existing PDL class or are not in a drug category currently on the OTC list, then the product will be designated as not covered until the P&T Committee reviews the product.

2. Drug Class Literature Scans and Abbreviated Drug Reviews:

    a. Literature of drug classes that have previously been reviewed for the PDL will be scanned and evaluated as needed to assess the need to update drug policies based on clinically relevant information and significant changes in costs published since the last review.
    ~~b. Abbreviated drug reviews will evaluate drugs for unfunded conditions. Evidence supporting these reports is derived primarily from information in the product labeling.~~

3. Non-drug Items Review:
    a. The P&T Committee will review non-drug items at the request of the OHA.
    b. Coverage decisions including recommendations for coverage, utilization management controls and inclusion of preferred products will be prioritized based on:
        i. Potential benefit or risk to patients and/or health and social care system
        ii. Use or potential use in the covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. Pragmatic usability details (e.g., user experience)
        vi. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.
    c. Evidence evaluation will follow similar methods as medication reviews with a focus on high-quality and comparative evidence that evaluates clinically relevant outcomes.

ProDUR Report for January through March 2026
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	3	2	0	1	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,144	502	0	1,641	1.1%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	9,505	2,565	3	6,933	5.1%	N/A
ER (Early Refill)	**Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)**	**Set alert/Deny claim**	**114,808**	**22,784**	**85**	**91,938**	**61.7%**	**19.8%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	44,135	11,309	0	32,795	23.7%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	921	190	0	731	0.5%	N/A
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	2	2	0	0	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	809	231	0	578	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	448	154	0	294	0.2%	N/A
PA (Drug/Age Precaution)	Products containing Codeine being billed and patient is less than 18 years of age	Set alert/Pay claim	6	1	0	5	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**181**	**74**	**0**	**107**	**0.1%**	**40.9%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	12,835	3,826	0	9,006	6.9%	N/A
		Totals	**185,797**					

ProDUR Report for January through March 2026
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	9,071	1,658	7,413	89,961	10.0%	18.3%
ER	Lexapro (Escitalopram)	6,657	1,120	5,536	67,019	9.9%	16.8%
ER	Prozac (Fluoxetine)	6,708	1,225	5,483	70,597	9.4%	18.3%
ER	Celexa (Citalopram)	1,818	287	1,531	20,293	8.9%	15.8%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	10,408	1,737	8,671	106,657	9.7%	16.7%
ER	Trazodone	7,937	1,573	6,364	80,464	9.8%	19.8%
ER	Cymbalta (Duloxetine)	5,539	997	4,542	53,480	10.3%	18.0%
ER	Effexor (Venlafaxine)	2,940	504	2,436	30,256	9.7%	17.1%
ER	Remeron (Mirtazapine)	2,606	492	2,114	21,388	12.2%	18.9%
ER	Elavil (Amitriptyline)	1,603	303	1,300	17,627	9.0%	18.9%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	5,575	1,323	4,252	39,105	14.2%	23.7%
ER	Abilify (Aripiprazole)	4,730	879	3,851	36,392	12.9%	18.6%
ER	Zyprexa (Olanzapine)	3,356	847	2,509	23,957	14.0%	25.2%
ER	Risperdal (Risperidone)	2,304	582	1,722	15,494	14.8%	25.3%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	4,744	827	3,917	46,380	10.2%	17.4%
ER	Lorazepam	231	68	163	12,994	1.7%	29.4%
ER	Alprazolam	161	40	121	7,611	2.1%	24.8%
ER	Diazepam	98	28	70	4,615	2.0%	28.6%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	7,926	1,467	6,459	60,725	13.0%	18.5%
ER	Intuniv (Guanfacine ER)	2,699	392	2,307	22,921	11.7%	14.5%
ER	Depakote (Divalproex)	1,780	493	1,287	13,058	13.6%	27.7%
ER	Suboxone (Buprenorphine/Naloxone)	86	32	54	1,647	5.2%	37.2%

ProDUR Report for January through March 2026
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC- Other
ER	January	4,977	99	284	733	5	3,572	24	2	258
ER	February	4,856	101	240	750	2	3,443	19	5	296
ER	March	5,792	125	341	825	12	4,175	29	5	280
	Total	**15,625**	**325**	**865**	**2,308**	**19**	**11,190**	**72**	**12**	**834**
	Percentage of Total Overrides		**2.1%**	**5.5%**	**14.8%**	**0.1%**	**71.6%**	**0.5%**	**0.1%**	**5.3%**

ProDUR Report for January through March 2026			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
January	DC	3	$180.67
	DD	33	$5,028.64
	ER	269	$62,714.60
	ID	35	$10,245.26
	MC	2	$91.99
	MX	5	$2,153.74
	TD	8	$3,955.89
	January Total	**355**	**$84,370.79**
February	DD	45	$7,493.77
	ER	297	$101,399.79
	HD	3	$441.26
	ID	51	$9,669.27
	LR	1	$309.63
	MC	2	$1,001.38
	TD	10	$2,657.87
	February Total	**409**	**$122,972.97**
March	DC	1	$21.69
	DD	36	$10,720.05
	ER	33	$8,313.31
	ID	10	$677.52
	March Total	**80**	**$19,732.57**
	Total 1Q2026 Savings		**$227,076.33**

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Billing Correction Review	High Cost OCC 3	Total Patients Identified	66	67	11	
		Total Claims Identified	66	70	11	
		Claims reviewed	15	3		
		Estimated Savings	$0	$0		
	OCC 4 with OCC 2 for different NDC	Total Patients Identified	7	13	1	
		Total Claims Identified	7	14	1	
		Claims reviewed	1	2		
		Estimated Savings	$0	$0		
	OCC 4 with OCC 2 for the same NDC	Total Patients Identified	6	12		
		Total Claims Identified	7	13		
		Claims reviewed	2			
		Estimated Savings	$0			
	OCC 4 with Primary Payer Rejection Code	Total Patients Identified	8	6		
		Total Claims Identified	9	6		
		Claims reviewed	3	2		
		Estimated Savings	$0	$0		

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	23	29	2	
		Unique Patients Identified	24	29	2	
		Total Faxes Successfully Sent	20	20		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	9	8		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$5,189	$1,209		
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	132	138	6	
		Unique Patients Identified	138	142	6	
		Total Faxes Successfully Sent	105	108	5	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	55	51		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$34,175	$19,574		

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	965	981		
		High risk patients identified	4	9		
		Prescribers successfully notified	4	7		
		Patients with continued antipsychotic therapy in the following 90 days	4	6		

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	32	74	8	
		Total prescribers identified	31	74	8	
		Prescribers successfully notified	31	72		
		Patients with claims for the same antipsychotic within the next 90 days	12	26		
		Patients with claims for a different antipsychotic within the next 90 days	2			

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	65	55		
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	24	29		
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	150	325		
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	37	27		
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	28	13		
		Letters Sent To Providers	19	6		
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	28	25		
		Letters Sent To Providers	29	27		
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	26	23		
		Letters Sent To Providers	10	11		
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	26	23		
		Letters Sent To Providers	8	8		
	Lock-In	RetroDUR Profiles Reviewed	7	7		
		Locked In	0	0		

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Antipsychotics for ages <=5 years	Patients identified with an ending PA	34	29	2	
		Total prescribers identified	32	29	2	
		Prescribers successfully notified	25	25		
		Patients with paid claims within next 60 days	19	20		
		Patients with denied claim within next 60 days	26	13		

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	53	114	14	
		Total prescribers identified	53	114	14	
		Prescribers successfully notified	52	114		
		Patients with discontinuation of therapy within next 90 days	13	40	14	
		Patients with new prescription for naloxone within next 90 days	5	4		
		Average number of sedative drugs dispensed within next 90 days	17	10	0	
		Average number of sedative prescribers writing prescriptions in next 90 days	17	10	0	
	Oncology Denials	Total patients identified	1			
		Total prescribers identified	1			
		Prescribers successfully notified	1			
	TCAs in Children	TCA Denials in Children	23	27	4	
		Total patients identified	6	14	1	
		Total prescribers identified	6	14	1	
		Prescribers successfully notified	3	9		
		Patients with claims for a TCA within the next 90 days	3	2		

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Respiratory Syncytial Virus (RSV) Prevention Update

Amanda Timmons, Oregon Immunization Program, Oregon Health Authority

In September 2024, this publication featured a comprehensive review of available immunizations for respiratory syncytial virus (RSV) . Since that time, the landscape has shifted considerably. This update summarizes current immunization recommendations from the Advisory Committee on Immunization Practices and available products as shown in **Table 1**.

Background

RSV causes infections of the lungs and respiratory tract. RSV is endemic in the United States (U.S.), with most children being infected before their second birthday. In adults and healthy older children, RSV presents like other upper respiratory infections, with runny nose, coughing and congestion. In very young infants it can present as irritability, decreased activity and breathing difficulties. It can be difficult to distinguish from other common viral infections such as influenza and COVID-19. RSV demonstrates significant seasonality. The Centers for Disease Control and Prevention (CDC) has traditionally described RSV season onset as the first of two consecutive weeks during which the mean percentage of specimens testing positive for RSV antigen is ≥10% or the mean percentage of specimens testing positive by polymerase chain reaction (PCR) ≥3%, whichever occurs first. Offset is the week before PCR testing falls to below 3%.

RSV tends to appear first in the Southeastern U.S. during the late summer or early fall, then moves to the West Coast later in the season.[1] In 2024, Oregon met RSV season onset criteria Dec. 21, and the season lasted until April 26, 2025. Oregon provides publicly available surveillance data at https://public.tableau.com/app/profile/oregon.public.health.division.acute.and.communicable.disease.pre/viz/OregonsRespiratoryVirusData/TestPositivity, and providers can register to receive Oregon Health Authority's (OHA) weekly RSV Surveillance Report at https://public.govdelivery.com/accounts/ORHA/signup/38395. Given Oregon's atypical seasonality, the Oregon Health Authority (OHA) recommends using local epidemiology to guide RSV immunizations and sends alerts to local health care providers when administration of RSV products is recommended to begin and end.

Severity of RSV is influenced by many factors. Infants younger than 12 months, particularly premature infants, adults over age 65, people with chronic heart or lung disease, and those with weakened immune systems are at greatest risk of severe disease.[2] OHA conducts year round population-based surveillance for laboratory-confirmed hospitalizations associated with RSV in Clackamas, Multnomah, and Washington Counties. In the 2024-2025 season, there were 466 hospitalizations, of which 158 occurred in children under 5 years of age and 162 were in adults 65 years of age or older. The cumulative hospitalization rate for last season is 25.7 per 100,000 people.[3]

To protect newborns, either maternal vaccination or infant immunization are recommended by the CDC, American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. Because these products provide comparable protection, most infants do not require both.

FDA Approved Products for RSV

Maternal vaccination with ABRYSVO[4], a recombinant vaccine containing RSV preF A and RSV preF B proteins, is available and is recommended to be administered between 32 and 36 weeks gestation during September through January or based on local epidemiology. Vaccination is recommended at the beginning of the 3rd trimester since it takes about 2 weeks for an immunized person to develop antibodies. Vaccination during pregnancy results in passive immunization of infants through transplacental antibody transfer, with protection lasting about 6 months.[5]

Monoclonal Antibodies

Infants whose mothers were not vaccinated during pregnancy or whose mothers were vaccinated fewer than 14 days before giving birth can receive one of two available monoclonal antibody (mAb) products—nirsevimab (BEYFORTUS)[6] or clesrovimab (ENFLONSIA)[7]. Both nirsevimab and clesrovimab are F protein-directed fusion inhibitors indicated for RSV prevention.

Dosing differs by product; nirsevimab dosing is weight-based, while clesrovimab is a single, fixed dose regardless of infant weight. Nirsevimab is also recommended for children ages 8-19 months at increased risk for severe RSV disease entering their second RSV season, including infants with chronic lung disease or prematurity who required medical support during the six months preceding the RSV season; severe immunocompromise; cystic fibrosis with manifestations of

severe lung disease or weight-for-length < 10th percentile; and all American Indian and Alaska Native children.
Palivizumab (SYNAGIS) has been voluntarily withdrawn by the manufacturer in favor of the newer single dose products and will no longer be available after December 31, 2025.

Current CDC recommendations are to administer RSV mAb products during October through March or based on local epidemiology. Clinicians should immunize infants within one week of birth for infants born during the RSV season. Monoclonal antibody products should not be administered to infants with a history of serious hypersensitivity reactions to the product or its excipients. Clesrovimab and Nirsevimab are generally well tolerated, with up to 4% of immunized infants experiencing local redness or swelling at the injection site and up to 3% experiencing a rash within 14 days of administration.

In clinical trials, Clesrovimab reduced medically-attended lower respiratory tract infections by 60% in the first 150 days. Efficacy against hospitalization was 90%.[7]

Vaccines

For adults, three different RSV vaccines (ABRYSVO[4], AREXVY[8], and mRESVIA[9]) are available and are recommended for all adults ages 75 and older, as well as adults ages 50-74 at increased risk for severe RSV, including those with chronic cardiovascular disease, chronic lung disease, end-stage renal disease, diabetes mellitus with complications, neurologic and neuromuscular conditions, chronic liver disease, chronic hematologic conditions, severe obesity, and moderate to severe immune compromise.[10] Clinical trial data show that each vaccine provides meaningful protection for two RSV seasons, with protection falling in the second year. Currently, there is no recommendation for revaccination and there is no preference for one brand over another. Additional surveillance and evaluation activities are ongoing to determine whether adults might benefit from receiving additional RSV vaccine doses in the future.[10]

Table 1. FDA-Approved Products for RSV

Drug	FDA-approved populations	Recommended populations	Dosing
Nirsevimab[6]* (Beyfortus)	Infants born during or entering their first RSV season; children < 2 years of age at increased risk for severe RSV disease	All infants < age 8 months born during or entering their first RSV season; children ages 8-19 months at increased risk for severe RSV disease	50 mg/0.5 mL for infants < 5 kg, 100 mg/1.0 mL for infants ≥ 5 kg, IM; 200 mg (2 x 100 mg injections) for children ages 8-19 months, IM
Clesrovimab[7]* (Enflonsia)	Infants born during or entering their first RSV season	All infants < age 8 months born during or entering their first RSV season	105 mg/0.7 mL regardless of weight, IM
Palivizumab (Synagis)	Discontinued effective 12/31/2025		
Abrysvo (bivalent, recombinant vaccine)	Pregnant individuals at 32-36 weeks gestational age; all people ≥ age 60; ages 18-59 at increased risk for severe RSV disease	Pregnant individuals at 32-36 weeks gestational age; all people ≥ age 75; ages 50-74 years at increased risk for severe RSV disease	0.5 mL, IM
Arexvy (adjuvanted, recombinant vaccine)	All people ≥ age 60; ages 50-59 at increased risk for severe RSV disease	All people ≥ age 75; ages 50-74 years at increased risk for severe RSV disease	0.5 mL, IM
mResvia (mRNA vaccine)	All people ≥ age 60; ages 18-59 at increased risk for severe RSV disease	All people ≥ age 75; ages 50-74 at increased risk for severe RSV disease	0.5 mL, IM

Abbreviations: IM = intramuscular; mL = milliliter; RSV = respiratory syncytial virus.
Key: * Monoclonal antibody

Contraindications, Precautions, and Adverse Events

Clesrovimab and nirsevimab are contraindicated in infants and children with a history of serious hypersensitivity reactions to a previous dose or any product excipients. The most common side effects include rash and injection site erythema and swelling. In clinical trials, adverse events were similar in recipients and controls.[6,7]

RSV vaccination is contraindicated in individuals with a history of severe hypersensitivity reactions to any component or excipient present in the product.

Pre-licensure clinical trials identified a small number of Guillain-Barre syndrome (GBS) in older participants that received ABRYSVO and AREXVY. Post licensure safety data evaluated risk in the 42 days after vaccination with a control period (days 43-90 postvaccination). Initial analysis did not demonstrate an increased risk of GBS associated with RSV vaccination but an elevated GBS risk could not be ruled out. Additional analyses will be conducted that includes review of medical records.[10]

Coverage of RSV Products

Both Clesrovimab and Nirsevimab are available to enrolled clinics through the Vaccines for Children program for eligible children. Children who are on the Oregon Health Plan, who are uninsured, or who are of Native American or Alaskan Native descent may receive the product at no cost. A vaccine administration fee not to exceed $21.96 per dose may be billed.

Insurance plans subject to the provisions of the Affordable Care Act should provide first dollar coverage for both monoclonal antibodies and RSV vaccines for eligible populations.

Medicare provides vaccine coverage through Medicare Advantage plans or through part D.

Conclusion

With multiple effective products available, many severe RSV infections are now preventable. Infants should receive protection, either through maternal immunization with ABRYSVO vaccine, or with a dose of mAb given at the beginning of their first RSV season. Children who continue to be at high risk may also receive a dose of nirsevimab at the beginning of their second RSV season.

High-risk adults over 50 years of age may receive a single dose of any of the three FDA-approved RSV vaccines. However, since coverage wanes over time and additional doses are not currently recommended, individual risk should be discussed with the patient when determining vaccination timing.

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Evaluating the Quality of Evidence from Observational Studies: Lessons from Acetaminophen Use in Pregnancy

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Observational studies are a valuable component of medical evidence, particularly when randomized controlled trials (RCTs) are not feasible. In fields such as obstetrics, where studies involving pregnant women would be unethical, much of what we know about medication safety arises from observational data. However, observational study conclusions depend heavily on how well the investigators control for study design factors, and even the best designed observation studies carry inherent bias.

The recent attention on the safety of acetaminophen (APAP) use during pregnancy provides a valuable example for examining these issues. There are numerous observational cohort and case-control studies investigating possible links between maternal APAP use and childhood neurodevelopmental disorders (NDDs), such as attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Some studies found a possible association, while others found no association. The discrepancies between them illustrate the importance of understanding the limitations of what can be inferred by observational studies.

This newsletter describes key factors to determining the quality of observational evidence, such as study design, confounding control, exposure assessment (i.e., documentation of treatment administration), and outcome measurement to assist readers in critically evaluating observational studies.

Background

Observational studies, also called epidemiological studies, are when researchers observe the effect of a treatment or other intervention without influencing the exposure to treatment.[1] Different types of observational study designs and their characteristics are described in **Table 1**.

Table 1. Observational Study Designs*[1,2]

Study Design	Measures of Association	Design Advantages	Design Disadvantages
Case Report or case series	Unable to calculate	Identify new disease or adverse events and hypothesis generation	Unable to calculate rates , risk or measure association
Cross-sectional	Point prevalence or odds ratio	Quick and inexpensive	Temporal association cannot be established
Case-control	Odds ratio	Study of rare outcomes and less expensive and faster than cohort	Not practical for study of rare exposure to treatment
Cohort	Relative risk, odds ratio or hazard ratio	Study of rare exposures and temporal association most clearly delineated. Direct estimates of risk and incidence can be calculated High risk of recall bias	Not as practical for study of rare outcomes. Increased cost and length
***Data are collected retrospectively except for cohort studies which can collect data prospectively and retrospectively.**			

Retrospective studies are those where data are collected from the past, either through medical records or by asking participants to recall their treatments or outcomes.[3] Retrospective studies cannot demonstrate temporality (e.g., relating to the sequence of time or to a particular time) as accurately and are more prone to several biases, particularly recall bias.[1] However, with the widespread use of electronic health records (EHR) the use of existing electronic data is more common, which minimizes the concern of temporality in case-control studies. Temporality is required to establish causation; however, temporality alone is not sufficient to demonstrate causality. Prospective studies recruit and follow participants forward through time, collecting data in the process. Prospective studies are less prone to some types of biases and can more easily demonstrate that the treatment preceded an outcome, thereby more strongly suggesting causation.[1]

1. Study Design and Cohort Selection

The strength of the conclusion derived from an observational study is dependent upon its design and methods.[3] A cohort selection follows a specific group of people based on a shared characteristic.[1] Cohort studies can be prospective and follow participants over time to assess outcomes after treatment exposure, while case-control studies are always retrospective and compare exposure history between those with and without an outcome.[2] How data are collected, how participants are

selected, and how the data are analyzed all influence study validity.

Determining the characteristics of the population studied is an important component of study design. Clearly defined eligibility criteria that is representative of the target population reduces variability (i.e., heterogeneity) so that stronger conclusions can be drawn. Many observational studies of maternal APAP use failed to produce reliable results because participants taking APAP also had higher rates of infections, depression, and chronic pain compared to non-users. It is important to note that observational studies allow for extrapolation of findings to a more general population which may be excluded from traditional RCTs.

Example: The Danish National Birth Cohort study followed 64,322 women during pregnancy and 6 months after pregnancy from 1996-2002 to research if there was an association with APAP use with fetal brain development.[4] Eligibility criteria was clearly defined enrolling only those with single births, complete records of APAP use, and documentation of measured major confounders. The study evaluated exposure rates in a broad general population, increasing applicability.

Takeaway: High quality observational studies are those that use large, prospective analysis of patients with similar characteristics (e.g., well designed eligibility criteria) to decrease bias and enhance the credibility of the results.

2. Implications of Recall Bias

Recall bias is under a larger umbrella of "information bias" which focuses on the accuracy with which data are collected, how they are interpreted and recorded, and how they are identified by the researchers. Study participants may be asked to recall medication timing, dosing and other administration details in retrospective observational studies, such as case-control designs. This type of design lends itself to recall bias, as participants often fail to remember specifics around therapies that were taken in the past.[3] Participants who had a negative outcome, such as a child developing autism, may be more likely to remember details around medication administration and even overreport use compared to those who did not have a negative experience.

Example: A 2021 study was conducted in a population-based cohort of more than 73,000 mother-child pairs across six European countries.[5] APAP use was determined through maternal questionnaires or interviews conducted prenatally and up to 18 months after birth.

The large sample size and multicenter design strengthen applicability; however, recall bias is a limitation in this example. Relying on self-reporting of exposure months or even years earlier can bias findings towards mothers who had children with developmental issues. Recall bias may influence results by magnifying apparent associations.

This study did minimize recall bias by collecting

Takeaway: When evaluating the effect of recall bias in an observational study, consider whether the exposure data were collected prospectively and assess the timeframe of recall that was utilized in studies with a retrospective design. Assess if exposure information is drawn from surveys or medical records as well as the completeness of medical records for the exposure under investigation.

3.The Effect of Confounding

A confounder is a variable associated with both the exposure and the outcome, which may create a distorted relationship.[3] Observational trials lack randomization, which can cause groups to differ for known as well as unknown factors, making cause and effect difficult to determine and subject to confounding. For example, in the studies of APAP use in pregnancy, the presence of a fever may increase the chance a mother takes acetaminophen. The fever itself may increase the risk of an NDD. Confounding can lead to false associations or mask real ones.[3] Statistical adjustments like multivariable regression help but rarely eliminate all confounding, especially for unmeasured variables.

Example: The US Nurses' Health Study II minimized confounding by employing a negative control exposure (NCE) design.[6] Negative control exposure evaluates residual confounding in observational studies, which is a treatment that is not causally related to the outcome but is affected by the same confounding factor as the exposure of interest (APAP).[6] This study prospectively evaluated APAP use in mothers that had children (n=8,856) born between 1993-2005.[6] This approach compared mothers who used APAP during pregnancy to those who used it before or after pregnancy. The NCE method helps to detect whether observed associations might be due to shared maternal factors rather than the exposure itself. The study found that in-pregnancy exposure to APAP, but not pre- or post-pregnancy use APAP, was modestly associated with ADHD (hazard ratio [HR] 1.34; 95% CI, 1.05–1.72).[6]

An additional example of limiting unmeasured cofounding is illustrated in a sibling control analysis. A sibling control analysis provides higher quality observational data that adjust for potential confounders (genetics, maternal health factors, acetaminophen dosage, etc.) by holding the mother constant.

Example: A nationwide cohort study in Sweden utilized a sibling control.[7] The study evaluated the association of APAP use in pregnancy and risk of ASD, ADHD, and intellectual disability.[7] The study concluded that APAP was not associated with ASD, ADHD, or intellectual disability (HR 0.85 to 0.88; p>0.05 for low, medium and high dose comparisons).[7]

Takeaway: Controlling for confounders is an important part of observational research. Uncontrolled confounders that are not measured or adjusted for can result in conclusions that are not reliable. Even observational data that controls for confounders can result in contradictory results as illustrated between the US Nurses' Health Study II and the cohort study in Sweden.

4. Exposure Assessment: Accuracy and Timing of Measurement

Another important component of observational research is how the exposure to treatment is measured. Details on how the study precisely captures when, how much, and for how long participants were exposed to the medication being studied can influence the conclusions.

Example: In the Boston Birth Cohort study, plasma biomarkers of APAP were measured in 996 mother–infant pairs between 1998 and 2018.[8] Because exposure was confirmed by biologic samples rather than maternal recall, this design reduces recall bias substantially. The researchers found a weak association between higher biomarker levels and an increased risk of developmental diagnoses such as ADHD and ASD.[8]

Takeaway: When evaluating an observational study determine if medication use was self-reported or objectively measured, how often it was assessed, and whether timing and dosage were recorded with sufficient accuracy to support conclusions.

However, even biomarker studies have limitations. A single plasma measurement represents only recent or short-term use, not the full exposure window during pregnancy. Therefore, while exposure misclassification is lower, temporal precision (which trimester, how often, at what dosage) remains imperfect. Confounders may still be present complicating interpretation of findings.

5. Outcome Measurement and Diagnostic Validity

A major determinant of study quality is how outcomes are defined and verified. Developmental disorders such as ADHD and ASD are behaviorally defined disorders that rely on diagnostic criteria which has changed over time and may vary between studies and provider assessments.

Example: The Danish National Birth Cohort followed children for seven years and assessed ADHD using parental reports, medication data, and clinical diagnoses.[4] While this strengthens outcome verification, it still introduces variability. Some parents may seek diagnoses more readily, or clinicians may differ in diagnostic thresholds.

In contrast, the evaluation of the US Nurses' Health Study II used validated diagnostic instruments and a NCE analysis to strengthen confidence in ADHD and ASD classification.[6] Quality of the data is still subject to accurate medical record linkage, consistent diagnosis coding criteria, and similar follow-up durations across groups.

Takeaway: Outcomes need to be clearly defined; validated diagnostic tools should be used and consistent follow-up time frames applied to avoid selection bias.

Additional Considerations

Beyond study design and cohort selection, several other key factors must be considered when evaluating the quality of observational studies. These factors determine whether findings are valid, reproducible, and potentially associated. **Table 2** highlights other potential limitations that should be considered. Limitations of observational studies can impact the study conclusions to a small or large extent.

Additionally, single studies should rarely be relied on to draw strong conclusions. Critical appraisal of the literature, regardless of study type, is needed to determine the degree of bias. Evaluating observational studies requires assessment of strengths and weaknesses to determine the causality. Adding what is already known from other studies and combining it with new data on a topic is important in clinical decision making. Observational studies provide value by contributing in this way.

Table 2. Limitations of Observational Studies[3]

Limitation	Explanation
Selection Bias	Occurs when participants selected for the study are different from those not included in ways related to exposure to the treatment and outcome.
Reverse Causation	Unclear if the exposure to treatment caused the outcome or the outcome influenced the exposure.
Residual Confounding	Unmeasured or poorly measured variables can distort results even after adjusting for measured confounders.
Observer and Reporting Bias	Investigators or participants may influence data collection or reporting.
Publication Bias	Studies with positive or significant results are more likely to be published than null findings.

Conclusion

Observational studies vary by design and methods, and these differences influence their inherent biases, confounding, and validity. Observational studies can identify potential associations but cannot establish causality. A body of evidence is needed, despite the study design, to determine causality. Additionally, associations between an exposure and an outcome should not be concluded by one study alone; multiple studies across different populations should be considered when making such assessments.[1] Use shared decision making with patients after discussing potential benefits and risks of therapies, especially when only observational evidence is available.

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Drug Class Update with New Drug Evaluation: Type II Topoisomerase Inhibitors

Date of Review: June 2026

Date of Last Review: August 2025
Dates of Literature Search: 06/01/2025 - 02/13/2026

Generic Name: Zoliflodacin

Brand Name (Manufacturer): Nuzolvence® (Innoviva Specialty Therapeutics, Inc.)
Dossier Received: no

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

Purpose for Class Update:
To create a new preferred drug list (PDL) class for the type II topoisomerase inhibitor drugs, to evaluate new evidence published since the last review done in August of 2025 and present and evaluate the evidence for the new drug, zoliflodacin.

Plain Language Summary:
- There is a new class of antibiotics called type II toperisomerase inhibitors. There are two antibiotics in this class, gepotidacin and zoliflodacin.
- Gepotidacin is used to treat urinary tract infections, also called bladder infections, and an infection due to sexually transmitted bacteria, called gonorrhea.
- Zoliflodacin is used to treat gonorrhea infections. It is taken by mouth and is taken as one single dose.
- The Centers for Disease Control and Prevention (CDC) recommend an injectable antibiotic called ceftriaxone as the first option for treatment for gonorrhea. Ceftriaxone is injected in the muscle or administered in the vein as one-time single dose.
- Guidelines recommend the antibiotics nitrofurantoin, trimethoprim-sulfamethoxazole (TMP/SMX), fosfomycin or pivmecillinam to be tried initially for the treatment of urinary tract infections.
- Providers are asked to prescribe antibiotics that are on the preferred drug list (PDL) if it is a good choice for the patient. If a provider prescribes a non-preferred antibiotic, they must explain to the Oregon Health Authority why the patient needs that medicine before Oregon Health Plan will pay for it. This is called prior authorization. The Drug Use Research and Management (DURM) group recommends keeping gepotidacin and zoliflodacin as non-preferred so antibiotics recommended by guidelines are tried first.

Research Questions:
1. What is the evidence for efficacy for the type II topoisomerase inhibitors for uncomplicated urinary tract infection (uUTI) and uncomplicated gonorrhea infections?
2. What is the evidence for the safety of the new drugs for uUTI and uncomplicated gonorrhea infections?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender, disease severity), for whom type II topoisomerase inhibitors are more effective or associated with less harm?

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4. What is the comparative safety and efficacy of zoliflodacin for the treatment of urogenital uncomplicated gonorrhea infections?

Conclusions:

- Type II topoisomerase inhibitors are a new class of antibiotics that are oral options for patients with severe allergies to b-lactams. Gepotidacin is approved for uUTI and uncomplicated gonorrhea and zoliflodacin is approved for uncomplicated gonorrhea treatment. For the treatment of gonorrhea, the option of an oral agent versus intramuscular injection.
- Evidence identified for this review includes one high quality guideline, one randomized clinical trial (RCT), one updated indication and one new drug update.
- The European Association of Urology (EAU) updated guidance on the treatment of urological infections in 2025.[1] The type II topoisomerase inhibitors were not approved for use before guideline publication. The guidelines recommend first line treatment for uUTI with pivmecillinam, fosfomycin trometamol or nitrofurantoin.[1]
- Gepotidacin was approved for the additional indication to treat uncomplicated urogenital gonorrhea caused by *Neisseria gonorrhoeae (N. gonorrhoeae)* in adult and pediatric patients 12 years of age and older in December of 2025.[2] Approval was based on one noninferiority RCT comparing gepotidacin to ceftriaxone plus azithromycin (first line treatment recommendation at trial initiation) in which gepotidacin was found to be noninferior to the comparator regimen.[2]
- There was low quality evidence that a newly approved type II topoisomerase inhibitor, zoliflodacin, was noninferior to ceftriaxone plus azithromycin in an open-label, noninferiority RCT comparing single dose treatment for uncomplicated urogenital gonorrhea.[3] The primary outcome was microbiological cure rate at test-of-cure (TOC) day 6 (treatment difference [TD] -5.3%; 95% confidence interval [CI], 1.4 to 8.6).[3] Both treatments were well tolerated and there were no serious adverse events.

Recommendations:

- No changes to the PDL are recommended based on the review of the evidence for the use of type II topoisomerase inhibitors. Nonpreferred antibiotics are subject to the non-preferred prior authorization (PA) criteria.
- Maintain zoliflodacin as nonpreferred.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Gepotidacin was evaluated in August of 2025 for the treatment of uUTI. The P&T Committee voted to keep it nonpreferred on the PDL.

Background:

Urinary tract infections (UTIs) are common infections, affecting more women than in men.[1] The incidence of UTI is at least one infection per year in 10-20% of adult women in the United States (US). Urinary tract infections are designated as uncomplicated or complicated based on infection location. Uncomplicated infections are confined to the bladder and occur in healthy, non-pregnant women or men.[1] A complicated UTI is a systemic infection extending beyond the bladder to the kidneys (e.g., pyelonephritis). The European Association of Urology (EAU) has recommended new nomenclature for the definitions of UTI which are localized (i.e., cystitis without any signs of systemic infection in either sex) and systemic UTI (i.e., an infection with signs and symptoms of systemic infection with or without localized symptoms that may originate from any site in the urinary tract of either sex, including pyelonephritis and prostatitis).[1]

Patients presenting with uUTI are most often treated empirically. Most uUTIs are caused by *Escherichia coli* (*E. coli*), accounting for approximately 75%-95% of infections.[4] Less common bacteria associated with uUTIs are *Proteus mirabilis* (*P. mirabilis*), *Klebsiella pneumonia* (*K. pneumonia*) and *Staphylococcus saprophyticus* (*S. saprophyticus*).[4] Resistant uropathogens are more commonly seen in women 50 years and older, patients with recurrent uUTI, and patients with diabetes.[5] The most recent guidelines from the Infectious Disease Society of America (IDSA), published in 2011, recommend treatment options for women based on resistance patterns and the likely causative organisms.[4] Patient allergy, compliance, availability and cost should be considered. Empirical treatment of uUTI recommended by the EAU are nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) , trimethoprim-sulfamethoxazole (TMP/SMX) (160/800 mg twice daily for 3 days), fosfomycin (3 gm single dose) or pivmecillinam (400 mg twice daily for 5 days).[4] The 2025 EAU guidelines recommend that TMP/SMX only be used empirically if resistance rates in the area of use are <20% for *E. coli*.[1] Fluoroquinolones (i.e., ofloxacin, ciprofloxacin and levofloxacin) can be considered as an option but are associated with adverse events and resistance. In 2016 the Food and Drug Administration (FDA) issued a Safety Announcement advising against the use of fluoroquinolones for uUTIs in people that have other treatment options, due to the serious side effects associated with their use (i.e., tendon rupture, peripheral neuropathy and central nervous system effects).[6] Guidance by the EAU enacted stringent regulatory actions recommending against the use of fluoroquinolones due to disabling and long-lasting adverse events associated with use.[1] The EAU guidance recommends fluoroquinolones only be used when it is inappropriate to use other antibiotics. Beta-lactam antibiotics (e.g., amoxicillin/clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil) may also be considered as alternatives, with consideration of high *E. coli* resistance rates with these medications. Resistance rates seen with TMP/SMX are approximately 25%, followed by approximately 21% being fluoroquinolone resistant. Beta-lactam antibiotics can have resistant rates up to 15% in the US.[1]

Type II topoisomerase inhibitors are also used to treat gonorrhea infections. Gonorrhea is a common sexually transmitted infection (STI) with an estimated US prevalence of over 600,000 cases reported in 2023.[7] Gonorrhea is diagnosed most often in adolescents and young adults equally in men and women and more commonly in Black/African American populations.[7] Antibiotic therapy is always indicated for patients diagnosed with gonorrhea, as complications and transmission to others may occur if not appropriately treated. Gonorrhea has developed resistance to many types of antibiotics (i.e., azithromycin, tetracycline and ciprofloxacin). The 2021 CDC guidance on STIs recommends ceftriaxone, 500 mg intramuscular (IM) or intravenous (IV) for those 150 kg or less and 1 g IM or IV if the patient is 150 kg or more, as first-line empiric therapy for uncomplicated gonorrhea with cefixime as a second-line option.[8] Recommendations by Canada's Drug Agency also state that ceftriaxone therapies have the most evidence for the treatment of uncomplicated gonorrhea but additional comparative evidence is needed.[9]

Type II topoisomerase inhibitors are a new class of antibiotics used for the treatment of uUTIs and gonorrhea, in which there are two approved therapies, gepotidacin and zoliflodacin. Gepotidacin is approved to treat uUTIs and uncomplicated urogenital gonorrhea in adults and pediatric patients.[10] Zoliflodacin is approved for the treatment of uncomplicated urogenital gonorrhea in adults and pediatric patients.[11]

Important outcomes in the study of uUTI are resolution of symptoms and microbiological cure to prevent the progression of the infection to pyelonephritis. The FDA requires therapeutic success to be based on combined clinical success (i.e., symptom resolution) and microbiological success (i.e., reduction of qualifying uropathogens to $<10^3$ CFU/mL).[12] Microbiological cure, 7-14 days after treatment, and prevention of complications are important outcomes in treatment of gonorrhea.[13]

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, Canada's Drug Agency (CDA-AMA), 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, no systematic reviews met inclusion criteria 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:

EAU – Urological Infections 2025
The EAU 2025 Guidelines provide updated recommendations for the use of antibiotics for urological infections.[1] Recommendations pertaining to antibiotic use will be presented. Type II topoisomerase inhibitors were not approved at the time of guideline publication and therefore were not included in the publication. Evidence is graded from 1a (Highest Quality of Evidence) to 4 (Expert Opinion). Antibiotic selection should be guided by spectrum and susceptibility patterns, efficacy, tolerability, adverse reactions, costs and availability. Strength of recommendations range from Strong to Weak and are presented in **Table 1**. Cystitis is considered localized (i.e., no systemic infection in either sex) or systemic (i.e., pyelonephritis, prostatitis, etc.).[1] Oral cephalosporins are not recommended for empiric therapy for cystitis due to risk of adverse effects on the environment (i.e., creating highly resistant organisms) and aminopenicillins are not recommended due to high resistance rates and increased selection for Extended-Spectrum Beta-Lactamase (ESBL)-producing bacteria, but both can be used in select cases (Strong recommendation).[1] Fluoroquinolones should not be used unless it is considered inappropriate to use other antibiotics.

Table 1. EAU Antibiotic Recommendations for People with Urological Infections[1]

Diagnosis	Antibiotic Recommendation	Comments / Strength of Recommendation
Cystitis	Pivmecillinam 400 mg three times daily for 3-5 days	• First-line option in women / Strong
	Fosfomycin trometamol 3 g as a single dose	• First-line option in women / Strong
	Nitrofurantoin monohydrate/macrocrystal or nitrofurantoin macrocrystal prolonged release 100 mg twice daily for 5 days	• First-line option in women / Strong
	TMP/SMX 160/800 mg twice daily for 3 days or trimethoprim alone 200 mg twice daily for 5 days	• Alternative option • First choice only in areas with known resistance rates for *E.coli* of <20%
	Cephalosporins (e.g. cefadroxil 500 mg twice daily for 3 days)	• Other comparable cephalosporins can be used
	TMP/SMX or fluoroquinolone for at least 7 days	• First-line in men due to risk of prostate involvement

Cystitis in Pregnancy	Penicillins, cephalosporins, fosfomycin, nitrofurantoin, trimethoprim and sulfonamides can be considered	• Check for patient allergies • Trimethoprim should not be used in the first trimester of pregnancy and TMP/SMX is not recommended in the last trimester of pregnancy
Prevention of Recurrent Cystitis	- Nitrofurantoin 50 mg or 100 mg once daily - Fosfomycin trometamol 3 g once a week - Trimethoprim 100 mg once daily	• No evidence of statistically significant difference in efficacy between antibiotics for recurrent cystitis
	- Cephalexin 125 or 250 mg once daily - Cefaclor 250 mg once daily	• Recommended for pregnant women with cystitis
Pyelonephritis (outpatient)	- Fluoroquinolones (i.e., ciprofloxacin, levofloxacin) - Cephalosporins (i.e., cefpodoxime, ceftibuten) - TMP/SMX	• Fluoroquinolones are first-line / Strong • Only classes recommended for oral empirical therapy • If any class is used besides a fluoroquinolone, an initial intravenous dose of long-acting parenteral antimicrobial (e.g., ceftriaxone) should be used
Urethritis	Ceftriaxone and azithromycin for genitourinary urethritis	• Recommended first-line / Level 2a • Use nucleic acid amplification test (NAAT) to guide treatment
	- Ceftriaxone 1-2 gm intramuscular or intravenously as a single dose - Doxycycline 100 mg twice daily for 7 days	• For gonococcal infections
	Doxycycline 100 mg twice daily for 7 days	• For non-gonococcal infections (e.g., *Chlamydia trachomatis*)
	Azithromycin 1 gm day one and 500 mg days 2-4	• For *Mycoplasma genitalium*
	Doxycycline 100 mg twice daily for 7 days	• For *Ureaplasma urealyticum*
	Metronidazole 1.5-2 gm as a single dose	• For *Trichomonas vaginalis*
Acute Bacterial Prostatitis	Fluoroquinolone for 4-6 weeks	• First-line for empirical treatment
	Doxycycline 100 mg twice daily for 10 days	• Only for *C. trachomatis* or mycoplasma infections
	Azithromycin 500 mg once daily for up to 3 weeks	• Only for *C. trachomatis*
	Metronidazole 500 mg three times daily for 14 days	• Only for *T. vaginalis*
Chronic Bacterial Prostatitis	Fluoroquinolone	• First-line / Strong
	Doxycycline	• Only for *C. trachomatis*
	Macrolide	• If intra-cellular bacteria / Strong
	Metronidazole	• For *Trichomonas vaginalis* / Strong
Abbreviation: TMP/SMX – trimethoprim/sulfamethoxazole		

New Indications:

Gepotidacin (BLUJEPA): In December of 2025 gepotidacin was approved for the additional indication of the treatment of uncomplicated urogenital gonorrhea caused by *N. gonorrhoeae* in adult and pediatric patients 12 years of age and older and weighing at least 45 kilograms.[10] Prior to this expanded indication, gepotidacin was only approved to treat uUTI. The dose is different than the dose used for uUTI. Gepotidacin should be given as 3,000 mg (four 750 mg tablets) orally for one dose followed 12 hours later by a second dose of 3,000 mg (four 750 mg tablets).[10] Approval was based off of one, open-label, noninferiority, randomized trial comparing gepotidacin to ceftriaxone 500 mg IM in combination with a single 1 gram oral dose of azithromycin (**Table 2**).[2] Microbiological success was similar in the gepotidacin group (92.6%) and the ceftriaxone/azithromycin group (91.2%) (TD -0.1%; 95% CI, -5.6 to 5.5).[2]

New FDA Safety Alerts:

None identified.

Randomized Controlled Trials:

A total of 57 citations were manually reviewed from the initial literature search. After further review, 56 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 trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Ross, et al[2] (EAGLE-1) NI, OL, Phase 3, RCT	Gepotidacin as 2 doses (3,000 mg given 10-12 hours apart) Vs. Ceftriaxone 500 mg IM and azithromycin 1g orally for one dose	Ages 12 years and older, body weight of 45 kg or more, suspected uncomplicated urogenital gonorrhea or positive lab test for *N. gonorrhoeae* or both	Microbiological success (culture-confirmed bacterial eradication at test-of-cure days 4-8)	Gepotidacin: 92.6% Ceftriaxone /azithromycin: 91.2% TD -0.1% (95% CI, -5.6 to 5.5) noninferiority margin met	- Majority of participants were male (92%) and MSM (71%). - Mean age was 33.1 years a range of 17-64 years. There was no breakdown of number of pediatric patients - Patients from the US comprised only 14% of the participants. Other sites included United Kingdom, Spain, Germany, Austria and Mexico (all areas of relatively low to moderate resistance) - Mild-moderate GI AE seen in gepotidacin group more than comparator

Abbreviations: AE = adverse events; CI = confidence interval; GI = gastrointestinal; IM = intramuscular; MSM = men who have sex with men; NI = noninferiority; OL = open label; RCT = randomized controlled trial; TD = treatment difference.

NEW DRUG EVALUATION: NUZOLVENCE (zoliflodacin)

Zoliflodacin is indicated for the treatment of uncomplicated urogenital gonorrhea due to *N. gonorrhoeae* in adults and pediatric patients who are least 12 years old and weight a least 35 pounds.[11] Zoliflodacin works by inhibiting spiropyrimidinestrione bacterial type II topoisomerase. Zoliflodacin is given as a suspension that should be mixed with water and given within 15 minutes of mixing.[11] The recommended dose is 3 g (one packet) given as a single oral dose for adult and pediatric patients. Patients that weigh 35 kg to up to 50 kg should take zoliflodacin on an empty stomach and those who weigh 50 kg or more should take zoliflodacin with food.[11] Mixing zoliflodacin with other liquids or sprinkling on foods should not be done.

See **Appendix 4** 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. Pharmacology and pharmacokinetic properties are listed in **Appendix 5**.

Clinical Efficacy:

Approval of zoliflodacin is based off one open-label, noninferiority RCT (**Table 3**).[2] Patients with signs and symptoms of urogenital gonorrhea, a positive test confirming urogenital gonorrhea within the preceding 14 days or a history of unprotected sex with a partner with confirmed *N. gonorrhoeae* infection were included. Patients were randomized 2:1 to zoliflodacin 3 gm dose (n=621) or ceftriaxone 500 mg IM plus a single oral 1 gm dose of azithromycin (n=309).[3] The mean age was 30 years old with a range of 16-73 years. There were 14 patients under the age of 18 years included in the study.[3] Patients from the US represented 17% of the population. Analysis was done on the microbiological intention-to-treat urogenital population. Patients with baseline antibiotic susceptibility testing showing no preexisting resistance to both ceftriaxone and azithromycin were included in the primary endpoint analysis.[3] Sites of gonorrhea infection were from the following regions: urogenital (80%), rectal (12%) and pharyngeal (9%).[3] Baseline isolate resistance to azithromycin (6-11%), ciprofloxacin (75-86%) and tetracycline (92-100%) were similar across anatomical sites. Only one patient had a baseline isolate resistant to ceftriaxone. The primary outcome was proportion of patients with microbiological cure at the urogenital site assessed at TOC visit on day 6 (±2 days).[3] Microbiological cure was defined as negative or indeterminate *N. gonorrhoeae* culture. The noninferiority margin was less than 12% for the upper bound of the two-sided 95% CI, which is higher than the 10% noninferiority margin recommended by the FDA.[14] Participants were followed up to day 30.

Microbiological TOC rates in the microbiological intent to treat (ITT) population were 90.9% in the zoliflodacin group and 96.2% in the comparator group (TD 5.3%; 95% CI, 1.4 to 8.6) groups, which met the noninferiority margin.[3] Secondary analysis of the per protocol population found 96% of patients taking zoliflodacin cured and 99.5% of the comparator group cured (TD 3.5%; 95% 1.0 to 5.8).[3] Efficacy of zoliflodacin at other sites besides urogenital were not powered to determine efficacy; however, cure rates were similar between rectal and pharyngeal sites.

Limitations to the study include the open-label design in which providers and patients were not blinded to treatment. The use of an objective primary outcome, such as microbiological cure, helps to minimize bias; however, other outcomes such as adverse events may be subject to bias. Most of the patients were male from areas with high prevalence of gonorrhea infections which may reduce the external validity to other populations.

Clinical Safety:

The most common adverse events with zoliflodacin use, occurring in 2% or more of the study population, were headache, neutropenia, leukopenia, dizziness, nausea and diarrhea.[11] Most adverse events were mild to moderate and there were no serious adverse events. Animal studies have demonstrated embryo-fetal

toxicity and zoliflodacin use should be avoided during pregnancy.[11] Potential embryo-fetal toxicity related to males with female partners of reproductive potential has been identified and contraception should be advised for at least 3 months after administration of zoliflodacin.[11] Zoliflodacin has also been associated with a potential to cause testicular toxicity and impair male fertility based on animal studies.[11] Plasma concentrations of zoliflodacin may be reduced when used with other moderate or strong CYP3A4 inducers so concomitant use is not recommended.

Zoliflodacin has not been studied beyond a single dose and patients were only followed for 30 days after use. Additional safety studies are needed on repeated dosing and long-term use.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Microbiological eradication
2) Symptom improvement
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Microbiological cure

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. Luckey, et al [3] NI, OL, Phase 3, RCT	1. Zoliflodacin 3 g orally as a single dose 2. Ceftriaxone 500 mg IM plus azithromycin 1 g orally as a single dose	Demographics: Mean age: 29.7 years Younger than 18 years: 14 (2%) Male: 88% African American: 55% White: 12% HIV positive: 22% US participants: 158 (17%) Key Inclusion Criteria: - 12 years of age and older - Signs and symptoms of urethral or endocervical gonorrhea - Positive lab test confirming urogenital gonorrhea in the preceding 14 days or history of unprotected	ITT: 1. 621 2. 309 Microbiological ITT: 1. 506 2. 238 PP: 1. 434 2. 218 Attrition: 1. 50 (9%) 2. 24 (11%)	Primary Endpoint: Proportion of patients with microbiological cure on day 6* in the microbiological ITT population: 1.460 (90.9%) 2.229 (96.2%) TD 5.3% (95% CI, 1.4 to 8.6) non-inferiority margin set at 12% or less and was met Secondary Endpoints: Proportion of patients with microbiological cure on day 6 in the per protocol population*: 1. 434 (96%) 2. 218 (99.5%) TD 3.5% (95% CI, 1.0 to 5.8)	NA	Headache: 1. 61 (10%) 2. 14 (5%) Neutropenia: 1. 42 (7%) 2. 24 (8%) Leukopenia: 1. 24 (4%) 2. 7 (2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Computer-generated random numbers and treatment allocation via a web-based randomization system. Randomized 2:1. Baseline characteristics were similar between groups. Performance Bias: (high) Treatment assignment was known to participant and clinical trial site personnel. Detection Bias: (low) Microbiology staff was blinded to treatment allocation. Attrition Bias: (low) Low amount of attrition and similar between groups. Per protocol population is preferred for non-inferiority trials. Reporting Bias: (low) The study was conducted as outlined in the methods. Other Bias: (unclear) The study was funded by several ministries of health and public health organizations. Many of the authors had conflicts of interest with industry. **Applicability**:

		sexual contact in the preceding 14 days with a partner with confirmed *N. gonorrhoeae* Key Exclusion Criteria: - Systemic or intravaginal antibiotic with activity against *N. gonorrhoeae* - Pregnant - Breastfeeding						Patient: Study results are most applicable to male participants who are diagnosed with urogenital gonorrhea and from areas of high gonorrhea activity and less commonly from the US. Patients were not resistant to ceftriaxone or azithromycin at baseline. Intervention: The combination of ceftriaxone and azithromycin was formerly a recommended treatment of choice but has fallen out of favor due to rising azithromycin resistance. Comparator: Dose of zoliflodacin was based off phase 2 trials. Outcomes: Microbiological cure is an appropriate primary outcome. Setting: Seventeen outpatient clinics in Belgium, the Netherlands, South Africa, Thailand, and the US.
Key: *Determined by eradication of Neisseria gonorrhoeae via urethral or endocervical cure at test-of-cure date (day 6 ± 2) Abbreviations: ARR = absolute risk reduction; CI = confidence interval; g = grams; HIV = human immunodeficiency virus; IM = intramuscular; ITT = intention to treat; mg = milligrams; N = number of subjects; NA = not applicable; NI = non-inferiority; NNT = number needed to treat; OL = open-label; PP = per protocol; RCT = randomized controlled trial; TD = treatment difference; US = United States								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
gepotidacin mesylate	BLUJEPA	TABLET	N
zoliflodacin	NUZOLVENCE	ORAL SUSP	

Appendix 2: Abstracts of Comparative Clinical Trials

Oral gepotidacin for the treatment of uncomplicated urogenital gonorrhoea (EAGLE-1): a phase 3 randomised, open-label, non-inferiority, multicentre study
Jonathan D C Ross, Janet Wilson, Kimberly A Workowski, et al

Background: Gepotidacin, a first-in-class, bactericidal, triazaacenaphthylene antibacterial that inhibits bacterial DNA replication, was shown to be efficacious and well tolerated in the treatment of uncomplicated urinary tract infections. We evaluated the efficacy and safety of gepotidacin for the treatment of uncomplicated urogenital gonorrhoea.
Methods: EAGLE-1 (NCT04010539) was a phase 3, open-label, sponsor-blinded, multicentre, non-inferiority study evaluating oral gepotidacin (two 3000 mg doses administered 10-12 h apart) compared with 500 mg intramuscular ceftriaxone plus 1 g oral azithromycin for the treatment of gonorrhoea. Eligible participants were aged 12 years and older, had a bodyweight over 45 kg, and had suspected uncomplicated urogenital gonorrhoea (including mucopurulent discharge), a positive laboratory test for Neisseria gonorrhoeae, or both. Participants were randomly allocated in a 1:1 ratio to each treatment group, stratified by sex (original urogenital anatomy at birth) and sexual orientation (men who have sex with men [MSM], men who have sex with women [MSW], and female) in combination, and age group (age <18 years, ≥18 to 65 years, or >65 years). The primary efficacy endpoint was microbiological success, defined as culture-confirmed bacterial eradication of N gonorrhoeae from the urogenital body site at test-of-cure (days 4-8). The non-inferiority margin was prespecified at -10%. The primary outcome was assessed in the microbiological intention-to-treat (micro-ITT) population, all participants randomly allocated to a study treatment who received at least one dose of their study treatment and had confirmed ceftriaxone-susceptible N gonorrhoeae isolated from the baseline culture of their urogenital specimen. The safety population comprised all participants who received one or more doses of any study treatment.
Findings: Between Oct 21, 2019, and Oct 10, 2023, 628 participants were randomly allocated (314 allocated to each treatment group). Overall, 39 (6%) of 628 participants discontinued the study prematurely (20 in the gepotidacin group and 19 in the ceftriaxone plus azithromycin group), with the primary reason being lost to follow-up. The micro-ITT population included 406 participants (202 in the gepotidacin group and 204 in the ceftriaxone plus azithromycin group). Most participants in the micro-ITT population were male (372 [92%] vs 34 [8%] female), and there was a higher percentage of participants who were MSM (290 [71%]) compared with participants who were MSW (82 [20%]). Participants were predominantly White (299 [74%]) or Black or African American (61 [15%]), with 70 (17%) identifying as Hispanic or Latino. Results of the primary analysis of microbiological response at test-of-cure demonstrated microbiological success rates of 92·6% (187 of 202 [95% CI 88·0 to 95·8]) in the gepotidacin group and 91·2% (186 of 204 [86·4 to 94·7]) in the ceftriaxone plus azithromycin group (adjusted treatment difference -0·1% [95% CI -5·6 to 5·5]). Gepotidacin was non-inferior to ceftriaxone plus azithromycin. No bacterial persistence of urogenital N gonorrhoeae was observed at test-of-cure for either group. The gepotidacin group had higher rates of adverse events and drug-related adverse events, mainly due to gastrointestinal adverse events, and almost all were mild or moderate. No treatment-related severe or serious adverse events occurred in either group.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 13, 2026
Search Strategy:

#	Searches	Results
1	gepotidacin.mp.	123
2	zolifodacin.mp.	1
3	1 or 2	124
4	limit 3 to yr="2024 -Current"	57

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUZOLVENCE safely and effectively. See full prescribing information for NUZOLVENCE.

NUZOLVENCE® (zoliflodacin) for oral suspension
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
NUZOLVENCE is a spiropyrimidinetrione bacterial type II topoisomerase inhibitor indicated for the treatment of uncomplicated urogenital gonorrhea due to *Neisseria gonorrhoeae* in adults and pediatric patients 12 years of age and older, weighing at least 35 kg. (1.1)

Usage to Reduce Development of Drug-Resistant Bacteria
To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZOLVENCE and other antibacterial drugs, NUZOLVENCE should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Pregnancy Testing: Obtain a pregnancy test in females of reproductive potential prior to initiating NUZOLVENCE. (2.1)
- NUZOLVENCE must be mixed with water before administering. (2.2)
- Do **not** mix NUZOLVENCE with other liquids or sprinkle on food. (2.2)
- Administer the entire dose within 15 minutes of mixing. If the dose is not administered within 15 minutes of mixing, a new dose of NUZOLVENCE must be prepared. (2.2, 2.4)
- Adults and pediatric patients 12 years of age and older, weighing at least 35 kg: Recommended dose is 3 g (one packet) administered as a single dose orally. (2.3)
- Patients weighing 35 kg to less than 50 kg: Administer NUZOLVENCE on an empty stomach, 1 hour before or 2 hours after food. (2.3)
- Patients weighing greater than or equal to 50 kg: Administer NUZOLVENCE with food. (2.3)
- See full prescribing information for complete details on preparation and administration of NUZOLVENCE. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For oral suspension: 3 g of zoliflodacin in each unit-dose packet of NUZOLVENCE. (3)

----------CONTRAINDICATIONS----------
- Known history of hypersensitivity to NUZOLVENCE. (4)
- Concomitant use with moderate or strong CYP3A4 inducers because this is predicted to result in decreased plasma concentrations of zoliflodacin and may reduce NUZOLVENCE efficacy. (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------
- Embryo-Fetal Toxicity: Potential Risk for Pregnant Females: May cause fetal harm when administered during pregnancy based on data from animal studies. Advise pregnant females about the potential risk to the fetus with maternal exposure to NUZOLVENCE. Avoid use of NUZOLVENCE during pregnancy. (5.1, 8.1, 8.3)
- Embryo-Fetal Toxicity: Potential Risk Related to Males with Female Partners of Reproductive Potential: Advise males with female partners of reproductive potential to use effective contraception for at least 3 months after administration of NUZOLVENCE. (5.2, 8.3, 13.1)
- Testicular Toxicity and Risks to Male Fertility: May cause testicular toxicity and impair male fertility based on data from animal studies. An assessment of spermatogenesis has not been conducted in humans. Advise males of the potential risk. (5.3, 8.3, 13.1)
- Hypersensitivity Reactions: Hypersensitivity reactions, including rash and pruritus, have been reported in patients receiving NUZOLVENCE. Discontinue NUZOLVENCE and institute appropriate supportive measures, if an allergic reaction occurs. (5.4)
- *Clostridioides difficile* Infection: Evaluate if diarrhea occurs. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions including laboratory abnormalities (incidence ≥2%) with NUZOLVENCE are neutropenia, headache, leukopenia, dizziness, nausea, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Entasis Therapeutics, Inc. at 1-800-651-3861 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2025

Appendix 5. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Spiropyrimidinetrione bacterial type II topoisomerase inhibitor
Oral Bioavailability	High-fat meal increases AUC by 40%
Distribution and Protein Binding	Fasted: 177 L / Fed: 98.7 L Protein binding 83%
Elimination	Fecal
Half-Life	Fasted: 19.1 L / Fed 12.5 L
Metabolism	CYP-mediated (mostly CYP 3A4/5 enzymes, with lesser contributions from CYP1A2, CYP2C9, CYP2C8 and CYP2C19) and non-CYP mediated pathways

Abbreviations: AUC = area under the curve; CYP = cytochrome; L = liter

Appendix 6: Key Inclusion Criteria

Population	Patients with uncomplicated urinary tract infection or uncomplicated gonorrhea
Intervention	Type II topoisomerase inhibitors
Comparator	Placebo or active comparison
Outcomes	Microbiological cure and symptom improvement
Setting	Outpatient

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

Orphan Drug Evaluation: Zycubo (copper histidinate) powder for injection

Date of Review: June 2026
Generic Name: Copper histidinate

End Date of Literature Search: 3/31/26
Brand Name (Manufacturer): Zycubo (Sentynl Therapeutics)

Dossier Received: No

Purpose for Review:

- To review evidence of safety and effectiveness of copper histidinate injection for pediatric patients with Menkes disease.
- To establish prior authorization (PA) criteria to support medical appropriateness and necessity.
- The estimated wholesale acquisition cost (WAC) per member over 12 months is $681,455 to $1,362,910 based on $1867/2.9mg syringe copper histidinate (equivalent to 0.5 mg elemental copper). Dosing is 1.45 mg copper histidinate once or twice daily subcutaneously based on age. A reconstituted vial is stable when refrigerated at (36°F to 46°F) for up to 24 hours. Package insert instructs to discard unused portion after each use; do not administer more than one dose from the vial.[1]

Plain Language Summary:

- Menkes disease is a rare, inherited condition that occurs when the body cannot absorb enough copper or move copper properly to different places in the body. It affects mostly boys and is usually diagnosed in the first year of life.
- People with Menkes disease can have many symptoms, including seizures, delayed development. It usually causes death by three years of age. Occipital Horn Syndrome is a less severe version of this disease that does not usually cause symptoms until ages 5 to 10 years, and people with it may live past 50 years of age.
- In 2026, the Food and Drug Administration (FDA) approved copper histidinate injection (ZYCUBO) to treat children and adolescents with Menkes disease. It is not approved for Occipital Horn Syndrome.[1]
- In 66 people with Menkes disease who were treated with copper histidinate, survival over a 3-year period was better than when compared to historic records of patients who did not receive copper histidinate treatment. This was true for people who started treatment both before (early treatment) and after 4 weeks of age (late treatment).
- The Drug Use Research and Management group recommends that the Oregon Health Authority pay for copper histidinate injection in patients with Menkes disease who are receiving appropriate monitoring and dosing. The provider must document medical appropriateness through a process called prior authorization.

Research Questions:

1. What is the effectiveness and safety of copper histidinate injection for pediatric patients with Menkes disease?
2. Are there subpopulations based on age, symptom severity, or other demographics for which copper histidinate injection is more effective or safe?

Author: Sara Fletcher, PharmD, MPH, BCPS

Conclusions:

- There is low-quality data of improved survival from two pooled, open-label studies of copper histidinate treatment compared to historic controls in patients with Menkes disease. Survival in the early treatment group (N=31) where copper histidinate was started within 4 weeks of birth was 52% versus 12% in the historic control group (N=17) with a hazard ratio (HR) of 0.22 (95% confidence interval [CI] 0.10 to 0.49) at the end of treatment (up to 36 months). Survival in the late treatment group (N=35) where copper histidinate treatment was started later than 4 weeks after birth was 34% versus 12% in the historic control (N=16) with a HR of 0.27 (95% CI 0.12 to 0.57).[1,2]
- There is insufficient evidence for safety.[1] All data is from open-label, uncontrolled research. There is a theoretical concern for copper toxicity due to accumulation in certain organ systems over time, specifically kidneys, liver, and hematopoietic system and monitoring for toxicity is recommended in the package labeling.[1]
- There is insufficient evidence for use of copper histidinate in treating symptoms of Occipital Horn Syndrome.[1]

Recommendations:

- Implement PA criteria to verify appropriate diagnosis, monitoring and dosing.

Background:

- Menkes disease (MD) is an X-linked disorder associated with severe copper deficiency due to inadequate intestinal uptake.[2] MD is caused by *ATP7A* mutations, affecting transmembrane copper-transporting P-type ATPase in enterocytes and across the blood-brain barrier.[2,3] Extracellular efflux of copper is also affected by *ATP7A*, and accumulation is seen in all tissues except liver and brain.[2] There is some genotype-phenotype correlation for certain mutations, but it is difficult to predict phenotype perfectly from mutation type.[2,4]
- The disease is a progressive condition with primarily neurologic symptoms such as developmental delay and epilepsy. Bony abnormalities may also occur. Classical Menke (90% of cases) is usually fatal between age 6 months and 3 years.[2] Intermediate-phenotype Menke disease is generally milder with 5-10% prevalence within MD diagnosis. Patients can present similarly to classic disease or live to adulthood. Occipital Horn Syndrome (OHS), with prevalence of approximately 3% of MD cases and has the least severe presentation. Symptoms appear at age 5 to 10 years for patients with OHS. Patients with OHS have slightly low to normal levels of copper and ceruloplasmin, often have bony exostoses described as occipital horns on skull radiographs, and may live to be over 50 years old.[2]
- Copper histidinate is considered standard of care for MD, though no FDA approved product was available historically.[2]
- Incidence is estimated at 1:50,000 to 1:250,000 live male births.[2]
- Serum copper and ceruloplasmin concentrations are low in patients with MD. Ceruloplasmin is the most common copper-binding protein transporter. Healthy newborns may often have low copper and ceruloplasmin levels, making these assessments alone inadequate for diagnosis of MD.[2]
- Testing is not on the Oregon newborn screening panel.[5]
- In the Oregon Health Plan, there are 14 patients with the E83.09 diagnosis (other disorders of copper metabolism), which includes other diagnoses in addition to Menkes disease. Most of these identified patients are female and over age 18 years, making it unlikely that most of these patients have Menkes disease based on the demographics.

Drug Information

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 and Safety:

Clinical trials used to support FDA approval are described and evaluated below in **Table 1**. Noteworthy trial design and patient characteristics include:

- Trial duration: Treatment administered up to age of 1 year using twice daily dosing; after 1 year of age, dosing was decreased to once daily, for up to 3 years. Treatment duration ranged between 1.1 and 36 months.[1]
- Number of participants: 129 in the safety analysis (median exposure duration 24 months [range 1 to 39 months]) and 66 patients who met final inclusion criteria for MD who were treated and analyzed for efficacy.[1]
- Comparator: External control (historic) cohort collected under a protocol amendment.[2] Early treatment historic controls had no prior ZYCUBO or copper treatment, were asymptomatic for significant neurological signs and symptoms at approximately 4 weeks after birth, and survived at least 4 weeks after diagnosis.[1] Late treatment historic controls were a subset of the historic control-early treatment groups who were diagnosed with MD after 4 weeks since birth and survived at least 2 weeks after diagnosis.[2]
- Key inclusion criteria: Menkes disease with severe pathogenic variant of *ATP7A* gene (duplication/deletion, nonsense, or a canonical splice junction variant); born after 1999.[1] Inclusion criteria for both studies were changed via protocol amendments and originally included additional conditions (e.g. occipital horn syndrome, unexplained copper deficiency) as diagnosis criteria used only clinical features and biochemical profiles (study 0149) and low copper concentration (study 0059) resulting in larger safety population than the final efficacy population.[2] Patients in the historic control group were born during or after 2000, overlapping with the drug treatment population.[2]
- Key exclusion criteria: diagnosis of Wilson disease, any disease that may adversely affect gastrointestinal absorption, history of cerebrovascular accident, and chronic/severe cardiac disease.[1]
- Baseline disease severity and population characteristics: Most patients were male (98%), White (63%) and had premature birth (66-77% in treatment groups; 81-82% in historic controls).[1] The most common *ATP7A* mutation variant was nonsense (51.2%- 71%).[2]
- Setting: Majority of patients from United States (94.3-100% copper histidinate cohorts; 62.5-64.7% historic cohorts). Most remaining patients were from Europe.[2]
- Magnitude of benefit and clinical relevance of results: Both the early treatment (within 4 weeks of birth) and late treatment (after 4 weeks from birth) showed significant benefits compared to historic controls for overall survival and estimated median survival. The early treatment group (52%) and late treatment group (34%) survival was significantly improved over the historic controls (12% for both historic cohorts) at the end of the evaluation period.[1] Estimated median survival time was longer for both the early treatment group (177.1 months, 95% CI 33 to not estimable) compared to historic control (17.6 months, 95% CI 11.5 to 28.6), and for the late treatment group (62.4 months, 95% CI 29.6 to 80.7) compared to the historic control (20.7, 95% CI 12.6 to 28.6). [1]
- Safety signals: Due to the pathophysiology of MD with impaired copper transport throughout the body, patients with MD may have copper accumulation and organ impairment, particularly in the kidneys, liver, and hematopoietic system. It is anticipated the supplemental copper could increase accumulation and toxicity.[1] Risk may be higher for those under 2 years of age due to the immaturity of the hepatic and renal systems at that age.[1] Dose adjustment is not recommended based only on serum copper or ceruloplasmin, however, should be considered if other lab work indicate potential toxicity.[1] The FDA has recommended a post-marketing study to characterize the serum copper and ceruloplasmin concentrations in patients with MD.[2] Full adverse reaction table from package insert is summarized in **Table 2**.

- Subgroup analyses: FDA ran nine sensitivity analyses due to data discrepancies with censored dates (e.g., date of last contact), dates of death, gene variant status and documentation of gene variant status.[2] These analyses were performed to address issues with quality of the efficacy and safety data, clinical heterogeneity and lack of genotype-phenotype correlation, and comparability of the external control to the treated cohorts.[2] All of the sensitivity analyses demonstrated consistent survival benefit. [2]

See **Table 1** for major evidence limitations including:

- Full risk of bias assessment unable to be performed due to unpublished study and protocol. There is risk of selection bias of single arm study with protocol amendment to add historic control cohort. Lack of documentation of past medical history of external control subjects' onset of symptoms was noted, though survival data was considered verifiable. There was significant attrition overall and a large percentage for undescribed "other" reasons.

Table 1. Comparative Evidence Table.[1,2]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Trial 1 (0149) Phase 1/2 NCT00001262 Trial 2 (0059) Phase 3 NCT00811785 OL, SA, N=129 safety N=83	1. CuHis 1.45 mg SC Once daily if age 1 year and older Twice daily if under 1 year old Duration up to 3 years	Demographics: -Age-range 0 to 48 months -Male 98% -White 63% -Hispanic 13% -Black 10% -Premature birth 66-77% treatment groups, 81-82% control cohorts -Most common *ATP7A* variant nonsense (56.2-71.0%) Key Inclusion Criteria: -Menkes disease with -severe pathogenic variant of *ATP7A* (duplication/deletion, nonsense, or a canonical splice junction variant) -Born after 1999 Key Exclusion Criteria: -Pre-existing liver or kidney disease -History of bleeding diatheses	Cohorts CuHis-ET N=31 HC-ET N=17 CuHis-LT N=35 HC-LT N=16 Attrition: CuHis-ET 12/31 (38.7%) CuHis-LT 24/35 (68.6%)	Primary Endpoint: Survival of CuHis-ET versus HC-ET Patients alive # (%): CuHis-ET 16 (52%) HC-ET 2 (12%) Estimated Median survival time using Kaplan-Meier method (mo): CuHis-ET 177.1 (95% CI, 33 to NE) HC-ET 17.6 (95% CI, 11.5 to 28.6) HR 0.22 (95% CI, 0.1 to 0.49) Secondary Endpoint: Survival of CuHis-LT versus HC-LT Patients alive # (%): CuHis-LT 12 (34%) HC-LT 2 (12%) Estimated Median survival time using Kaplan-Meier method (mo): CuHis-LT 62.4 (95% CI, 29.6 to 80.7) HC-LT 20.7 (95% CI, 12.6 to 29.6) HR 0.27 (95% CI, 0.12 to 0.57) CuHis-LT 11 (34%) of patients survived > 6 years, 1 patient (2.9%) survived > 12 years. HC-LT no patient survived > 6 years	0.4/ 3 0.22/ 5	D/C due to AE: Cu-His ET 7 (22.6%) Cu-His LT 11 (31.4%) Cardiac (10.1% pooled) and respiratory, thoracic, & mediastinal (7% pooled) disorders most common cause for d/c	NA	**Studies are unpublished and full risk of bias assessment unable to be performed.** **Risk of Bias (low/high/unclear)**: Selection Bias: (High) Single arm study. Original study inclusion criteria narrowed for analysis as clinical features and low copper concentration are not adequate for MD diagnosis. Historic control cohort added via protocol amendment during second trial. Performance Bias: (Unclear) Methods not fully published, though primary outcome is objective. Potential differences in other care associated with study participation versus historic control. Detection Bias: (Unclear) Final efficacy outcome objective after protocol changes from other outcomes. Safety monitoring strategy unclear. Attrition Bias: (Unclear) Missing data noted in FDA summary. If death dates were unknown, patients were censored at the last known date alive. High rates of overall study discontinuation, with 12.9% (CuHis-ET) and 20.0% (CuHis-LT) due to "other" causes (not AE, withdrawal of consent, or LTFU). Reporting Bias: (Unclear) Study and protocol unpublished. Multiple protocol amendments as medical knowledge of the disease changed over time. Other Bias: (Unclear) Original sponsorship/research through NIH. First transferred to Cyprium Therapeutics, Inc. and later to Sentynl Therapeutics. **Applicability**:

		-Wilson disease -Disease affecting gastrointestinal absorption -Chronic/severe cardiac disease						Patient: Most patients are male, which is representative of disease population. Some racial diversity noted in study population. Intervention: Dose chosen based on 1989 case series of 4 patients, not clinical PK or dose ranging studies. Comparator: Historic controls with concerns for missing data. Outcomes: Survival is appropriate for progressive, fatal condition. Assessment of quality of life and neurological development/milestones would be useful. Setting: Almost all treatment patients were from the US; most historic controls were from the US or Europe.
Abbreviations: AE = adverse event; CI = confidence interval; CuHis = copper histidinate; D/C = discontinue; ET = early treatment; FDA = Food and Drug Administration; HC-ET = historic control early treatment; HC-LT = historic control-late treatment; HR = hazard ratio; LT = late treatment; LTFU = lost to follow up; MD = Menke disease mo = months; N = number of subjects; NA = not applicable; NE = not estimable; NIH = National Institutes of Health; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PK = pharmacokinetic; PP = per protocol; SA = single arm; SC = subcutaneously; US = United States.								

Table 2: Adverse Events occurring in at least 7% of Patients with Menkes Disease[1]

Adverse Events	Menkes Disease N=129 N (%)
Pneumonia	38 (30)
Viral Infection	35 (27)
Respiratory failure • Cardiopulmonary failure	30 (23) • 11 (9)
Seizure	29 (23)
Bacterial infection • Renal and urinary tract infection	26 (20) • 12 (9)
Hemorrhage	23 (18)
Hypotension	20 (16)
Vomiting	19 (15)
Tachycardia	16 (12)
Pyrexia	16 (12)
Volume depletion	16 (12)
Fracture	16 (12)
Dyspnea	16 (12)
Transaminases elevation	13 (10)
Diarrhea	13 (10)
Fungal infection	12 (9)
Anemia	11 (9)
Local administration reaction	9 (7)

References:

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4. De Feyter S, Beyens A, Callewaert B. ATP7A-related copper transport disorders: A systematic review and definition of the clinical subtypes. *Journal of Inherited Metabolic Disease*. 03 2023;46(2):163-173. doi:https://dx.doi.org/10.1002/jimd.12590
5. NW Regional Newborn Bloodspot Screening Program. Newborn Bloodspot Screening Practitioner's Manual, 16th Edition; 2026 Available at: https://www.oregon.gov/oha/PH/LABORATORYSERVICES/NEWBORNSCREENING/Documents/Practitioner%20Manual.pdf.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZYCUBO safely and effectively. See full prescribing information for ZYCUBO.

ZYCUBO® (copper histidinate) for injection, for subcutaneous use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
ZYCUBO is a copper replacement product indicated for the treatment of Menkes disease in pediatric patients. (1)

Limitations of Use
ZYCUBO is not indicated for the treatment of Occipital Horn Syndrome. (1)

----------DOSAGE AND ADMINISTRATION----------
- Before initiating ZYCUBO, obtain baseline serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count. (2.1)
- The recommended dosage of ZYCUBO in pediatric patients:
  - Less than 1 year of age is 1.45 mg twice daily (8-12 hours between injections). (2.2)
  - 1 year of age to less than 17 years of age is 1.45 mg once daily. (2.2)
- Monitor serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count (CBC). (2.3)
- Reconstitute ZYCUBO and administer subcutaneously. (2.4, 2.6)
- See Full Prescribing Information for additional preparation, storage, and administration instructions. (2.4, 2.5, 2.6)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection: 2.9 mg of copper histidinate (equivalent to 0.5 mg elemental copper) as a lyophilized powder or cake in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
Copper Accumulation and Risk of Toxicity: Treatment with ZYCUBO may lead to further copper accumulation and has the potential to result in drug-induced kidney injury, liver dysfunction, and hematological abnormalities. Monitor patients during ZYCUBO treatment. Adjust dosage if necessary. (2.2, 5.1, 6.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥7%) were pneumonia, viral infection, respiratory failure, seizure, bacterial infection, hemorrhage, hypotension, vomiting, tachycardia, pyrexia, volume depletion, fracture, dyspnea, transaminases elevation, diarrhea, fungal infection, anemia, and local administration reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sentynl Therapeutics, Inc. at 1-888-507-5206 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2026

Copper histidinate (ZYCUBO)

Goal(s):
- Promote appropriate use of copper histidinate based on available evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- Copper histidinate (ZYCUBO)

Covered Populations: FFS and CCO patients beginning 05/1/26 (pharmacy or 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.	
2. Is the request for a patient with a prior FFS approval for the requested drug?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved age and indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is patient both treatment naïve AND over 3 years of age?	**Yes**: Go to #5	**No:** Go to #6
5. Is there documentation that Occipital Horn Disease has been ruled out?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the drug prescribed by or in consultation with a specialist with experience treating Menkes disease (e.g., medical geneticist, pediatric neurologist)?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documentation of baseline lab work within past 3 months including: serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and complete blood count (CBC)?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested dose/interval appropriate based on FDA labeling?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there documentation of genetic testing indicating severe loss of function variant of *ATP7A* gene (mutation types: deletion/duplication, nonsense, or canonical splice junction variants)?	**Yes**: Pass to RPh; Pend. Refer to DMAP for secondary review. Approve based on age: < 12 months: enough units to reach 1st birthday with twice daily dosing; ≥ 12 months: approve for 6 months enough units for once daily dosing. Note: all vials are single use only.	**No:** Go to #10

Approval Criteria		
10. Is genetic testing pending?	**Yes**: Pass to RPh; Pend. Refer to DMAP for secondary review. Approve for one month while awaiting results. Dose based on age: < 12 months: twice daily dosing; ≥ 12 months: once daily dosing Note: all vials are single use only.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of appropriate laboratory monitoring based on labeling recommendations and current length of therapy? Note: product labeling recommends serum copper and ceruloplasmin levels, serum electrolytes, kidney and liver function, and CBC every 6 weeks for first 6 months, then every 3 months for 18 months, and then every 6 months thereafter while on treatment.	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is dosing interval appropriate based on FDA labeling and *current* age? Note: dosing should be adjusted to once daily after 1 year of age.	**Yes:** Pass to RPh; Pend. Refer to DMAP for secondary review. Approval duration: 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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Drug Class Update: Benzodiazepines for Catatonia

Date of Review: June 2026

Date of Last Review: March 2019
Dates of Literature Search: 1/1/2019 - 4/1/2026

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

Purpose for Class Update:
Evaluate new comparative evidence of benzodiazepines used in the treatment of catatonia.

Plain Language Summary:
- Catatonia is a condition that involves a lack of ability to control emotions, speech, and movement.
- Symptoms of catatonia may include reduced or absent speech, extreme lack of movement, refusal to move or respond to requests, unusual body positions held for long periods, repetitive movements or sounds, restlessness, and strange facial behaviors.
- Catatonia may be linked to brain chemical issues, genetics, abnormal immunity, and environmental factors.
- Periods of long immobility can lead to dehydration, malnutrition, muscle weakness, blood clots, and mood disorders.
- A class of medicines called benzodiazepines (especially lorazepam) are often used for short periods to treat catatonia.
- Rapid recognition and treatment are important to prevent complications and reduce risk of hospitalizations and death.
- The Drug Use Research and Management (DURM) group recommends that evidence-based and compendia-supported medicines for catatonia be available at higher doses if necessary for short term treatment (< 1 month) when prior authorization criteria is met.

Research Questions:
1. What is the comparative efficacy and effectiveness of benzodiazepines in the treatment of patients with catatonia?
2. What are the comparative harms of benzodiazepines in the treatment of patients with catatonia?
3. Are there subgroups of patients based on demographic characteristics (e.g., age, race, ethnicity, socioeconomic status), concurrent medications, comorbidities, or pregnancy for which there are differences in the benefits and harms of benzodiazepines used for the treatment of catatonia?

Conclusions:
- There were no clinically important differences between lorazepam and oxazepam for symptomatic improvement of catatonia in people with comorbid schizophrenia or other serious mental illnesses (1 study, N= 17; very low-quality evidence).[1]

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- There were no high-quality guidelines identified to provide recommendations for the treatment of people with catatonia. Guidelines based on lower quality evidence have recommended prompt, short-term (<1 month) treatment with lorazepam (occasionally necessary at higher than FDA-approved doses) and/or electroconvulsive therapy (ECT) as first-line therapy options.[2]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on clinical evidence. Evaluate costs in executive session.
- Update benzodiazepine prior authorization (PA) criteria to 1) align with current evidence for the treatment of catatonia and 2) minimize therapy interruptions for treatment of patients with conditions previously approved for long-term use. (**Appendix 1**).

Summary of Current Policy:

- Prior authorization is not required for short-term use (≤ 4 weeks) of benzodiazepines but is required for treatment durations exceeding 30 days use over the previous 120 days to help prevent inappropriate long-term benzodiazepine utilization. Authorization for long-term benzodiazepine use beyond 4 weeks depends upon indication, funding, and whether specific clinical requirements are met. Unfunded diagnoses are denied unless patient is eligible for EPSDT review. Long-term approvals of 6 months may be granted when all PA requirements are met. Longer approval periods of up to 12 months may be authorized for indications such as end-of-life/palliative care and seizure disorders. Shorter approval periods of up to 1 month are reserved for short-term, outpatient treatment of alcohol withdrawal.

Background:

Catatonia is a severe, debilitating neuropsychiatric syndrome that affects emotion, communication, and movement that exists across a wide range of psychiatric and medical conditions.[3] Patients with catatonia may present with a spectrum of clinical features such as stupor, catalepsy, waxy flexibility, and mutism.[4] Other symptoms such as repetitive behavioral symptoms (e.g. echolalia, echopraxia, etc.) may also be present in people with catatonia.[4] With more than 50 observable or elicited signs, the clinical features of catatonia have varying degrees of diagnostic utility.[5] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision **(**DSM-5-TR) lists 12 common catatonia features with descriptors (see **Table 1**) where 3 or more symptoms are considered indicative of catatonia**.**[6] Akinetic catatonia is the most common form of catatonia where the patient may be physically still and verbally non-responsive but is mentally aware of their surroundings.[5] In contrast, patients with excited catatonia display impulsive, agitated behaviors that can result in self-harm or harm to others.[4] A third type of catatonia known as malignant catatonia has been described as a hazardous, rapid onset catatonic state that creates autonomic instability, severe agitation, and delirium.[7] Often times various forms of malignant catatonia may be considered a medical emergency.[7] Catatonia symptoms may occur rapidly and last anywhere from a few hours to several weeks.[4] Although most cases are acute, some individuals may experience recurring episodes of catatonia.[4] Due to prolonged immobility, there is the potential for secondary complications such as dehydration, malnutrition, muscle wasting, and thrombosis/pulmonary embolism.[8] Therefore, prompt recognition and management of patients with catatonia is crucial to reduce risk of hospitalizations and mortality.[4,8]

Table 1. Diagnostic criteria for catatonia in DSM-5-TR (modified)[6]

Feature	Description
Stupor	No psychomotor activity; not actively relating to environment
Catalepsy	Passive induction of a posture held against gravity
Waxy flexibility	Slight, even resistance to positioning by examiner
Mutism	No, or very little, verbal response (excluded if known aphasia)

Negativism	Opposition or no response to instructions or external stimuli
Posturing	Spontaneous and active maintenance of a posture against gravity
Mannerism	Odd, circumstantial caricature of normal actions
Stereotypy	Repetitive, abnormally frequent, non-goal-directed movements
Agitation	Irritability not influenced by external stimuli
Grimacing	Involuntary facial muscle movements
Echolalia	Mimicking another's speech
Echopraxia	Mimicking another's movements

There are no known age or gender-related differences in the development of catatonia although prevalence may be higher in people with schizophrenia.[9] Catatonia may be associated with other underlying psychiatric or medical conditions as well.[9] It is estimated that up to 20% of acute psychiatric patients experience catatonia.[10-12] Catatonia secondary to mood disorders (e.g. depression, bipolar disorder), neurodevelopmental disorders (e.g. autism), infectious disease (e.g. viral or bacterial meningitis/encephalitis, HIV), environmental toxicities, or traumatic brain injury are commonly observed in neurology and intensive care unit settings.[13-15] Use of antipsychotics (typically first-generation) and rapid discontinuation of psychotropics such as benzodiazepines, gabapentin, and zolpidem have also been implicated in catatonia development.[14] When malignant catatonia arises from exposure to dopamine antagonists or abrupt discontinuation of dopamine agonists, notably with extreme hyperthermia (>100.4°F or >38.0°C) and diaphoresis, it is often referred to as neuroleptic malignant syndrome (NMS).[11]

There are numerous neurological, biological, and environmental factors that contribute to the development of catatonia.[16] Dysregulation of the glutamatergic and Gamma-aminobutyric acid (GABA)-related systems are linked to catatonia pathogenesis.[16] Both N-methyl-D-aspartate (NMDA) receptor antagonism and excitation-inhibition imbalance of GABA-related neurons are believed to cause abnormal neurotransmission resulting in abnormal motor function.[16] Genetic factors may also predispose an individual to catatonia development as observed in 22q11.2 deletion syndrome or in WKL1 gene mutations.[17] Recent findings of anti-NMDA receptor encephalitis have suggested that neuroinflammation from autoimmune involvement may play a significant role in catatonia symptom development.[17,18] Environmental stressors or trauma may also precipitate episodes of catatonia.[19]

Catatonia is associated with a wide range of serious health-related complications that arise from prolonged immobilization and autonomic dysfunction.[20] Besides physiological complications, there are potential psychological issues such as delirium that can worsen patient prognosis and necessitate careful management to reduce mortality risk.[21] Proper treatment of catatonia involves addressing the syndrome, any contributing conditions, and preventing complications.[20] Since catatonia is not a single, uniform illness with a fixed course, clinicians must plan for the potential of reoccurrence.[20] The standard of care for the management of catatonia is benzodiazepines with or without electroconvulsive therapy (ECT).[2] Benzodiazepines, notably lorazepam, are highly effective and produce rapid improvement of symptoms.[22] Acute catatonia may be treated with lorazepam given orally, sublingually, via intramuscular (IM) injection, or intravenously (IV).[2] Benzodiazepines are typically titrated over several days and given in divided daily doses.[2] Patients with catatonia may require doses higher than the suggested FDA labeling and titration should escalate until symptoms resolve or the lorazepam daily dose reaches 16 mg.[2] Generally, patients should experience positive effects within hours following treatment with lorazepam with complete resolution observed in 3-7 days.[2,14] ECT is also highly effective and can be especially useful as an add-on treatment or if benzodiazepines fail.[2] ECT should be used during the early signs of catatonia if the symptoms are severe or life-threatening or if there is malignancy noted.[2]

The assessment of catatonia in adults is generally performed through use of the Bush Francis Catatonia Rating Scale (BFCRS).[23] A modified form of the BFCRS called the Pediatric Catatonia Rating Scale (PCRS) has been used to assess catatonia in children and adolescents.[24] The BFCRS contains 23 items (e.g. excitement, immobility/stupor, mutism, etc.) and each section is rated on a 3-point symptom scale (0 = Absent; 1 = Occasional; 2 = Frequent; 3 = Constant) with 69 points possible.[23] All items are scored in order and if a symptom is not clearly observed then a score of 0 is given for the section.[23] It has been suggested that a clinically meaningful change for the BFCRS is between 4 and 6 points based on observational clinical studies but the minimal clinically important difference (MCID) has not been validated.[25,26] The PCRS is similar to the BFCRS in the 3-point rating scale, however, it contains 6 additional symptom screening questions (20 total) with a maximum possible score of 60.[24] The MCID for the PCRS is unclear. The Kanner Catatonia Rating Scale (KCRS) is another catatonia assessment tool used in clinical practice and is often used in conjunction with the BFCRS.[27] The emphasis of the KCRS is on patients with intellectual or developmental disabilities or who may be nonverbal.[27,28] It is a 2-part assessment that both identifies and quantifies catatonic signs.[27,28] Part 1 of the KCRS functions as a screening tool and Part 2 establishes symptom severity.[27,28] The KCRS tool has 18 questions with 144 points possible (higher scores = greater severity of symptoms) but no MCID threshold has been reported. [27,28] Catatonia may also be assessed with the Northoff Catatonia Rating Scale (NCRS).[28] The NCRS contains a 3-part scoring system that includes 40 individual descriptions of catatonia in terms of behavior (15 items), motor (13 items), and affective (12 items) categories with each item rated 0 to 2 (80 points possible; higher scores = greater impairment).[28] There has been no MCID proposed for the NCRS tool.[28]

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, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) 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:

Cochrane: Benzodiazepines for Catatonia in People with Schizophrenia or other Serious Mental Illnesses[1]

A 2019 Cochrane review assessed the efficacy and safety of benzodiazepines over 3 days for the treatment of catatonia in adults 18 years or older with schizophrenia or other serious mental illnesses. Literature was searched through February 2019.[1] Of 22 relevant studies, only one (N=21) met inclusion criteria.[1] The study was a double blind, randomized, cross-over design.[1] Participants had a mean age of 50.8 years (range 21-77 years) with a history of mutism and psychomotor retardation (diagnosis of schizoaffective disorder, schizophrenia, or schizophreniform disorder, major depressive disorder with or without psychotic features, bipolar disorder (all DSM-III-R)).[1] The study intervention compared lorazepam versus oxazepam to assess a clinically important change in symptoms of catatonia measured as 50% improvement on the Visual Analogue Scale (VAS).[1] There was no placebo control.[1] Lorazepam was most commonly administered as a 2 mg single dose.[1] The review found no difference between groups in the numbers of participants showing a clinically important change in their catatonic symptoms (Relative risk [RR] 0.95, 95% confidence interval [CI] 0.42 to 2.16).[1] The quality of evidence was rated as very low due to small sample size and high risks of bias in the methods such as excluded data from 4 participants.[1] No data were reported for other clinically important outcomes such as

hospital stay, satisfaction with care, adverse effects, or general functioning.[1] More high-quality research is needed to consider whether benzodiazepines are safe or efficacious for the treatment of catatonia in people with schizophrenia or other serious mental illnesses.[1]

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), 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:
No high-quality guidelines identified.

Additional Guidelines for Clinical Context:
Evidence-based consensus guidelines for the management of catatonia: Recommendations from the British Association for Psychopharmacology [2]
The British Association for Psychopharmacology released guidance for the management of catatonia.[2] Available evidence was categorized and graded for quality (see **Table 2**).[2] There were no recommendations based solely on evidence derived from meta-analysis or high quality RCTs.[2] The guideline is included for clinical context only because many of the recommendations were largely based on expert opinion.

Strength of Recommendations:

A: Based on evidence from meta-analysis of RCTs or at least one RCT.
B: Based on evidence from non-randomized, controlled studies, quasi-experimental studies, or extrapolated from higher quality studies.
C: Based on evidence from non-experimental descriptive studies (e.g., case-control studies) or extrapolated from higher quality studies.
D: Based on evidence from expert opinions or clinical experience or extrapolated from higher quality studies.
S: Consensus-based in absence of systematic evidence.

Key Points with Strength of Evidence

- No recommendations are supported solely by RCT evidence (no Strength A recommendations).
- Most recommendations rely on lower-quality evidence (Strength B–D) or expert consensus (Strength S).

Table 2. Catatonia Treatment Recommendations- British Association for Psychopharmacology (modified)[2]

Treatment	Recommendation	Strength
Assessment & Diagnosis	Use a validated instrument such as BFCRS or NCRS.	C
	When diagnosis is uncertain, consider a lorazepam diagnostic challenge.	B
	Use a lorazepam challenge to help predict benzodiazepine treatment response.	B
	Titrate benzodiazepines and clozapine slowly and monitor vital signs closely.	S
	Consider a zolpidem diagnostic challenge when lorazepam is unclear or unavailable.	C
Treatment Initiation	Start treatment promptly—do not delay while awaiting diagnostic results.	D
	Consider underlying disorders, side-effect profiles, and availability of ECT when selecting treatment.	S
First-Line Treatment	Use benzodiazepines and/or ECT as first-line therapy.	C
Lorazepam	Lorazepam is the preferred benzodiazepine for catatonia.	S

	High doses beyond labeled maximum may be required; a trial is considered "adequate" when symptoms resolve, side effects limit dosing, or at least 16 mg/day has been reached.	C
Clozapine	Consider clozapine for mild, chronic catatonia associated with schizophrenia.	C
	Restart clozapine in cases of withdrawal-related catatonia; use ECT if needed.	D
	When used with benzodiazepines, titrate slowly with close monitoring.	S
Drug Discontinuation	Do not abruptly discontinue benzodiazepines; taper based on benefit, withdrawal risk, and dependence risk.	S
	In benzodiazepine withdrawal, restart benzodiazepine therapy.	D
Electroconvulsive Therapy (ECT)	Ensure ECT is available and accessible in treatment settings.	S
	Use ECT when benzodiazepines fail.	B
Lack of Response	Reassess diagnosis if no response to first-line therapy.	D

Abbreviations: BFCRS = Bush Francis Catatonia Rating Scale; ECT = electroconvulsive therapy; NCRS = Northoff Catatonia Rating Scale

After review, all other guidelines were excluded due to poor quality.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts[29,30]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
alprazolam	XANAX	9/2020	Warnings	Newborn risks of: -Neonatal withdrawal syndrome -Sedation / excessive sleepiness -Respiratory depression -Low muscle tone (hypotonia)
chlordiazepoxide	LIBRIUM			
clonazepam	KLONOPIN			
diazepam	VALIUM			
lorazepam	ATIVAN		Boxed Warnings	Strengthened warnings for: -Abuse and misuse -Addiction -Physical dependence -Severe withdrawal reactions -Risks when combined with opioids
oxazepam	(formerly SERAX)			

Randomized Controlled Trials:
A total of 9 citations were manually reviewed from the initial literature search. After further review, all 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).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL	Carveout
alprazolam	ALPRAZOLAM INTENSOL	ORAL CONC		Y
alprazolam	ALPRAZOLAM ER	TAB ER 24H		Y
alprazolam	ALPRAZOLAM XR	TAB ER 24H		Y
alprazolam	XANAX XR	TAB ER 24H		Y
alprazolam	ALPRAZOLAM ODT	TAB RAPDIS		Y
alprazolam	ALPRAZOLAM	TABLET		Y
alprazolam	XANAX	TABLET		Y
amitriptyline/chlordiazepoxide	CHLORDIAZEPOXIDE-AMITRIPTYLINE	TABLET		Y
chlordiazepoxide HCl	CHLORDIAZEPOXIDE HCL	CAPSULE		Y
clorazepate dipotassium	CLORAZEPATE DIPOTASSIUM	TABLET		Y
diazepam	DIAZEPAM	ORAL CONC		Y
diazepam	DIAZEPAM	SOLUTION		Y
diazepam	DIAZEPAM	TABLET		Y
lorazepam	LOREEV XR	CAP ER 24H		Y
lorazepam	LORAZEPAM	ORAL CONC		Y
lorazepam	LORAZEPAM INTENSOL	ORAL CONC		Y
lorazepam	LORAZEPAM	TABLET		Y
oxazepam	OXAZEPAM	CAPSULE		Y
chlordiazepoxide/clidinium Br	CHLORDIAZEPOXIDE-CLIDINIUM	CAPSULE		
clonazepam	CLONAZEPAM	TAB RAPDIS	N	
clonazepam	CLONAZEPAM	TABLET	Y	
clonazepam	KLONOPIN	TABLET	Y	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 09, 2026

1	exp Alprazolam/	1926
2	exp Chlordiazepoxide/	3904
3	chlordiazepoxide-amitriptyline.mp.	12
4	exp Clorazepate Dipotassium/	325
5	exp Diazepam/	18429
6	exp Lorazepam/	3137
7	exp Oxazepam/	1315
8	chlordiazepoxide-clidinium.mp.	18
9	exp Clonazepam/	2758
10	exp Benzodiazepines/	72431
11	exp Catatonia/	3084
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	72431
13	11 and 12	489
14	limit 13 to English language and humans and yr="2019 -Current" and (clinical trial, phase iii or guideline or meta analysis or practice guideline or randomized controlled trial or "systematic review")	9

Appendix 3: Key Inclusion Criteria

Population	Adult and pediatric patients with catatonia disorder
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1, ECT, or placebo
Outcomes	Efficacy: symptom improvement, function, quality of life, time to onset of effectiveness, duration of effectiveness Safety: withdrawals due to adverse events, serious and long-term (>12 months) adverse events
Setting	Outpatient

Benzodiazepines

Goal(s):

- Approve only for OHP-funded diagnoses.
- Prevent inappropriate long-term benzodiazepine use beyond 4 weeks for new starts (no history within the last 120 days).
- Approve long-term use only for indications supported by the medical literature.

Length of Authorization:

- Initial: 1 month to 12 months (criteria-specific)
- Renewal: 12 months to 2 years (criteria-specific)

Requires PA:

- All benzodiazepines used beyond 4 weeks. Short-term use (≤4 weeks) does not require PA.

Note: Benzodiazepines indicated for seizure rescue (routes: rectal, nasal, buccal) are subject to the Non-preferred Drugs in PDL classes criteria.

Covered Populations: FFS and CCO enrolled patients for drugs in in standard therapeutic classes 7 or 11 (pharmacy claims only).

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 malignant neoplasm or other end-of-life diagnosis (ICD10 C00.xx-D49.xx or Z51.5)?	**Yes:** Approve for 12 months	**No:** Go to #3

Approval Criteria		
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #5
4. Is this a request for a patient to be treated for any of the following: • Add-on therapy for ongoing seizure regimen? • Documentation of catatonia diagnosis in the chart notes AND symptom improvement with a benzodiazepine? • Short-term outpatient management of alcohol withdrawal syndrome in a patient enrolled in a program? Note: benzodiazepines are not indicated for alcohol dependence.	**Yes:** Approve for the following: • Adjunct therapy for seizure disorders: up to 12 months • Catatonia: Initially up to 6 months. Subsequent renewal requests up to 1 year. • Alcohol withdrawal: up to 1 month	**No:** Go to #5
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber evaluated the PDMP at least once in the past 3 months for this patient?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for a decrease in daily dose OR a change in drug with the intent to taper the dose?	**Yes:** Approve for up to 6 months or length of taper, whichever is less.	**No:** Go to #7
7. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #8

Approval Criteria		
8. Is the request for treatment of post-traumatic stress disorder (PTSD)? Note: Risks of benzodiazepine treatment outweigh benefits for patients with PTSD. Treatment with benzodiazepines is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #9
9. Is the request for treatment of anxiety or panic disorder?	**Yes:** Go to #10	**No:** Go to #11
10. Is there documentation of the following: • The medication is prescribed by or in consultation with a prescribing mental health specialist OR • Trial and failure, contraindication, intolerance, or inability to access recommended first-line treatments*? *Note: First-line treatments include **antidepressants PLUS psychotherapy** [e.g. behavioral therapy, relaxation response training, mindfulness meditation training, eye movement desensitization and reprocessing]) →An adequate trial to determine efficacy of an SSRI or SNRI is 4-6 weeks.	**Yes:** Go to #13 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
11. Is the request for treatment of psychosis, schizophrenia or schizoaffective disorder?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Is there documentation of the following: • The medication is prescribed by or in consultation with a prescribing mental health specialist OR • Trial and failure, contraindication, intolerance, or inability to access recommended first-line treatments*? *Note: First-line treatments include **second-generation antipsychotics AND psychotherapy** [e.g. counseling, cognitive behavioral therapy, social skills training, or psychoeducation])? →For continued symptoms, assess adherence and dose optimization. For patients on an adequate dose of antipsychotic, guidelines recommend trial of a second antipsychotic or augmentation with a mood stabilizer.	**Yes:** Go to #13 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
13. Is the patient on a concurrent sedative, hypnotic, muscle relaxant, or opioid?	**Yes:** Go to #14	**No:** Go to #16

Approval Criteria		
14. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: Documented taper strategy should include: • Planned dose reductions. • Length of time between each dose modification. • Documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). • Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Go to #15
15. Has the prescriber supplied documentation of the following: • Implementation of a specific risk mitigation plan OR • Clinical justification for concurrent sedative therapy (i.e. evidence that prescriber has evaluated risks associated with combination therapy and determined that benefits outweigh risks)?	**Yes:** Approve concurrent sedative therapy for the duration specified in the plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
16. RPh only: Is there appropriate rationale to support long-term benzodiazepine use for this indication? Note: For anxiety, panic disorder, or schizophrenia, provider rationale should include information from relevant chart notes. For other diagnoses, provider must document supporting medical literature.	**Yes:** Approve for up to 6 months.	**No:** Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for an increase in dose?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient failed all clinically appropriate first-line adjunct treatment options OR, when applicable, is the patient adherent to recommended first-line treatment options for their condition?	**Yes:** Go to #3	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of alternative therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
3. Is there documentation based on medical records that provider and patient have discussed whether benefits of long-term therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) continue to outweigh risks of therapy (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability)?	**Yes:** First-time renewals: Approve for up to 12 months. Second-time renewals: Approve for 2 years	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of gradual taper plan. Approval may be granted for up to 3 months to allow time to develop a taper plan. Subsequent requests must document progress toward taper.

P&T Review: *6/26 (DE); 8/22; 3/19 (SS); 9/18, 3/14*
Implementation: *TBD; 10/1/22; 5/1/19; 11/1/2018; 5/1/16*

Clinical Notes:

How to Discontinue Benzodiazepines.

Adapted from the following guidance on benzodiazepine tapering:

- Tapering Benzodiazepines; The Oregon Health Authority Mental Health Clinical Advisory Group, May 2022. Available at https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Tapering-Benzodiazepines.pdf.

1. Importance of Deprescribing Benzodiazepines

- Long-term use causes tolerance, physical dependence, cognitive impairment, falls, accidents, and overdose risk when combined with opioids.
- Benzodiazepines lose effectiveness for anxiety/insomnia after weeks of continuous use.
- They worsen PTSD outcomes and can increase aggression and depression.

2. Recommended Tapering Schedule of Benzodiazepines

Duration of Use	Taper Recommendation
2–8 weeks	≥2 weeks; slower if high-dose or alprazolam; triazolam may not need taper
8 weeks–6 months	≥4 weeks; go slower in later taper; avoid alcohol/stimulants
6 months–1 year	≥8 weeks
>1 year	6–18 months

Note: Taper duration should be individualized based on patient factors, severity of dependence, and withdrawal response.

3. Best Practices for Safe and Effective Tapering

- Use one prescriber and pharmacy; maintain regular, scheduled follow-ups.
- Avoid alcohol and stimulants during tapering.
- Plan initial taper steps but adjust based on patient response.
- Longer intervals between reductions improve comfort and safety.

4. Diazepam Transition Strategy

- Most patients benefit from transitioning to diazepam due to its long half-life, smoother serum level decline, and availability of small tablet strengths.
- Short-acting benzodiazepines such as alprazolam produce more withdrawal symptoms.
- Diazepam allows twice-daily dosing, reducing focus on medication.
- Avoid diazepam in hepatic impairment; taper the original benzodiazepine instead.

Benzodiazepines Grouped by Duration of Action and Diazepam Dose Equivalence

Duration of Action	Benzodiazepine	Approx. Diazepam Equivalent
Short-acting (half-life of drug and metabolites < 6 hours)	Oxazepam 20 mg	≈10 mg diazepam
	Triazolam 0.5 mg	
Intermediate-acting (half-life of drug and metabolites 6-24 hours)	Alprazolam 0.5 mg	
	Lorazepam 1 mg	
	Temazepam 20 mg	
Long-acting	Clonazepam 0.5 mg	

(half-life of drug and metabolites > 24 hours)	Chlordiazepoxide 25 mg	
	Clorazepate 15 mg	
	Diazepam 10 mg	Reference standard

Note: Equivalencies are approximations; individual response varies and adjustments may be required during taper.

Tapering Approach
- Transition one dose at a time to diazepam, usually starting with the nighttime dose.
- Dose reductions typically ~10% every 1–2 weeks; smaller reductions required at low doses.
- Avoid PRN benzodiazepine doses as they disrupt neuroadaptation.

For specific tapering examples, see https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Tapering-Benzodiazepines.pdf.

4. **Managing Withdrawal Symptoms**
   - Symptoms fluctuate; avoid increasing doses when symptoms worsen.
   - Supportive medications may be used briefly for pain, GI upset, nausea, or muscle spasms.
   - There is no evidence that adding antidepressants, antiepileptics, or melatonin improves taper success.

Possible Treatments for Withdrawal Symptoms

Condition	Recommended Treatment
Headache or pain	Acetaminophen 1000 mg q4–6h; Ibuprofen 400 mg TID
Diarrhea	Loperamide: 4 mg initially, then 2 mg after loose stools
Nausea	Metoclopramide 10 mg q4–6h; Ondansetron 8 mg daily
Muscle Spasms	Methocarbamol 1500 mg TID; Cyclobenzaprine 5–10 mg TID

Note: Symptom management should be short-term only; adding long-term medications does not improve taper success.

7. Counseling and Patient Engagement
- Shared decision-making is essential—patients should understand risks, withdrawal expectations, and the long-term benefits of discontinuation.
- Educate that withdrawal may occur but is manageable with a gradual taper.
- Encourage CBT, mindfulness, relaxation practices, and avoidance of alcohol/cannabis substitution

Drug Use Research & Management Program
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New Drug Evaluation: Cardamyst (etripamil), nasal spray

Date of Review: June 2026
Generic Name: Etripamil

End Date of Literature Search: 02/25/2026
Brand Name (Manufacturer): CARDAMYST (Milestone Pharmaceuticals)

Dossier Received: Yes

Plain Language Summary:

- This new drug evaluation looks at the evidence for the safety and effectiveness of CARDAMYST (etripamil), a nasal spray recently approved by the Food and Drug Administration (FDA) for management of an arrhythmia with an unusually fast heart rate known as paroxysmal supraventricular tachycardia (PSVT).
- People with PSVT can have very fast heartbeats which suddenly start and stop without warning. Symptoms of PSVT include dizziness, shortness of breath, feeling very tired, light-headedness, and chest pain.
- Etripamil is used to help restore normal heartbeat in adults with PSVT. The medicine is taken as one spray in each nostril for up to 2 doses. If symptoms do not improve after 2 doses, a medical provider should be contacted immediately, or the patient should get emergency help.
- In a clinical trial which compared self-administered etripamil nasal spray with placebo (fake medicine), people with PSVT were restored to a normal rate heart rate within 30 minutes more often than people who received placebo.
- Side effects reported with etripamil nasal spray include nose or throat irritation, runny or stuffy nose, and nosebleeds.
- The Drug Use Research and Management program recommends that a prescriber submit documentation why a person needs etripamil nasal spray. This process is called prior authorization.

Research Questions:

1. What is the evidence for the efficacy of etripamil nasal spray in converting PSVT to normal sinus rhythm in adults?
2. What is the safety of etripamil nasal spray in resolving PSVT?
3. Are there populations based on specific demographic characteristics (e.g., age, gender, race/ethnicity, socioeconomic status, etc.) for which etripamil is better tolerated or more effective than other available calcium channel blockers when used for managing tachycardia?

Conclusions:

- Etripamil nasal spray is FDA-approved for the conversion of PSVT episodes to normal sinus rhythm in adults, as a one-time dose, with a second dose if needed.[1]
- One double blind, placebo-controlled, phase 3 randomized controlled trial (RCT) which included adults (n=692) with a documented history of sustained PSVT episodes (typically lasting 20 minutes or longer) evaluated the safety and efficacy of etripamil 70 mg (**Table 2**).[2] All patients were required to successfully complete a test dose of etripamil to evaluate tolerability before they were randomized to active drug or placebo.[2] Of the randomized patients, 184 patients

experienced a confirmed PSVT episode during the trial and self-administered either etripamil or placebo.[2] Approximately one third of enrolled patients were taking oral beta-blockers and 24% were taking an oral calcium channel blocker (verapamil or diltiazem).[2] Analysis of the prespecified primary efficacy population (184 patients who experienced a PSVT episode during the 24-month trial period) showed 64.3% and 31.2% in the etripamil and placebo arms converted to sinus rhythm within 30 minutes after taking the study drug, respectively (hazard ratio [HR] = 2.62; 95% confidence interval [CI], 1.66 to 4.15; p<0.001; moderate-quality evidence).[2] Sixty-six percent of patients who received etripamil required a second dose for persistent symptoms, compared with 79% of patients who received placebo.[2] In the placebo-treated group, 25% of patients required additional medical intervention after randomized treatment (adenosine) compared with 15% of etripamil-treated patients (p=0.103). Twenty-one percent of placebo-treated patients required an emergency department visit after randomized treatment compared with 14% etripamil-treated patients (p=0.209).[2]

- The most common adverse events reported with etripamil nasal spray in the clinical trials included nasal discomfort, nasal congestion, rhinorrhea, throat irritation, and epistaxis.[1] Rates of adverse events compared to placebo are summarized in **Table 1**.
- Etripamil has not been compared to oral calcium channel blockers or beta-blockers to assess efficacy in preventing PSVT. The safety and effectiveness of etripamil in pediatric patients has not been established.

Recommendations:

- Maintain etripamil as nonpreferred on the Preferred Drug List (PDL).
- Implement PA criteria to ensure appropriate utilization of etripamil nasal spray (**Appendix 3**).

Background:

People with supraventricular arrhythmias are often symptomatic, requiring management with drugs and electrophysiological procedures.[3] The term supraventricular tachycardia (SVT) indicates an atrial rate greater than 100 beats per minute at rest.[3] Supraventricular tachycardias originate from or conduct through the atria or atrioventricular (AV) node.[4] SVT has been used to describe many types of tachycardias apart from ventricular tachycardias and atrial fibrilliation.[3] Prominent types of SVT include AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT) and atrial tachycardia.[4] Narrow QRS tachycardia indicates a QRS duration ≤120 milliseconds (ms).[3] A wide QRS tachycardia refers to a QRS duration >120 ms.[3] In clinical practice, SVT may present as narrow or wide QRS tachycardias, most of which present as regular rhythms.[3] The presence of SVT may result in palpitations, fatigue, light-headedness, chest discomfort, dyspnea, and altered consciousness.[3] In older patients, symptoms may be more extreme—with dizziness, presyncope, and syncope—due aging characteristics of the circulation; drops in blood pressure are usually immediate and tend to recover quickly.[3] Supraventricular tachycardias may be unrecognized at initial medical evaluation and the clinical characteristics can mimic panic disorder.[3]

Epidemiological studies on the SVT population are limited.[3] In the general population, the SVT prevalence is 2.25/1,000 persons and the incidence is 35/100,000 person-years.[3] Women have a risk of developing SVT that is 2-times greater than that of men, and persons aged 65 years or older have more than 5-times the risk of developing SVT than younger individuals.[3] Patients with lone paroxysmal SVT versus those with cardiovascular disease are younger, have a faster supraventricular tachycardia rate, have an earlier onset of symptoms, and are more likely to have their condition first documented in the emergency department.[3]

Patients with SVT are recurrent visitors to emergency departments, with an estimated 50,000 visits each year in the United States (US).[3] Emergency physicians may be the first to evaluate patients whose tachycardia mechanism is unknown and to diagnose the mechanism of arrhythmia.[5] It is important to record a 12-lead electrocardiogram (ECG) to differentiate tachycardia mechanisms according to whether the AV node is a component, because treatment that targets the AV node will not reliably terminate tachycardias that are not AV node-dependent.[5] Also, if the QRS duration is greater than 120 ms, it is crucial to distinguish

ventricular tachycardia from SVT with aberrant conduction, pre-existing bundle-branch block, or pre-excitation.[5] In particular, the administration of verapamil or diltiazem for treatment of either ventricular tachycardia or a pre-excited atrial fibrillation may lead to hemodynamic compromise or may accelerate the ventricular rate and lead to ventricular fibrillation.[5]

The initial approach to acute management of SVT tends to be non-drug-based (i.e., vagal maneuvers), with escalation to intravenous (IV) drugs or electrical cardioversion in the absence of early correction.[3] Adenosine, an endogenous purine nucleoside, is the drug-of-choice, as electrophysiological influences are mediated through cardiac adenosine receptors.[3] Calcium channel blockers (verapamil/diltiazem) and beta-blockers (e.g. esmolol/metoprolol) administered via the IV route are also recommended if the SVT is unresponsive to adenosine or vagal maneuvers, particularly in patients with frequent atrial or ventricular premature beats.[3] However, these drugs should be avoided in patients with hemodynamic instability, heart failure with reduced left ventricular ejection fraction (<40%), a suspicion of VT, or pre-excited atrial fibrillation.[3] Beta-blockers such as short-acting esmolol or metoprolol are more effective in reducing the tachycardia rate than in terminating it.[3] In rare instances, cardioversion is needed to terminate the arrythmia.[4] Most of the available drug therapies for acute events require IV administration and appropriate medical supervision in an emergency room or inpatient hospital stay.[4] Beta-blockers (metoprolol, atenolol, propranolol, nadolol) and calcium channel blockers (diltiazem, verapamil) may be prescribed to prevent future PSVT episodes.[4]

Catheter ablation is also used extensively for most varieties of SVT, and patient-reported outcome measures have shown that patients experience significant improvements in their quality-of-life following ablation.[3] Patient-reported outcome measures using various questionnaires are useful in the audit of ablation techniques.[3] Women are more often prescribed antiarrhythmic drugs before ablation for SVT than men, and recurrence rates following AVNRT ablation are higher in young women.[3] However, overall, no significant differences in health-related quality of life or access to healthcare resources between men and women have been reported.[3]

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. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:
Etripamil is FDA-approved for the conversion of PSVT episodes to normal sinus rhythm in adults.[1] Etripamil is an analog of the non-dihydropyridine calcium channel blocker, verapamil, and is administered intranasally.[4] The pharmacologic action of etripamil is directed towards prolonging AV nodal refractoriness and slowing conduction through the AV node.[4] One phase 3, double blind, placebo-controlled RCT contributes to the efficacy data for this indication, which is described and evaluated in **Table 2**.

Etripamil was studied in a 3-part multi-center RCT (NODE-301).[2] Etripamil was self-administered by study participants at home. Each episode was documented by an ambulatory Cardiac Monitoring System (CMS) that was placed on the chest by the participants or caregiver when symptoms began and recorded at least 5 hours of continuous electrocardiogram (ECG).[2] Part 1 of the study included participants (n=198) that received the randomized study drug to treat an episode of PSVT until the 150th positively adjudicated PSVT episode.[4] Participants were randomized to etripamil 70 mg or placebo in a 2:1 ratio.[4] This was a phase 2 dose-ranging safety and efficacy analysis.[4]

Part 2 of the study was a phase 3 RCT (also referred as the RAPID study) which included adults (n=706) with a documented history of sustained PSVT episodes (typically lasting 20 minutes or longer) who did not receive the randomized study drug in Part 1.[2] Before randomization in the RAPID study, all participants

received a test dose of etripamil consisting of an initial dose of etripamil 70 mg followed by a second dose of etripamil 70 mg 10 minutes later to evaluate tolerability and to train participants on the study procedures.[2] All patients were required to successfully complete a test dose of etripamil to evaluate tolerability before they were randomized to active drug or placebo.[2] Nine patients did not tolerate the test dose, so 692 patients were randomized 1:1 to placebo or etripamil. Of the 692 randomized patients, 184 patients experienced a confirmed PSVT episode during the 24-month trial duration and self-administered either etripamil or placebo.[2] When experiencing a PSVT episode, participants were instructed to administer a first dose of randomized study drug (70 mg etripamil or placebo) followed 10 minutes later, if PSVT symptoms persisted, by a second dose of study drug (70 mg etripamil or placebo).[2] After having administered the randomized study drug for a perceived episode of PSVT, participants could enter Part 3 of the study, which was an open-label period during which they had the possibility to treat a second episode of PSVT with open-label etripamil (70 mg etripamil with optional second dose of 70 mg etripamil).[2]

An independent committee of 4 to 6 cardiac electrophysiologists, masked to study assignments, examined all data from the 5-hour ECG cardiac monitoring systems and adjudicated the following: whether ECG tracings were consistent with an atrioventricular-nodal-dependent PSVT; whether an event was terminated with vagal maneuver; whether the first dose of the drug was taken during an event (to exclude those that had already spontaneously terminated); whether PSVT, if converted to sinus rhythm, remained converted for at least 30 seconds; the time of any additional medical intervention; the time (in minutes and seconds) to conversion of atrioventricular-nodal-dependent PSVT to sinus rhythm; and safety surveillance for bradyarrhythmias and tachyarrhythmias.[2]

The primary efficacy endpoint in Part 2 of the study was percent of patients with adjudicated conversion of confirmed atrioventricular-nodal-dependent PSVT to sinus rhythm for at least 30 seconds within 30 minutes of drug administration.[2] This endpoint was centrally and independently assessed.[2] Secondary efficacy endpoints were time to conversion at time points before and after 30 minutes; the percentage of patients requiring additional medical intervention in emergency departments to terminate an episode of PSVT; rating from the Treatment Satisfaction Questionnaire for Medication (TSQM-9); changes in predefined symptoms of PSVT from a questionnaire based on the Patient Symptom Global Impressions of Improvement (PGI-I); and sensitivity analyses to assess the robustness of the primary endpoint results. Secondary analyses were hierarchically prespecified.[2]

The efficacy population comprised all randomly assigned participants who self-administered study drug at the time of a confirmed episode of atrioventricular-nodal-dependent PSVT (n=184); only one episode could be included for each participant.[2] The efficacy population excluded participants who took study drug after PSVT conversion, those who had an episode that was adjudicated as non-atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia (e.g., atrial flutter or sinus tachycardia), and those for whom substantial loss of ECG signal occurred.[2]

Of the 184 subjects with confirmed PSVT, 31.2% and 64.3% converted to sinus rhythm within 30 minutes in the placebo and etripamil arms, respectively (hazard ratio [HR] = 2.62; 95% confidence interval [CI], 1.66 to 4.15; p<0.001).[2] In the modified intent-to-treat (mITT) population (n=255) with perceived PSVT episodes, 22.7% and 49.6% converted to sinus rhythm within 30 minutes in the placebo and etripamil arms, respectively (HR 2.59; 95% CI 1.64 to 4.09; p<0.001).[4] The percentage of subjects converted to sinus rhythm within 30 minutes by treatment arm is lower in the mITT population than the estimate based on efficacy population.[4] This is due to the 27.8% of subjects in the mITT population who took study drug for a perceived episode of PSVT but were not confirmed PSVT.[4] These episodes cannot be converted by the treatment but nevertheless these subjects took the study drug because they thought they had an episode of PSVT based on the symptoms they experienced.[4]

The first key secondary endpoint was time to confirmed conversion within 10 minutes, which was 14.76% for the placebo arm and 24.41% for the etripamil arm (p=0.052).[4] Since the endpoint was not statistically significant, the remaining secondary endpoints were not formally tested due to the prespecified hierarchical design.[4] Sixty-six percent of patients who received etripamil required a second dose for persistent symptoms compared with 79% of patients who received

placebo.[2] In the placebo-treated group, 25% of patients required additional medical intervention after randomized treatment (adenosine) compared with 15% of etripamil-treated patients (p=0.103). Twenty-one percent of placebo-treated patients required an emergency department visit after randomized treatment compared with 14% etripamil-treated patients (p=0.209).[2]

Trial Limitations

The FDA commented that it is unclear if the success of the primary endpoint was evaluated in the appropriate intent-to-treat (ITT) population. The manufacturer prespecified the efficacy population as the primary analysis population. The FDA considered the modified intent-to-treat (mITT) population as a more appropriate analysis population for conducting efficacy analyses.[4] The objective of the RAPID study was to demonstrate the safety and effectiveness of etripamil in the treatment of spontaneous episodes of PSVT when self-administered by subjects, prompted by their symptoms of PSVT, in a medically unsupervised setting.[4] As the medicine was developed for self-administration at a home setting (to reduce the hospital burden), patients need to decide whether and when to take the medicine based on their symptoms, after some training.[4] The reported accuracy of patients' perception of PSVT symptoms was 75.4%. That is, only 75.4% of subjects who thought they had an episode of PSVT were verified by adjudicators to have had PSVT.[4] In the manufacturer's report, the median conversion time of 17 minutes for the etripamil arm was reported.[4] This information can be misleading, as only subjects with confirmed PSVT were counted.[4] As subjects self-administered the treatment in a home setting, the actual probability of conversion among subjects who took medication is lower than the estimate based on the efficacy population.[4] About one quarter of subjects are considered not treatable by the study drug and not counted in the efficacy population.[4] The estimate of treatment effect based on the mITT population resembles the clinical practice and provides a more realistic estimate of the treatment effect.[4]

Clinical Safety:

The most common adverse events reported with etripamil nasal spray in the etripamil clinical trials (Phase 2 , Phase 3 and the open-label phase of the NODE trial) included nasal discomfort, nasal congestion, rhinorrhea, throat irritation, and epistaxis.[1] Rates of adverse events compared to placebo are summarized in **Table 1**, as reported by the manufacturer. Because of effects on blood pressure, heart rate, and cardiac conduction, etripamil may cause dizziness or syncope, especially in patients with a history of syncope and high-grade AV block or sinus node dysfunction, or those with a history of syncope during an episode of PSVT.[1] In the phase 3 RAPID RCT, 9 patients (0.4%) experienced clinically significant hypotension during test dosing prior to randomization, which precluded further participation in the study.[1] Patients with a history of hypotensive episodes or those at increased risk for hemodynamic instability should be monitored appropriately when initiating etripamil.[1] Contraindications to etripamil include New York Heart Association (NYHA) Class II to IV heart failure, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes, sick sinus syndrome without a permanent pacemaker, and second degree or higher degree of AV block.[1] No clinical drug interaction studies have been conducted with etripamil.

Table 1. Most Frequent Adverse Events Observed in Etripamil Clinical Studies[1]

Adverse Event	Placebo N=223	Etripamil 70 mg x 1 dose N=235	Etripamil 70 mg x 2 doses N=86
Nasal Discomfort	6%	28%	23%
Nasal Congestion	1%	14%	12%
Rhinorrhea	2%	12%	10%
Throat Irritation	1%	7%	6%
Epistaxis	1%	6%	7%

Look-alike / Sound-alike Error Risk Potential: No results reported in Micromedex

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Time to convert PSVT to normal rhythm
2) Need for additional medical intervention to terminate PSVT (e.g., emergency department visit or hospitalization)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Time to conversion of confirmed PSVT to sinus rhythm for at least 30 seconds within 30 minutes of drug administration

Table 2. 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. Stambler, BS et al.[2,4] Part 2 RAPID study NCT03464019 DB, MC, PC, RCT	1. Etripamil 70 mg in each nostril once. If symptoms persisted, a second 70 mg dose could be administered 10 minutes later, PRN. Vs. 2. Placebo	Demographics: -Mean age: Placebo: 56.7y Etripamil: 50.8 y -Female Placebo: 73% Etripamil: 70% -Race White: 93% Black: 2.5% Asian: 1% Other: 3% -Mean number of PSVT episodes in past year Placebo: 9.2 Etripamil: 6.4 -Mean number of lifetime ED visits for PSVT Placebo: 4.6 Etripamil: 5.2 -Percent of enrolled patients taking a beta blocker Placebo: 32% Etripamil: 33% -Percent of enrolled patients take a calcium channel blocker Placebo: 21%	ITT: 1. 135 2. 120 PP: 1. 99 2. 85 Attrition: 1. 13 (9.6%) 2. 17 (14.2%)	Primary Endpoint: Percent of patients with adjudicated termination of a confirmed episode of PSVT and conversion to SR for at least 30 seconds within 30 minutes of drug dosing (PP population) 1. n = 63/99 (64.3%) 2. n = 26/85 (31.2%) HR 2.62 95% CI 1.66 to 4.15 P<0.001 Secondary Endpoint: Conversion of PSVT within 10 minutes of drug administration 1. 14.76% 2. 24.41% HR 1.74 95% CI 0.96 to 3.14 P=0.52 Patients obtaining additional medical treatment after randomized treatment 1. n=21 (25%) 2. n=15 (15%)	NA	Any TEAE 1. n=68 (50%) 2. n=12 (11%) Any Serious TEAE 1. n=19 (14.1%) 2. n=1 (0.8%) TEAE leading to drug discontinuation 1. 3 (2.2%) 2. 0 Nasal Discomfort 1. n=31 (23%) 2. n=6 (5%) Epistaxis 1. n=8 (6%) 2. n=2 (2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IRT if subject tolerated 2 tests doses of active drug during sinus rhythm. Baseline demographics balanced between the 2 groups. Performance Bias: Unclear. Investigators and patients blinded. Blinding potentially broken for participants due to differences observed with adverse events between study arms. Detection Bias: Unclear. No details about blinding of outcome assessors. FDA had concerns there was potential detection bias from which populations were selected for the primary endpoint (PP vs. mITT). Attrition Bias: Low. Low attrition rates in both arms. Tolerance to active drug assessed prior to randomization. Reporting Bias: Low. Study protocol is available online. All results reported as prespecified. Other Bias: High. Funded by manufacturer. Several authors are consultants for the manufacturer. **Applicability**: Patient: Enrolled patients were mostly female, which reflects prevalence of PSVT. Enrollment was primarily White, which limits applicability to other racial and ethnic groups. Population studied already demonstrated

		Etripamil: 24% Key Inclusion Criteria: -Age ≥18 y with electrographically documented PSVT and history of sustained episodes of PSVT (≥ 20 minutes). Key Exclusion Criteria: -SBP < 90 mm Hg at screening -History of severe hypotension symptoms, especially syncope during PSVT episodes -History of atrial arrythmia that did not involve the AV node (e.g., atrial fibrillation, atrial flutter, intra-atrial tachycardia) -On digoxin, amiodarone, Class I or II antiarrhythmic drug -Second- or third-degree AV-block -History of ventricular arrythmia -NYHA Class II to IV HF -History of stroke		p=0.103 ED visits after treatment 1. n=18 (21%) 2. n=14 (14%) P=0.209				tolerability of drug, which would not apply to new patients in real world setting. Intervention: Dosing assessed in phase 2 RCT. Comparator: Placebo used as a comparator. No other oral medicines are approved to convert PSVT in an outpatient setting. Outcomes: Termination of PSVT was assessed by trained cardiologists. Additional medical treatment and ED outcomes were included as secondary outcomes. Setting: 160 centers, 8 countries in North America and Europe
Abbreviations: ARR = absolute risk reduction; AV = atrioventricular; SBP = systolic blood pressure; CI = confidence interval; DB = double blind; ED = emergency department; HF = heart failure; Hg = mercury; HR = hazard ratio; IRT = interactive response technology; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; mm = millimeters; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = New York Heart Association; PC = placebo controlled; PP = per protocol; PRN = if needed; PSVT = paroxysmal supraventricular tachycardia; RCT = randomized clinical trial; TEAE = treatment-emergent adverse event; y = years.								

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CARDAMYST™ safely and effectively. See full prescribing information for CARDAMYST™.

CARDAMYST™ (etripamil) nasal spray
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------

CARDAMYST is a calcium channel blocker indicated for the conversion of acute symptomatic episodes of paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm in adults (1).

----------DOSAGE AND ADMINISTRATION----------

- For intranasal use only (2.1).
- Initial dosage: A dose of 70 mg is administered as two nasal sprays, one spray into each nostril. Each nasal spray device delivers two sprays. The two sprays together contain a total of 70 mg etripamil (2.1).
- Repeat dosage (if needed): Should symptoms persist for 10 minutes after administration of CARDAMYST, take a second dose of 70 mg administered as two nasal sprays, one spray into each nostril. Do not exceed 140 mg in a 24-hour period (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

Nasal spray: 70 mg etripamil per device (3).

----------CONTRAINDICATIONS----------

- Hypersensitivity to CARDAMYST or any of its components (4).
- Heart failure - New York Heart Association (NYHA) Class II to IV (4).
- Wolff-Parkinson-White (WPW), Lown-Ganong-Levine (LGL) syndromes, or manifest pre-excitation (delta wave) on a 12-lead ECG (4).
- Sick sinus syndrome (except in patients with a permanent pacemaker) (4)
- Second degree atrioventricular (AV) Mobitz 2 block or higher degree of AV block (4)

----------WARNINGS AND PRECAUTIONS----------

- Syncope: May cause dizziness and/or syncope, especially in patients with a history of syncope. Administer in a sitting position (5.1).

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence > 5%) are nasal discomfort, nasal congestion, rhinorrhea, throat irritation, and epistaxis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Milestone Pharmaceuticals USA, INC. at toll-free phone 1-877-207-4764 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: A lactating woman should pump and discard breastmilk for 12 hours after CARDAMYST administration (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Calcium Channel Blocker
Oral Bioavailability	Not Applicable
Distribution and Protein Binding	Volume of Distribution; 2,200 to 3,500 Liters 50% Protein Binding
Elimination	29% via urine and 25% via feces
Half-Life	2.5 hours
Metabolism	Hepatic primarily via blood esterases and CYP3A4 and CYP3A5

Abbreviations:

Appendix 3: Proposed Prior Authorization Criteria

Etripamil (Cardamyst™) Nasal Spray

Goal(s):

- To ensure appropriate use of etripamil nasal spray that is consistent with medical evidence.

Length of Authorization:

- Up to 12 months

Requires PA:

- Etripamil nasal spray (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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is there a positive history of premature supraventricular tachycardia (PSVT) documented by ECG requiring emergency care in the last 12 months?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the medication prescribed by or in consultation with a cardiologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have any of the following conditions: • New York Heart Association (NYHA) Class II to IV heart failure or • Wolff-Parkinson-White syndrome or • Lown-Ganong-Levine syndrome or • Sick sinus syndrome without a permanent pacemaker or • Second degree or higher degree of AV block?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Does the provider attest that catheter ablation is not suitable or has been considered but is not appropriate at this time?	**Yes:** Approve requested number of nasal sprays for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/2026 (DM)
Implementation: TBD

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Spinal Muscular Atrophy

Date of Review: June 2026

Generic Name: onasemnogene abeparvovec-brve

Date of Last Review: February 2023
Dates of Literature Search: 02/10/2022 – 03/09/2026
Brand Name (Manufacturer): Itvisma® (Novartis)
Dossier Received: no

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

Purpose for Class Update:
The purpose of the class update is to review new, high-quality evidence for the management of spinal muscular atrophy (SMA) published since the last Pharmacy and Therapeutics (P & T) Committee review in 2023 and to evaluate evidence for the safety and efficacy of ITVISMA (onasemnogene abeparvovec-brve), a new formulation of gene therapy for SMA.

Plain Language Summary:
- Spinal muscular atrophy (SMA) is an inherited condition which destroys nerve cells that control muscles involved in speaking, walking, breathing, and swallowing. In SMA, the muscles weaken over time and waste away. There are 4 types of SMA: Type 1 has the most severe symptoms. People with Type 2, Type 3, and Type 4 SMA may live longer lives, as their symptoms are usually less severe.
- There are 4 medicines approved in the United States to treat SMA: SPINRAZA (nusinersen), ZOLGENSMA (onasemnogene abeparvovec-xioi), ITVISMA (onasemnogene abeparvovec-brve), and EVRYSDI (risdiplam). SPINRAZA is injected into the fluid surrounding the spinal cord in the lower back every 4 months. ZOLGENSMA is administered only once as in infusion into the veins. EVRYSDI is a pill or liquid that is taken by mouth every day for life. ITVISMA is the medicine most recently approved by the FDA and is a one-time injection into the fluid surrounding the spinal cord in the lower back.
- ITVISMA was studied in children with SMA who could sit on their own but could not walk. After one year, more children who received this medicine had an improvement in their ability to move than those who did not receive any medicine (sham injection).
- Studies have shown that all 4 medicines improve most muscle function. None of the medicines help the breathing muscles, so some patients may still need a machine called a ventilator to help with breathing.
- Most of the side effects of SPINRAZA and ITVISMA were because it is injected into the fluid around the spinal cord, which can cause headache, back pain, and nausea. ZOLGENSMA and ITVISMA can damage the liver, so people who receive this medicine must have their liver monitored with regular blood tests. Side effects reported with EVRYSDI include fever, diarrhea, joint pain, mouth ulcers, and constipation.

Author: Deanna Moretz, PharmD, BCPS

- Doctors who prescribe one of these medicines must get approval from the Oregon Health Plan. This process is called prior authorization.

Research Questions:

1. What is the comparative efficacy of nusinersen (SPINRAZA), onasemnogene abeparvovec-xioi (ZOLGENSMA), and risdiplam (EVRYSDI) for treating spinal muscular atrophy (SMA)?
2. What are the comparative harms of nusinersen, onasemnogene abeparvovec-xioi and risdiplam for treating SMA?
3. What is the evidence for the safety and efficacy of ITVISMA (onasemnogene abeparvovec-brve) in treating SMA?
4. What is the efficacy and harms of co-treatment or sequential use of treatments approved by the U.S. Food and Drug Administration (FDA) to treat SMA?
5. Are there populations of patients based on specific demographic characteristics (e.g., age, race, ethnicity, socioeconomic status, co-morbidities, etc.) in which a particular treatment for SMA would be more effective or associated with less harm?

Conclusions:

- Comparative studies of the SMA disease-modifying treatments are not available as heterogeneity of study populations and outcomes make the results difficult to interpret.[1]
- No recent high-quality systematic reviews were identified. Three high-quality guidelines were recently published.[2-4]
- In 2025, Canada's Drug Agency (CDA) evaluated published evidence for the safety and efficacy of nusinersen and risdiplam for adults with SMA.[2] Based upon the available evidence, CDA does not recommend reimbursement for initiation of nusinersen in patients in patients with later-onset or more slowly progressive forms of SMA aged 18 years and older or initiation of risdiplam in patients aged older than 25 years.[2] No changes have been made to the 2021 CDA guidance for risdiplam which supports use of risdiplam to treat SMA in patients aged 2 months and older with genetic documentation of the SMA diagnosis.[5] CDA guidance (2021) recommends onasemnogene abeparvovec-xioi use in SMA patients with genetic documentation of the condition who are aged 180 days or younger.[6]
- The National Institute for Health and Care Excellence (NICE) updated guidance for onasemnogene abeparvovec-xioi in April 2023.[3] Onasemnogene abeparvovec is an option for treating SMA in people with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in infants, only if:
    - they are aged 6 months or younger, or
    - aged 7 to 12 months if treatment is agreed by the national multidisciplinary team, and
    - tracheostomy or permanent ventilation for more than 16 hours per day is not needed.[3]
- The NICE updated guidance for risdiplam in December 2023.[4] Risdiplam is recommended as an option for treating SMA in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies.[4]
- In February 2025, FDA approved a new tablet formulation of risdiplam based on pharmacokinetic studies comparing it to previously approved formulations.[7] The oral tablets are indicated for patients 2 years of age and older who weigh 20 kg or more.[7]
- In March 2026, the FDA approved a higher dosing regimen for nusinersen. The high-dose regimen starts with 50 mg loading dose every 14 days for 2 doses, followed by a 28 mg maintenance dose every 4 months starting 4 months after the last loading dose.[30] The previously approved low-dose regimen consists of a 12 mg loading dose every 14 days for 3 doses, followed by a fourth 12 mg dose 30 days after the third dose.[30] The 12 mg maintenance dose is initiated once every 4 months after completing the 4-dose loading dose regimen.[30] The manufacturer does not stipulate which dosing regimen is preferred, as the provider will determine which dosing regimen (high versus low) is optimal for their patient.

- ITVISMA (onasemnogene abeparvovec-brve) is an adeno-associated viral (AAV) vector-based gene therapy approved by FDA in November 2025 as a one-time intrathecal injection.[8] It is indicated to treat SMA in adults and pediatric patients 2 years of age and older with a confirmed mutation in the SMN1 gene.[8] The safety and efficacy of onasemnogene abeparvovec-brve is supported by data from a single, phase 3 trial (STEER).[9]
    - The STEER trial was a 52-week, phase 3, multicenter, sham-controlled, double-blind randomized controlled trial (RCT) evaluating intrathecal onasemnogene abeparvovec-brve in patients with Type 2 SMA (n=126).[9]
    - The primary efficacy endpoint was change from baseline in Hammersmith Functional Motor Scale-Expanded (HFMSE) score. The published minimal clinically important difference (MCID) for the HFMSE is 3 points; however, the investigators used an MCID of improvement of 1.5 points, based on another study of patients with SMA type 2 and 3.[10] MCID values documented in the literature range from 1.5 to 4 depending on the statistical method used to evaluate clinical significance. MCID values may be different for symptoms that are improving compared to symptoms that are worsening.
    - Patients treated with onasemnogene abeparvovec-brve demonstrated an average improvement of 1.88 points in HFMSE score compared with sham injection after 52 weeks (least squares mean difference [LSMD], 1.88; 95% confidence interval [CI], 0.51 to 3.25; P = 0.0074; moderate-quality evidence).[9]
    - The most frequently reported adverse events reported with onasemnogene abeparvovec-brve was upper respiratory infections, pyrexia, and upper gastrointestinal symptoms.[8] A complete summary of adverse events is presented in **Table 6**.
    - Onasemnogene abeparvovec-brve has a black boxed warning for acute serious hepatic injury and elevated aminotransferases, and monitoring liver function is recommended.[8] Patients with preexisting hepatic impairment may be at higher risk for hepatic injury.[8]
- No high-quality RCTs have assessed the efficacy and harms of co-treatment or sequential use of SMA disease-modifying treatments approved by FDA. Observational, single-arm studies and case reports have been published to evaluate sequential use of SMA treatments. These observational reports do not support changes in current PA criteria, which do not permit sequential administration of SMA therapies.
- No subgroups of patients based on demographics have been identified to show that one SMA therapy is more effective than another beyond the age ranges in the FDA-approved label for each therapy.

Recommendations:
- No PDL changes are recommended based on available evidence.
- Revise prior authorization (PA) criteria for the SMA drugs to include onasemnogene abeparvovec-brve.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The P &T Committee last reviewed FDA-approved treatments for SMA at the February 2023 meeting. The committee approved recommendations to combine PA criteria for all SMA treatments into one document called “Spinal Muscular Atrophy Drugs” as presented in **Appendix 6** with updates to clarify duration of therapy and FDA-approved age ranges.
- The PDL status for the SMA drugs is listed in **Appendix 1.** Onasemnogene abeparvovec-xioi is preferred on the PDL while the other 2 medications are non-preferred. All SMA medications require PA to ensure appropriate use of these high-cost therapies.
- From April 2024 to March 2025, 93 patients in the Oregon Health Plan (OHP) had a SMA-related diagnosis: 24 were in enrolled in the fee-for-service (FFS) program and the remaining individuals were enrolled in a coordinated care organization (CCO). In the third quarter of 2025 (July 1 to September 30) there

were 5 FFS patients with claims for nusinersen. During the same time, there were no claims for onasemnogene abeparvovec-xioi and 3 claims for risdiplam in FFS population and 13 risdiplam claims in the CCO population.

- The Health Evidence Review Commission (HERC) has addressed SMA carrier screening for pregnant women Guideline Note D17 and recommends coverage of genetic screening for SMA once in a lifetime.[11]

Background:

Spinal muscular atrophy is a rare, autosomal recessive, and progressive neuromuscular disorder caused by mutations in the SMN1 gene, which reduces levels of functional SMN protein.[12] Insufficient levels of SMN protein in motor neurons in the brainstem and spinal cord leads to malfunction, deterioration, and the eventual death of those cells.[12] Spinal muscular atrophy is characterized by progressive weakness, atrophy of skeletal muscles and hypotonia.[13] Disease severity ranges from progressive infantile paralysis and premature death to limited motor neuron loss and normal life expectancy.[14]

The incidence of SMA is estimated at 4 to 10 in 100,000 live births.[12] Spinal muscular atrophy is the most common genetic cause of death in infants due to respiratory insufficiency.[15] The clinical phenotype and severity of SMA are influenced by the SMN2 gene, which acts as a disease modifier.[12] Higher SMN2 copy numbers provide partial compensation for SMN1 loss, with increased copy numbers associated with milder disease severity.[12] The phenotype is extremely variable. Patients are classified as SMA type 0 through 4 based on age at onset and motor milestone achievement. SMA Type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.[16] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. SMA Type 4 presents in adulthood (typically after age 30 years) has the mildest course and slowest progression.[12] The characteristics of each SMA type are described in **Table 1.**

Table 1. SMA classification and characteristics[2,17]

SMA Type	Typical SMN2 copy numbers	Age of Onset	Motor Function	Median Survival	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1% of cases
1 (severe)	1-2	Birth to 6 months	Never able to sit unassisted	Less than 2 years	3.2 – 7.1 (45% of cases)
2 (intermediate)	2-3	7 - 18 months	Able to sit, but unable to independently walk	10 to 40 years (~70% still alive at age 25)	1 – 5.3 (20% of cases)
3 (mild)	3-4	>18 months	Able to independently stand and walk, which may decline with disease progression	Adult	1.5 – 4.6 (30% of cases)
4 (adult)	≥ 4	Adult (2nd or 3rd decade)	Ambulatory	Adult	5% of cases

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. In part because of SMA's rapid progression and the importance of early diagnosis to preserve motor functioning, the disease was recently added as a recommended condition for which to screen all newborns in the United States.[18] Different methods for a newborn screening have been developed to diagnose SMA from DNA extracted from newborn blood spots, including a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis with the possibility to identify SMN1 and SMN2 deletion as well as to quantify copy numbers of both genes, and a real-time polymerase chain reaction.[19] Other laboratory tests can include muscle enzyme creatine kinase, electrophysiological testing such as electromyography (EMG), and nerve conduction study with repetitive

stimulation. These tests help to identify other muscle diseases, motor neuropathies, and disorders of neuromuscular junctions.[20] Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60 in the general population.[21] It is not possible to predict the severity of the SMA phenotype from carrier screening.[21]

Due to the difficulties in quantifying motor abilities in individuals with SMA, several functional motor scales were developed to assess functional status in people with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of children with SMA Type 1.[22] The CHOP-INTEND tool was validated in a small population of children (n=27) with SMA aged 3 to 260 months (mean age = 49 months).[23] The Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) was developed by physical therapists to assess individuals with SMA type 2 and 3.[24] The HFMSE motor assessment includes upper and lower limb activities as well as head and trunk control. Inter-rater reliability was tested on 35 children with an inter observer agreement greater than 99%.[24] The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.[25] Sequential use of the HINE can identify early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.[26] The HINE screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.[19] The Revised Upper Limb Module (RULM) was designed to assist in evaluation of young children's ability to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil. It has been validated for use in SMA assessments in a variety of settings. **Table 2** provides a summary of each tool, the intended population, and scoring.

Table 2. Motor Function Exams for SMA[27]

Instrument	Domain Evaluated	Intended Population	Number of Items	Grading Scale	Score Range	MCID
6MWT	Aerobic capacity and endurance	Ambulatory patients with SMA	1 item: the distance covered by walking a flat 25-meter course over a 6-minute period	N/A	N/A	50 to 70 meters
CHOP-INTEND	Motor function	Infants with SMA Type 1	16 items scored 0 to 4	0 = no response 4 = full response	0 to 64	Unknown; clinical trials have used a change of ≥ 4 points
HFSME	Motor function	SMA Types 2 and 3	33 items scored 0 to 2	0 = no response 2 = full response	0 to 66	Change of ≥ 3 points
HINE-2	Motor milestones	All infants aged 2 months to 24 months	8 milestones with: • 3 items scored 0 to 4 • 4 items scored 0 to 3 • 2 items scores 0 to 2	0 = absence of activity Increasing points correspond to an increased level of milestone achievement	0 to 26	Unknown; however, an increase of ≥ 1 point is unlikely in infants with SMA Type 1
RULM	Upper extremity and ADL function	All individuals with SMA; commonly used to assess non-ambulatory individuals	19 items scored 0 to 2 1 unscored entry item; serves as functional class identification.	0 = unable 2 = able, no difficulty	0 to 37	Unknown, can vary: • SMA Type 2: 1.2 to 2.7 points • SMA Type 3: 3 to 6 points • Ambulatory SMA: 0.5 to 1 point • Non-ambulatory SMA: 2 to 4 points

Abbreviations: 6MWT: 6-Minute Walk Test; ADL: activities of daily living; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFSME: Hammersmith Functional Motor Scale Expanded for SMA; HINE-2: Hammersmith Infant Neuromuscular Examination, Section 2; MCID: minimal clinically important difference; N/A: not applicable; RULM: Revised Upper Limb Module; SMA: spinal muscular atrophy

Management of SMA focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Respiratory care includes the use of devices that improve ventilation, especially during sleep and viral illnesses when hypoventilation is most likely to occur, as well as methods to mechanically augment cough and clearance of respiratory secretions.[28] Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Full–time, noninvasive ventilation greater than 16 hours per day may be required to provide respiratory support in patients with SMA type 1. Difficulties in feeding and swallowing can lead to gastrointestinal complications and malnutrition. Nutritional support includes the use of non-oral methods to deliver enteral nutrition, typically through a surgically placed feeding tube or temporary nasal tube, plus medical or surgical interventions to control gastroesophageal reflux.[28] Management of joint contractures and scoliosis involves aggressive physical therapy assessments, daily passive range of motion exercises, and use of bracing to facilitate and maintain optimal positioning of extremities and maintain the spine upright against gravity.[29]

Four treatments are approved by the FDA to treat SMA: 2 medications, nusinersen and risdiplam, and 2 gene therapies, onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve. Nusinersen was the first treatment approved for pediatric and adult patients with SMA in 2016.[30] It is an antisense oligonucleotide (ASO) which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein, which can partially compensate for mutations of the SMN1 gene.[30] Nusinersen must be administered via intrathecal injection every 4 months after the initial loading dose because ASOs do not efficiently cross the blood-brain barrier.[30] In 2020, risdiplam, an oral solution, received FDA approval to treat SMA.[31] Risdiplam is an SMN2 splicing modifier designed to promote the inclusion of exon 7 to produce full-length SMN2 mRNA, which results in an increased production of functional SMN protein from the SMN2 gene.[31] Risdiplam is FDA-approved for the treatment of all patients with SMA.[31] Dosing is weight-based and must be administered daily.[31]

Onasemnogene abeparvovec-xioi received FDA approval in 2019.[32] Onasemnogene abeparvovec-xioi is an adeno-associated viral serotype 9 (AAV9) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.[32] The AAV9 vector is an ideal method of administering gene therapy because it has rapid onset of transgene expression, can cross the blood-brain barrier, is small in size with a simple structure, and has low immunogenicity. Onasemnogene abeparvovec-xioi is a one-time intravenous treatment that is designed to deliver a functional SMN1 gene, potentially enabling the production of SMN protein to enable development of motor neurons.[32] The safety and effectiveness of repeated administration of onasemnogene abeparvovec have not been evaluated. In addition, its use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been studied.[32] The fourth treatment, onasemnogene abeparvovec-brve, recently received FDA approval in November 2025. This gene therapy is similar to ZOLGENSMA but is administered via the intrathecal route as a one-time dose and is formulated in a different concentration. More details about this gene therapy are provided in the New Drug Evaluation below. **Table 3** provides a comparison of the 4 FDA-approved SMA treatments.

Table 3. FDA-Approved SMA Treatments

Drug (BRAND NAME)	Route of Administration	Frequency of Administration	FDA-Approved Age Range
Nusinersen (SPINRAZA)[30]	Intrathecal Injection	Loading Dose: 4 doses over 2 months Maintenance Dose: Once every 4 months	All SMA patients
Onasemnogene abeparvovec-xioi (ZOLGENSMA)[32]	Intravenous Infusion	Once	Patients less than 2 years of age with bi-allelic mutations in SMN1 gene

Onasemnogene abeparvovec-brve (ITVISMA)[8]	Intrathecal Injection	Once	Patients 2 years of age and older with confirmed mutation in SMN1 gene
Risdiplam (EVRYSDI)[7]	Oral	Once daily	All SMA patients
Abbreviations: FDA: Food and Drug Administration; SMA = spinal muscular atrophy; SMN = survival motor neuron			

The efficacy and harms of co-treatment or sequential treatment with SMA therapies is considered investigational, as no high-quality RCTs have been published to evaluate sequential or concurrent treatment.[27] Most studies are observational, single-center, and include small numbers of patients (n=4 to 37).[33-37] The lack of comparative group or randomization makes it difficult to attribute any improvement in symptoms to a given therapy when treatment is administered following gene therapy. Comparative studies of the 4 SMA disease-modifying treatments are not available. Heterogeneity of SMA treatment study results and outcomes make the results difficult to interpret.[1] In addition, there are missing data across studies on patients at follow-up, as patients who do not perform well on the intervention tend to withdraw from the study.[1] Due to the rare occurrence of SMA, the number of SMA patients enrolled in clinical trials was small and ranged from 7 to 118 people.[1] The efficacy of these treatments for children with long-term disease remains unknown, as most studies were conducted from 6 months to 5 years.[1] The long-term effects of all 4 treatments are currently unknown, because of the relatively short follow-up periods in the clinical trials.[1]

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, Canada's Drug Agency (CDA-AMA), the Oregon Mental Health Clinical Advisory Group (MHCAG), 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:
The literature search did not identify recently published high-quality systematic reviews. After review, 7 systematic reviews 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 endpoints studied (e.g., non-clinical).[1,38-43]

New Guidelines:
High Quality Guidelines:
Canada's Drug Agency: Evidence Review for Nusinersen and Risdiplam for Adults with Spinal Muscular Atrophy (2025)
Two treatments, nusinersen and risdiplam, are publicly reimbursed in Canada, primarily for use in children.[2] The Canadian Drug Expert Committee (CDEC) reimbursement recommendations for both drugs highlighted serious limitations in the evidence for the effectiveness and safety of these treatments in adults

with SMA.[2] In particular, the evidence is limited by the lack of high-quality, comparative data, making it difficult to determine whether observed effects are due to the drugs or to other factors, and whether these effects are clinically meaningful in adults.[2]

Only one new study was found for nusinersen in adults with SMA.[2] This study compared adults treated with nusinersen with those who received no treatment over a follow-up period of up to 30 months.[2] The study had significant limitations, including a high risk of bias due to differences in patient characteristics between the treated and untreated groups (e.g., ability to sit or to walk at start of treatment), missing data, inconsistent findings within and across motor function outcomes, use of unvalidated thresholds to define clinically meaningful treatment effects, and incomplete outcome reporting.[2] These limitations make it difficult to draw reliable conclusions about the benefits or harms of nusinersen in adults with SMA.[2] No eligible comparative studies were found for risdiplam in adults aged older than 25 years with SMA.[2] No published studies were identified for nusinersen or risdiplam in adults with SMA who were previously treated with gene therapy (onasemnogene abeparvovec-xioi).[2]
Recommendation:

- CDEC does not support treatment with nusinersen in patients with later-onset or more slowly progressive forms of SMA that are aged 18 years and older or risdiplam in patients aged older than 25 years.[2]

National Institute for Health and Care Excellence: Onasemnogene Abeparvovec-xioi For Treating Spinal Muscular Atrophy
NICE guidance for onasemnogene abeparvovec-xioi in SMA was updated in 2023.[3] For infants with type 1 SMA who are 6 months or younger at the start of treatment, and who do not need permanent ventilation for more than 16 hours per day or a tracheostomy, evidence from clinical studies suggests that onasemnogene abeparvovec-xioi is effective.[3] But the studies are small and do not compare onasemnogene abeparvovec with other treatments, so it is difficult to establish how well it works.[3] Also, there is very limited evidence for infants with type 1 SMA who are older than 6 months at the start of treatment.[3] However, clinical experts advise that some infants aged between 7 and 12 months would be expected to have similar benefit to those 6 months and younger.[3] There is also a lack of long-term evidence, and no evidence in patients with more progressed type 1 SMA.[3]
Recommendations:

- Onasemnogene abeparvovec is an option for infants with clinical diagnosis of type 1 SMA with a bi-allelic mutation in the SMN1 gene, only if:
    - they are aged 6 months or younger (the primary population studied in clinical trials), or
    - aged 7 to 12 months if treatment is agreed by the national multidisciplinary team, and
    - tracheostomy or permanent ventilation for more than 16 hours per day is not needed.[3]

National Institute for Health and Care Excellence: *Risdiplam For Treating Spinal Muscular Atrophy*
NICE updated guidance for risdiplam in 2023.[4] Before the December 2023 license extension, risdiplam was only indicated for people 2 months and older with SMA.[4] Clinical evidence shows that risdiplam improves motor function in SMA types 1 to 3.[4] There is some evidence suggesting that people with type 1 SMA who have risdiplam live longer.[4] There is also some evidence suggesting risdiplam may be effective for people with pre-symptomatic SMA.[4] But there is no direct evidence comparing risdiplam with usual care for type 1 SMA.[4] And although it is likely that risdiplam has long-term benefits, there is no long-term evidence, so this is uncertain.[4]
Recommendation:

- Risdiplam is recommended as an option to treat SMA in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies.[4]

After review, 2 guidelines were excluded due to poor quality.[44,45]

New FDA Safety Alerts

Table 4. Description of New FDA Safety Alerts[46]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles
Nusinersen	SPINRAZA	5/2018	Warnings and Precautions	**Thrombocytopenia and Coagulation Abnormalities** Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. In sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) nusinersen-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients. In the sham-controlled study in patients with later-onset SMA (Study 2), two nusinersen-treated patients developed platelet counts less than 50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on day 28. Because of the risk of thrombocytopenia and coagulation abnormalities from nusinersen, patients may be at increased risk of bleeding complications. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of nusinersin and as clinically needed. **Renal Toxicity** Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Nusinersen is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 (58%) of nusinersen-treated patients had elevated urine protein, compared to 22 of 65 (34%) sham-controlled patients. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of nusinersin. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

New Formulations

- In February 2025, the FDA-approved a new 5 mg tablet formulation of risdiplam.[7] Prior to this approval, risdiplam was only available as an oral powder that must be reconstituted prior to administration to provide a 0.75 mg/mL solution.[7] The oral tablets are indicated for use in patients 2 years of age and older who weigh 20 kg or more.[7] The FDA based the approval of the risdiplam tablet formulation on the 3 clinical trials that led to approval of the oral powder formulation.

- In March 2026, the FDA approved a higher dosing regimen for nusinersen. The high-dose regimen starts with 50 mg loading dose every 14 days for 2 doses, followed by a 28 mg maintenance dose every 4 months starting 4 months after the last loading dose.[30] The previously approved low-dose regimen consists of a 12 mg loading dose every 14 days for 3 doses, followed by a fourth 12 mg dose 30 days after the third dose.[30] The 12 mg maintenance dose is initiated once every 4 months after completing the 4-dose loading dose regimen.[30] The manufacturer does not stipulate which dosing regimen is preferred, as the provider will determine which dosing regimen (high versus low) is optimal for their patient. Nusinersen is FDA-approved for treatment of SMA in pediatric and adult patients.[30]

  The efficacy of the nusinersen high-dose regimen was evaluated in a multicenter, double-blind, RCT which included 75 treatment naïve patients with infantile-onset SMA (2 SMN2 copies; symptom onset before 6 months of age) randomized 2:1 to the 50/28 mg or 12/12 mg nusinersen regimen.[47] The primary efficacy endpoint was the 6-month change in Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorder (CHOP-INTEND) score in the patients receiving the high-dose regimen compared to a prespecified matched sham group from the initial study (ENDEAR) that led to approval of the low dose regimen (n=20; matched on baseline disease duration and baseline CHOP-INTEND score).[47] At day 183, the CHOP-INTEND least-squares mean total score improved (+15.1 points) in those who received 50/28 mg nusinersen and worsened (−11.1 points) in matched ENDEAR participants who received sham (difference, 26.19 (95% confidence interval = 20.7 to 31.74); statistical testing was performed using the joint-rank test where the difference in ranks was 26.06 (95% confidence interval = 17.9 to 34.2; $P < 0.0001$).[47]

  The safety of the nusinersen high-dose regimen was studied in 2 clinical trials in symptomatic patients with SMA (approximately 14 days to 65 years of age at first dose).[30] In clinical studies, 128 patients (50% male, 63% Caucasian, and 22% Asian) were treated with the high-dose regimen, including 113 exposed for at least 6 months, 95 exposed for at least 1 year, and 67 exposed for at least 2 years.[30] The most common adverse reactions in at least 10% of nusinersen-treated patients who received the high-dose regimen and occurred at least 5% more frequently than in historic matched sham-control were: pneumonia, COVID-19, pneumonia aspiration, and malnutrition in patients with infantile-onset SMA.[30]

Randomized Controlled Trials:
A total of 286 citations were manually reviewed from the initial literature search. After further review, 286 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: Onasemnogene abeparvovec-brve for intrathecal injection

See **Appendix 3** 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. Pharmacology and pharmacokinetic properties are listed in **Appendix 4**.

Clinical Efficacy:

Onasemnogene abeparvovec-brve is an AAV vector-based gene therapy intended for a one-time intrathecal injection.[8] It is indicated to treat SMA in adults and pediatric patients 2 years of age and older with confirmed mutation in the SMN1 gene.[8] Unlike onasemnogene abeparvovec-xioi, onasemnogene abeparvovec-brve is administered as a fixed dose independent of patient weight.[12] Onasemnogene abeparvovec-brve is delivered intrathecally at a lower total dose than onasemnogene abeparvovec-xioi.[12] The safety and efficacy of onasemnogene abeparvovec-brve is supported by data from the STEER trial, which is described and evaluated below in **Table 6**.

The STEER (NCT05089656) trial was a 52-week, phase 3, multicenter, sham-controlled, double-blind RCT evaluating intrathecal onasemnogene abeparvovec-brve in patients with Type 2 SMA (n =126).[9] Enrolled patients were 2 to less than 18 years of age, were treatment-naive to any other SMA therapies, and were able to sit but never walked independently.[9] The study was conducted at 29 sites in 14 countries.[9] A total of 217 patients were screened for enrollment; 4 patients did not complete the screening phase and 77 patients failed screening based on exclusion criteria, with the main reasons being scoliosis with a Cobb angle greater than 40° while sitting or severe contractures, hepatic dysfunction, and AAV9 antibody titer greater than 1:50.[9] Patients treated in the study received a course of oral corticosteroid, equivalent to oral prednisolone at 1 mg per kg of body weight per day (mg/kg/day) for a total of 30 days, starting one day prior to gene therapy administration.[12] The corticosteroid dose was tapered after the 30-day period, based on the clinical status and liver function testing.[12] Participants randomized to the sham procedure arm received placebo instead of prednisolone and followed the same administration protocol.[10] After their procedures on study day 1, participants remained at the hospital for 24−48 hours for safety monitoring.[10]

Clinical investigations of medication for SMA (including pivotal studies of both risdiplam and nusinersen) have demonstrated reduction of treatment effect size for patients with increasing age.[10] Therefore, STEER was designed to evaluate motor function changes in two age subgroups: 2 to less than 5 years of age as secondary endpoints and 5 to less than 18 years of age as exploratory endpoints.[10] A total of 71 patients were in the 2 to less than 5 years age group (42 in the onasemnogene abeparvovec-brve group and 29 in the sham group), and 55 patients in the 5 to less than 18 years age group (33 in the onasemnogene abeparvovec-brve group and 22 in the sham group).[12] In total, 126 patients received onasemnogene abeparvovec-brve (n = 75) or a sham procedure (n = 51).[9]

The primary efficacy endpoint was change from baseline in Hammersmith Functional Motor Scale-Expanded (HFMSE) score. The published MCID for this exam is 3 points;[27] however, the investigators used an MCID of an improvement greater than 1.5 points, as established in a 2024 study of patients with SMA types 2 and 3.[10] This study sought to determine the MCID in HFMSE score for patients with SMA type 2 and type 3 using 2 distinct methods: standard error of measurement and anchor-based using receiver operating characteristic (ROC) curve analysis.[10] These investigators identified optimal HFMSE cutoff points of −2 for type 2 and −4 for type 3 patients use the ROC analysis, whereas using the standard error, the investigators found the optimal cutoff points to be 1.5 for improvement and −3.2 for deterioration.[10] Patients treated with onasemnogene abeparvovec-brve demonstrated a statistically significant increase in HFMSE score compared with sham (LSMD 1.88; 95% CI, 0.51 to 3.25; P = 0.0074).[9]

Secondary endpoints included achievement of a least a 3-point improvement in HFMSE score at week 52 in the overall study population and in a subgroup population aged 2 to less than 5 years of age, and change from baseline in Revised Upper Limb Module (RULM) at week 52 in the overall study population and the subgroup population aged 2 to less than 5 years of age.[9] There is no established MCID for the RULM. The secondary efficacy endpoints did not reach statistical significance (see **Table 6**).[12]

Possible limitations of this study include broad inclusion of all patients regardless of baseline HFMSE and wide age range in the eligibility criteria.[9] At the time of recruitment, many younger eligible patients in certain regions had already received intravenous gene therapy, which meant the trial population was on average older than those studied in previous trials; most patients were 6 years of age or older.[10] An observation period of 12 months may also not be sufficient to permit assessment of delayed adverse events for onasemnogene abeparvovec-brve or to observe full benefit in motor function.[9]

Clinical Safety:
The safety data for onasemnogene abeparvovec-brve is derived from 2 clinical studies: one RCT conducted in 126 patients with SMA and a second open-label single-arm study conducted in 27 patients with SMA who were previously treated with nusinersen or risdiplam.[8] In the RCT, serious adverse reactions were reported in 4 patients (5%) including elevated liver enzymes (n=1), sensory disturbance (n=2), and vomiting (n=1).[8] The most frequently reported adverse events from the RCT are summarized in **Table 6**. The open-label study did not identify any additional adverse events associated with onasemnogene abeparvovec-brve administration.[8] Monitoring and data collection were not sufficient to definitively determine if sensory events observed in some participants were linked to dorsal root ganglia toxicity, a concern previously noted in primate studies.[9]

Table 6. Adverse Events Reported in Onasemnogene abeparvovec-brve-Treated Patients Compared to Sham-Treated Patients[8]

Adverse Events	**Onasemnogene abeparvovec-brve** N=75	**Sham** N=51
Upper respiratory tract infection	31 (41%)	15 (29%)
Pyrexia	19 (25%)	12 (24%)
Upper gastrointestinal symptoms	20 (27%)	8 (16%)
Hepatic enzyme increased	6 (8%)	5 (10%)
Headache	8 (11%)	2 (4%)
Dizziness	4 (5%)	1 (2%)
Pain in extremity	3 (4%)	1 (2%)
Thrombocytopenia	3 (4%)	0
Sensory disturbance	3 (3%)	1 (2%)

The manufacturer's label for onasemnogene abeparvovec-brve has a black boxed warning regarding the risk of acute serious hepatic injury and elevated aminotransferases that can occur with administration of this gene therapy.[8] Patients with preexisting hepatic impairment may be at higher risk for hepatic injury.[8] The manufacturer recommends assessing liver function by clinical examination and laboratory testing prior to intrathecal injection.[8] Administer systemic corticosteroid before and after onasemnogene abeparvovec-brve injection.[8] Continue to monitor liver function for at least 3 months after injection, and at other times as clinically indicated.[8]

Look-alike / Sound-alike Error Risk Potential: Onasemnogene abeparvovec-xioi

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved motor function
2) Prolonged survival
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change from baseline to week 52 in motor function, as measured by the Hammersmith Functional Motor-Scale Expanded (HFSME).

Table 7. 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. Proud CM, et al.[9] NCT05089656 Phase 3 MC, DB, SC, RCT Trial Duration: 52 weeks	1. OAV IT injection 1.2 x 10^{14} vector genomes x 1 dose 2. Sham IT injection x 1 dose	Demographics: -Mean age: 5.9 y -Mean age at SMA onset: 12.7 mos -Male: 49% -Race: Asian: 59% White: 11% Black: 7% American Indian: 5% Unknown: 17% - SMN2 gene copies: 2 copies: 4% 3 copies: 94% ≥ 4 copies: 2% -Baseline HFMSE score: 17.97 points (OAV) and 18.17 points (sham) Key Inclusion Criteria: -Aged 2 to 17 y with genetically confirmed SMA -Treatment-naïve -Onset of SMA symptoms ≥ 6 mos of age -Able to sit, but never walked independently Key Exclusion Criteria: -Cardiomyopathy, hepatic dysfunction, kidney disorder,	ITT: 1. 75 2. 51 PP: 1. 73 2. 50 Attrition: 1. 2 (3%) 2. 1 (2%)	Primary Endpoint: LSM change in HFMSE at 52 weeks in ITT population 1. 2.39 points 2. 0.51 points LSM difference: 1.88; 95% CI 0.51 to 3.25 P = 0.0074 Secondary Endpoints: LSM change in HFMSE at 52 weeks for patients aged ≥ 2 to <5 y 1. 3.00 2. 1.56 LSM difference: 1.44; 95% CI -0.33 to 3.22; P=0.11 Proportion with 3-point HFMSE improvement at 52 weeks in ITT group 1. n = 29 (39.2%) 2. n = 13 (26%) OR: 2.03; 95% CI 0.90 to 4.57; P = 0.088 Proportion with 3-point HFMSE improvement at 52 weeks in ≥ 2 to <5 y age group 1. n = 20 (48.8%) 2. n = 11 (37.9%) OR: 1.27; 95% CI 0.46 to 3.56; P=0.64 LSM change from baseline in RULM score at end of 52 weeks in ITT population 1. 2.44 2. 0.92	 NA NS NS NS	Any AE 1. 73 (97%) 2. 46 (90%) Serious AE 1. 21 (28%) 2. 17 (33%) Severe AE 1. 8 (11%) 2. 9 (18%) Hepatotoxicity 1. 7 (9%) 2. 5 (10%) Transient Thrombocytopenia 1. 4 (5%) 2. 2 (4%) Dorsal root ganglia toxicity 1. 2 (3%) 2. 1 (2%) p-values and CIs not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not described. Baseline demographics balanced. Performance Bias: Low. Participants, caregivers, clinical evaluators, and study investigators were blinded. Detection Bias: Unclear. Adverse effects of active therapy may have caused unblinding. Attrition Bias: Low. Attrition rates were low. Reporting Bias: Low. Study protocol available on-line. All prespecified primary and secondary outcomes reported according to protocol. Other Bias: High. Funded by Novartis Pharma AG. Manufacturer also involved in study design, data collection, data analysis, and report writing. Several authors reported conflict of interest due to financial support from manufacturer for research or lectures. **Applicability**: Patient: Study enrolled patients with SMA type 2 aged 2 to 17 y reflects common ages treated in Medicaid population. Most patients were Asian, which may reflect the 7 Asian countries involved in the RCT.

		endocrine disorder, or severe respiratory compromise -AAV9 antibody titer > 1:50 -Active infection in past 30 days -Invasive or noninvasive ventilation in past 30 days -Surgery for scoliosis or hip fixation in past 12 mos		LSM difference: 1.52; 95% CI 0.34 to 2.71 P = 0.012 LSM change from baseline in RULM score at end of 52 weeks in ≥ 2 to <5 y age group 1. 3.27 2. 1.82 LSM difference: 1.45; 95% CI -0.22 to 3.12; P = 0.087	NA NS			Intervention: Safety and efficacy of fixed IT dose evaluated in Phase 2 trial conducted in patients aged 6 mos to < 60 mos. Comparator: Sham IT injection used as a comparator. Outcomes: Improvement in HFSME has been validated in Type 2 SMA patients. Setting: 29 sites in 14 countries including the United States, Brazil, China, Denmark, India, Malaysia, Mexico, Saudi Arabia, Singapore, South Africa, Taiwan, Thailand and Vietnam.
Abbreviations: ARR = absolute risk reduction; AAV9 = anti-adeno-associated virus serotype 9; AE = adverse event; CI = confidence interval; DB = double blind; HFMSE = Hammersmith Functional Motor Scale-Expanded; IT = intrathecal; ITT = intention to treat; kg = kilograms; LSM = least squares mean; MC = multi-center; mITT = modified intention to treat; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; OAV = onasemnogene abeparvovec-brve; OR = odds ratio: PP = per protocol; RCT = randomized clinical trial; RULM = Revised Upper Limb Module: SC = sham controlled; SAE = serious adverse event; SMA = spinal muscular atrophy; y = years.								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL	Carveout
onasemnogene abeparvovec-xioi	ZOLGENSMA	INTRAVEN	KIT	Y	Y
onasemnogene abeparvovec-brve	ITVISMA	INTRATHEC	VIAL	N	Y
nusinersen sodium/PF	SPINRAZA	INTRATHEC	VIAL	N	
risdiplam	EVRYSDI	ORAL	SOLN RECON	N	
risdiplam	EVRYSDI	ORAL	TABLET	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to March 05, 2026>

1	exp Muscular Atrophy, Spinal/th [Therapy]	1054
2	onasemnogene abeparvovec-xioi.mp.	1
3	onasemnogene abeparvovec.mp.	344
4	Oligonucleotides, Antisense/ or nusinersen.mp.	15797
5	risdiplam.mp.	338
6	2 or 3 or 4 or 5	16058
7	1 and 6	286
8	limit 7 to (english language and humans and yr="2023 -Current" and (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or "systematic review"))	

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ITVISMA safely and effectively. See full prescribing information for ITVISMA.

ITVISMA® (onasemnogene abeparvovec-brve) suspension, for intrathecal injection
Initial U.S. Approval: 2025

WARNING: SERIOUS LIVER INJURY
See full prescribing information for complete boxed warning.

- **Acute serious liver injury and elevated aminotransferases can occur with ITVISMA. (5.1)**
- **Patients with preexisting liver impairment may be at higher risk. (5.1)**
- **Prior to intrathecal injection, assess liver function by clinical examination and laboratory testing. Administer systemic corticosteroid before and after ITVISMA injection. Continue to monitor liver function for at least 3 months after injection, and at other times as clinically indicated. (2.1, 2.4)**

----------INDICATIONS AND USAGE----------
ITVISMA is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age and older with confirmed mutation in *SMN1* gene. (1)

----------DOSAGE AND ADMINISTRATION----------
For single-dose intrathecal injection only. (2)

- The recommended dose of ITVISMA is 1.2×10^{14} vector genomes (vg). (2.2)
- Administer ITVISMA as an intrathecal bolus injection over approximately 1 to 2 minutes. (2.4)
- Postpone ITVISMA in patients with infections until the infection has resolved and the patient is clinically stable. (2.1)
- Starting one day prior to ITVISMA injection, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. At the end of the 30-day period, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose gradually over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose gradually over the next 28 days or longer if needed. Do not stop systemic corticosteroids abruptly. (2.2)
- If at any time patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone, based on the patient's clinical course, prompt consultation with a gastroenterologist or hepatologist and adjustment to the recommended corticosteroid regimen may be considered. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Each single-dose vial contains 1.2×10^{14} vg of onasemnogene abeparvovec in 3 mL of suspension. ITVISMA has a nominal concentration of 4×10^{13} vg/mL, and each vial contains an extractable volume of not less than 3 mL. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Prior to ITVISMA injection, assess liver function of patients by clinical examination and laboratory testing. Continue to monitor liver function for at least 3 months after injection, and at other times as clinically indicated. (2.1, 2.4, 5.1)
- Thrombocytopenia: Monitor platelet counts before ITVISMA injection, and at least weekly for the first month and as clinically indicated until platelet counts return to baseline. (2.1, 2.4, 5.2)
- Peripheral Sensory Neuropathy: Consider complete neurologic evaluation and other testing and/or symptom management based on the patient's clinical presentation. (5.3)
- Thrombotic Microangiopathy (TMA): Prompt attention to signs and symptoms of TMA is advised, as TMA can result in life-threatening or fatal outcomes. If clinical signs, symptoms and/or laboratory findings occur, consult a hematologist and/or nephrologist immediately to manage as clinically indicated. (5.4)
- Elevated Cardiac Troponin I: Increases in cardiac troponin I have occurred following ITVISMA injection. Consider cardiac evaluation after ITVISMA administration and consult a cardiologist as needed. (5.5)
- AAV Vector Integration and Risk of Tumorigenicity: There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. Report cases of tumors in patients who received ITVISMA, to Novartis Gene Therapies, Inc. (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reactions that occurred in at least 10% of patients were upper respiratory tract infection, upper gastrointestinal symptoms, pyrexia, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Gene Therapies at 1-833-828-3947 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Adjust patient's vaccination schedule to accommodate concomitant corticosteroid administration prior to and following ITVISMA injection. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2025

Appendix 4. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	AAV vector that uses the AAV9 capsid to deliver a functional copy of the SMN1 gene
Oral Bioavailability	N/A
Distribution and Protein Binding	Vector DNA concentrations were highest in the liver, followed by the dorsal root ganglia and spinal cord, with the lowest concentrations detected in the gonads. Vector DNA concentrations in the spinal cord tended to remain stable between 6-weeks and 12-months post-administration at all dose levels assessed. Protein binding was not reported.
Elimination	Shedding of onasemnogene abeparvovec DNA was primarily via feces. Peak shedding in participants was observed within 10-, 3-, 2-, and 8 days post-dose for stool, urine, saliva and nasal secretion, respectively. Over 90% of the vector DNA is excreted within 2 weeks after dose administration.
Half-Life	N/A
Metabolism	N/A

Abbreviations: AAV = adeno-associated virus; DNA = deoxyribonucleic acid; N/A = not applicable; SMN = survival motor gene

Appendix 5: Key Inclusion Criteria

Population	Children and adults with spinal muscular atrophy
Intervention	Nusinersen, onasemnogene abeparvovec-xioi, risdiplam, and onasemnogene abeparvovec-brve
Comparator	Placebo, sham injection, or standard of care
Outcomes	Improved motor function as assessed by exams presented in **Table 2**
Timing	1 to 5 years
Setting	Inpatient for gene therapy injections, provider office or inpatient for nusinersen injections, outpatient for risdiplam. Outcomes were followed on an outpatient basis.

Spinal Muscular Atrophy Drugs

Goal(s):

- Approve nusinersen (SPINRAZA), onasemnogene abeparvovec-xioi (ZOLGENSMA), risdiplam (EVRYSDI), or onasemnogene abeparvovec-brve (ITVISMA) for conditions supported by evidence of benefit (e.g., spinal muscular atrophy).
- ~~Incorporate 2-step review process for drugs on the high-cost drug carve-out list.~~

Length of Authorization:

- Nusinersen: Up to 8 months for initial approval and up to 12 months for renewal.
- Onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve: Once in a lifetime dose.
- Risdiplam: Up to 6 months for initial approval and 12 months for renewal.

Requires PA:

- Nusinersen, onasemnogene abeparvovec-xioi, or onasemnogene abeparvovec-brve (pharmacy or provider administered claims)
- Risdiplam (pharmacy claims)

Covered Populations:

- Onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve: FFS and CCO enrolled populations beginning 1/1/26
- Risdiplam and nusinersen: FFS populations only

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. FDA-Approved Dosing For Risdiplam

Age and Body Weight	Recommended Daily Dose of Risdiplam
Less than 2 months of age	0.15 mg/kg
2 months to less than 2 years of age	0.2 mg/kg

Age and Body Weight	Recommended Daily Dose of Risdiplam
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code. Go to #2	
2. Is this a request for continuation of nusinersen or risdiplam therapy? Note: Onasemnogene abeparvovec-xioi and onasemnogene abeparvovec-brve are only approved as a single, one-time dose per lifetime	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing?	**Yes:** Go to #4 Document results of genetic testing	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the requested medication prescribed by a pediatric neurologist or a provider with experience treating SMA?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient ventilator-dependent (using at least 16 hours per day on at least 21 of the last 30 days)? Note: This assessment does not apply to patients who require ventilator assistance	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Has baseline motor assessment appropriate for age and/or intended population been assessed within the past 6 months? Examples include, but are not limited to, the following validated assessment tools: • Hammersmith Infant Neurological Examination, Section 2 (HINE-2) • Hammersmith Functional Motor Scale (HFMSE) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • The Motor Function Measure 32 items (MFM-32) • Upper Limb Module (ULM) • 6-minute walk test (6MWT)	**Yes:** Document date and assessment results Date: _____ Assessment:_____ Results:_____ Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the provider documented goals of therapy for this treatment?	**Yes:** Go to #8~~7~~	**No:** Pass to RPh. Deny; medical appropriateness.
8. For able patients, is there baseline documentation of pulmonary function measured by spirometry (FEV1, FVC, etc.) or other validated pulmonary function test within the past 6 months?	**Yes:** Go to #9 Document baseline results.	**No:** Pass to RPh. Deny; medical appropriateness.
~~7.~~9. Has the patient had previous administration of onasemnogene abeparvovec-xioi (ZOLGENSMA) or onasemnogene abeparvovec-brve (ITVISMA), either in a clinical study or as part of medical care?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the request for concomitant therapy with nusinersen and risdiplam?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
~~8.~~11. Is the request for risdiplam?	**Yes**: Go to #12	**No**: Go to #14

Approval Criteria		
~~9.~~12. Is the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Recommended FDA-approved dosage is determined by age and body weight.
~~10.~~13. In people of child-bearing potential, is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~14.Is the request for nusinersen?	**Yes**: Go to #15	**No**: Go to #16
~~12.~~15.Is there documentation of recent safety monitoring in the past 4 months as recommended by the FDA (including platelet counts above the lower limit of normal and urinary protein concentrations < 0.2 g/L)?	**Yes:** -Approve for up to 8 months.	**No:** Pass to RPh. Deny; medical appropriateness.
16. Is the request for onasemnogene abeparvovec in an FDA-approved age? Note: onasemnogene abeparvovec-xioi (ZOLGENSMA) is approved for < 2 years of age. Onasemnogene abeparvovec-brve (ITVISMA) is approved for ≥2 years of age.	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness
~~13.~~17.Have all the following labs been obtained: a) a baseline platelet count; b) baseline liver function tests (AST, ALT, total bilirubin, and PT); AND c.) baseline troponin-I?	**Yes:** Go to #18~~1~~	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~14.~~18.Does the patient have a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec?	**Yes:** Pass to RPh. Approval pending secondary review by DMAP. Duration: Approvals cover one lifetime dose. Approval valid for 12 months and will be extended if needed to cover treatment journey.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness
2. Has the patient received a formulation of the gene therapy onasemnogene abeparvovec?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #3

Renewal Criteria		
3. Is the patient meeting goals of therapy as documented by the provider in the initial approval?~~Has the patient shown a positive treatment response in one of the following areas?~~ ~~Documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened~~ ~~-OR-~~ ~~Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease~~ ~~-OR-~~ ~~Documentation of an improvement or lack of decline in pulmonary function compared to baseline~~	**Yes:** Approve for 12 months	**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: 6/26 (DM); 2/23 (DM); 9/19 (DM); 7/17; 3/17
Implementation: TBD; 4/1/23; 11/1/19: 9/1/17; 5/17

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OHSU Drug Effectiveness Review Project Summary Report – Newer Agents for Myasthenia Gravis

Date of Review: June 2026

Date of Last Review: Amifampridine (Nov 2019)
Efgartigimod (Feb 2023)
Remaining agents subject to Orphan Drug policy
Literature Search: through 12/12/24

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

Plain Language Summary:

- Generalized myasthenia gravis (gMG) and Lambert-Eaton myasthenic syndrome (LEMS) are diseases that cause muscle weakness. The weakness often worsens over time and with more activity.
- People with these diseases often take a medicine called pyridostigmine and oral medicines that affect the immune system to manage symptoms. Some patients may still have many symptoms, or a crisis, even with these medicines. A myasthenia crisis is when a ventilator is needed to help patients breathe because the muscles used for breathing become too tired.
- The Food and Drug Administration has approved several new medicines that may help myasthenia gravis symptoms, including patients who still have many symptoms on standard treatment. These medicines affect the immune system and cannot be used with one another. Most of them must be injected into a vein or the skin.
- These medicines have been tested compared to placebo (saline injection). None of these medicines have been compared to another to know which is better or safer.
- The Drug Use Research and Management group recommends medicines be available with prior authorization. Prior authorization is when providers explain to the Oregon Health Authority why a patient needs that medicine before the Oregon Health Plan will pay for it.

Research Questions:

1. What is the effectiveness of the newer agents for generalized myasthenia gravis (gMG) and Lambert-Eaton myasthenic syndrome (LEMS) in adults?
2. What are the harms of the newer agents for generalized myasthenia gravis (gMG) and Lambert-Eaton myasthenic syndrome (LEMS) in adults?

Author: Sara Fletcher, PharmD, MPH, BCPS

Conclusions:

- There is no head-to-head comparative evidence between agents.[1]
- All evidence is based on 1 to 2 RCTs using placebo comparisons.[1] These studies vary widely in study size, population (e.g. antibody types), duration, design, and include both phase 2 and phase 3 trials.[1] Most certainty of evidence (CoE) is low to very low and all studies were rated as having moderate or high risk of bias (RoB).[1]
- There is insufficient evidence to show clinical superiority or improved safety for one agent over another. Agents vary by route of administration and administration interval.[1]

Recommendations:

- No changes recommended to preferred drug list (PDL) or prior authorization (PA) criteria based on clinical evidence.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

- Newer agents for myasthenia gravis are separated into multiple classes (orphan drug policy, biologic agents for rare diseases, potassium channel blockers). All have prior authorization restricting use to indications approved by the Food and Drug Administration (FDA). Efgartigimod alfa-fcab was reviewed for use in myasthenia gravis in April 2022. Amifampridine for LEMS was reviewed in November 2019. Other agents were added to the orphan drug policy without a specific review of the evidence.
- Rituxumab, an off-label therapy for myasthenia gravis, is available through the Targeted Immune Modulators therapy prior authorization criteria. It was not included in this DERP summary.

Methods:

The June 2025 drug class report on Myasthenia Gravis 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.

Summary Findings:

Both generalized myasthenia gravis (gMG), and Lambert-Eaton myasthenic syndrome (LEMS), are chronic autoimmune disorders which are characterized by chronic, progressive muscle weakness resulting from miscommunication at the neuromuscular junction.[1] Myasthenia gravis prevalence is estimated at 37:100,000 people in the United States and is more common in people over 50, though women often have a younger age of onset and it is slightly more

common in African American individuals.[1] Common autoantibodies present in gMG include anti-acetylcholinesterase receptor antibodies (AChR), anti-muscle-specific kinase antibodies (MUSK), and anti-low-density lipoprotein–related protein 4 antibodies (LPR4). About 85% of individuals are AChR positive (AChR+).[1] Thymomas, present in roughly 10% of gMG patients, also result in autoantibody production.[1] LEMS is more rare than gMG, though gender and age distribution are similar.[1] Other forms of myasthenia gravis (ocular, congenital, and transient neonatal) were not the focus of this report.

Muscle weakness fluctuates with rest and activity. Patients can present with a myasthenic crisis when ventilator support is needed to support breathing.[1] Initial treatment for gMG often begins with acetylcholinesterase inhibitors such as pyridostigmine and chronic oral immunotherapies such as glucocorticoids or nonsteroidal immunosuppressive agents (i.e. azathioprine).[1] Other therapies can include intravenous immune globulin, rituximab, plasmapheresis, and thymectomy.[1] Newer antibody-based therapies, often employed for more refractory cases, are the focus of this review (**Table 1**).[1]

Multiple outcomes were used across the studies. Symptom severity was most commonly assessed using Myasthenia Gravis Composite (MGC; range 0-50, higher scores correlate to greater severity, minimum clinically important difference [MCID] 3) or Quantitative Myasthenia Gravis (QMG; range 0-39, higher scores correlate to greater severity, MCID 2.6-3.5 based on baseline with most studies using 3).[1] The Myasthenia Gravis Activities of Daily Living (MG-ADL) was used as a function outcome marker for many approval studies and relates to functional activities of ocular, bulbar, respiratory, and gross motor or limb impairment.[1] Scores range from 0 to 24 points with higher scores indicating greater disease severity.[1] A change of 2 points is considered a MCID and was used in these trials.[1] Quality of life (QoL) was often assessed with the original or revised 15 item Myasthenia Gravis Quality of life scale (MG-QoL 15; range 0-60, no MCID)(MG-QoL 15r; range 0-30; no MCID).[1] Higher scores correlate to worse severity for both versions.[1] Alternative assessment tools were also used in some studies.

Literature search found 896 records from database searches. After eligibility review, 13 randomized controlled trials (RCTs) were included.[1] All were placebo-controlled RCTs with no head-to-head comparisons between agents in completed or ongoing studies of currently approved agents.[1] One ongoing study was identified for inebilizumab-cdon. Inebilizumab-cdon received FDA approval for gMG after publication of this DERP report but was included as a pipeline agent. Ongoing studies of amifampridine, efgartigimod, and nipocalimab were also identified, in addition to several pipeline agents without current gMG or LEMS approval.[1]

Table 1. FDA approved newer agents for adults with gMG or LEMS included in report[1]

Generic Name	Brand Name	Indications*	Mechanism of Action	Route and Maintenance Interval of Administration
Amifampridine phosphate	Firdapse, Rizurgi	LEMS; ≥6y	Potassium channel blocker	Oral; daily
Eculizumab	Soliris; biosimilars	AChR+ gMG; ≥6y	Complement inhibitor	IV; every 2 weeks
Efgartigimod alfa-fcab	Vyvgart	AChR+ gMG;	Neonatal FC receptor inhibitor	IV; weekly for 4 weeks, other cycles as needed
Efgartigimod alfa + hyaluronidase-qvfc	Vyvgart Hytrulo	AChR+ gMG	Neonatal FC receptor inhibitor	SC (provider administered); weekly for 4 weeks, other cycles as needed
Inebilizumab-cdon	Uplizna	AChR+ or MUSK+ gMG	Anti-CD19 antibody	IV; every 6 months

Nipocalimab	Imaavy	AChR+ or MUSK+ gMG; ≥12y	Neonatal FC receptor inhibitor	IV; every 2 weeks
Ravulizumab-cwvz	Ultomiris	AChR+ gMG	Complement inhibitor	IV; every 8 weeks
Rozanolixizumab-noli	Rystiggo	AChR+ or MUSK+ gMG	Neonatal FC receptor inhibitor	SC (provider administered); weekly for 6 weeks, other cycles as needed
Zilucoplan	Zilbrysq	AChR+ gMG	Complement inhibitor	SC; daily
Abbreviations: AChR+ = Acetylcholine receptor antibody positive; gMG = generalized myasthenia gravis; IV = intravenous; LEMS = Lambert-Eaton myasthenic syndrome; MUSK+ = anti-muscle specific tyrosine kinase antibody positive; SC = subcutaneous; y = years. *some agents have additional indications unrelated to gMG and LEMS				

Amifampridine in LEMS[1]

Evidence is based on 2 RCTs (n=64; both high RoB) and very low CoE for all outcomes. Study duration was 2 weeks for one RCT (n=38) and 4 days for the other RCT (n=26).

Efficacy

- Symptom severity increased for all patients, was statistically significantly smaller in amifampridine treated patients, but this was not always clinically meaningful.
- Function measures were mixed where one study showed statistically significant improvement and the other no difference compared to placebo.
- Quality of life was not assessed in these RCTs.

Safety

- No difference in total adverse events (AEs) in one RCT, while the other reported 3 events with amifampridine and 11 with placebo treated patients. Most common AEs were muscle weakness, fatigue, oral and digital paresthesia, headache, nausea, and diarrhea.
- No severe adverse events (SAEs) reported in either group.

Amifampridine in gMG[1] (off-label)

Evidence is based on 1 RCT (n=7; high RoB) and very low CoE for all outcomes for the MuSK antibody positive subtype, while AChR antibody status not reported. The RCT had a cross-over design where amifampridine or placebo was given in 1-week intervals with no washout period between treatment arms for a 3 total of weeks. Patients receiving 2 weeks of a treatment (ex. placebo, then amifampridine, then placebo) would be counted twice for that treatment.

Efficacy

- Symptom severity scores worsened for all participants for both outcome measures used, though amifampridine had a statistically significantly smaller and clinically meaningful smaller increase.
- Function and QoL measures showed statistically significant and clinically meaningful improvement.

Safety

- Total AEs were not separated by treatment group, though paresthesias were most common.
- No SAEs were reported in either group.

Eculizumab in gMG[1]

Evidence is based on 2 RCTs, one (n=14) crossover study of 16-week treatment periods and a 5-week washout with high RoB and one (n=126) with 26-week duration and moderate risk of bias. All patients were AChR+ and had inadequate control with standard immunotherapy; MuSK antibodies were not reported.

Efficacy

- Symptom severity scores of QMG (very low CoE) and MGC (low CoE) both decreased for all participants and eculizumab had a statistically significant and clinically meaningful decrease compared to placebo.
- Function measures were statistically significantly improved in both studies but only clinically meaningful in 1 RCT (very low CoE).
- QoL measures were statistically significantly and clinically meaningfully improved (low CoE).

Safety

- Total AEs were similar in both groups and were most commonly headache, upper respiratory infection, nasopharyngitis, nausea, and diarrhea (very low CoE).
- SAEs were similar between groups but varied between studies (1% vs. 1% and 15% vs. 29%) (low CoE).

Efgartigimod in gMG[1]

Evidence is based on 2 RCTs with high RoB, one (n=24) where all patients were AChR+ and MuSK status was not reported; patients were followed for 80 days. The second trial (n=167) included a mixed population of antibody status (77% AChR+, 4% MuSK+) and patients were followed for 10 weeks.

Approval of the combination product with hyaluronidase was based on pharmacokinetic data and comparison of antibody reduction to the single agent product.

Efficacy

- Symptom severity scores using two scales showed clinically meaningful reductions, but benefits waned over time after conclusion of a treatment cycle (low CoE).
- Function scores showed statistically significant and clinically meaningful reductions which waned over time (low CoE).
- QoL improved for all participants and the score reduction was statistically significantly greater than placebo with the maximum difference around week 4, with the difference waning over time (low CoE).
-

Safety

- Most patients experienced an AE, and the most common AEs were headache, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, itching, and urinary tract infection (moderate CoE).
- Very few SAEs were reported, and there was no difference between groups (low CoE).

Nipocalimab in gMG[1]

Evidence is based on a single phase 2 RCT (n=68 divided into 4 dosing groups or placebo) over 8 weeks in patients with refractory gMG with moderate RoB. Patients had mixed antibody profiles (MuSK+ 7.1% and AChR+ 92-93%) and insufficient symptom control with standard immunotherapy.

Efficacy

- Symptom severity ratings were no different between all groups (low CoE).
- Function scores were no different between all groups (low CoE).
- QoL had no overall difference between drug and placebo, though the 30 mg/kg every 4-week dosage was statistically significantly different than placebo (low CoE). This is not the current FDA approved dosing interval.

Safety

- There were no differences in AEs between treatment and placebo, and the most common AEs were headache, diarrhea, nasopharyngitis, and rash (moderate CoE).
- There were few SAEs and no differences between various treatment and placebo groups (low CoE).

A phase 3 trial (n=196) was published after the literature search end date which did show a statistically significant, but not clinically significant difference in function (MG-ADL).[2] The treatment effect was more pronounced in male patients compared to female patients.[2] Total AE and SAE were similar between treatment and placebo groups.[2]

Ravulizumab in gMG[1]

Evidence is based on 1 RCT (n=175) of 26-week duration and moderate RoB. All patients were AChR+ while MuSK status was not reported.

Efficacy

- Symptom severity decrease was statistically significant compared to placebo, but the change was not clinically meaningful (low CoE).
- Function status improvement was statistically significant compared to placebo, but the change was not clinically meaningful (low CoE).
- QoL scores improved, but were not statistically significant between groups (low CoE).

Safety

- Roughly 34% of patients experienced an AE attributed to the treatment, and there were no differences between groups (low CoE). The most common AEs were headache, diarrhea, and nausea.
- SAEs were reported in both groups (23% vs. 16%) with no difference between groups (moderate CoE).

Rozanolixizumab in gMG[1]

Evidence is based on 2 RCTs. One was a phase 2a study (n=43) over 4 weeks where most patients were AChR+ (90%-95%) and few were MuSK+ (0%-5%) with high RoB. The other was a phase 3 trial (n=200) over 6 weeks with 88%-91% AChR+ and 8%-12% MuSK+ patient representation. Two treatment dosage groups were included in addition to placebo.

Efficacy

- Symptom severity was statistically significantly improved in both RCT using two screening tools, but only clinically meaningful in the larger, phase 3 trial (very low CoE).
- Function was statistically significantly improved in both RCT, but only clinically meaningful in the larger, phase 3 trial (very low CoE)
- QoL assessment was not included.

Safety

- There were statistically significantly more AEs in the 10mg/kg dosage group in 1 study, while 7mg/kg did not differ from placebo in either study (moderate CoE). The most common AEs were nausea, vomiting, diarrhea, headache, fatigue, dizziness, fatigue, muscle pain, and nasopharyngitis.
- There was no difference in SAEs between study groups (0% for 7 mg/kg dosage, 3% for 10 mg/kg dosage) (moderate CoE).

Zilucoplan in gMG[1]

Evidence is based on 2 RCT. One was a 12-week phase 2 study (n=45) where all patients were AChR+ and MuSK status was not reported (high RoB). The other was a phase 3 RCT (n=174) of 12-week duration where all patients were AChR+ and 0% were MuSK+ (moderate RoB).

Efficacy

- Symptom severity was statistically significantly improved using two screening tools for 0.3 mg/kg dosage, the difference was just below the MCID threshold (low CoE).
- Function improvement was statistically significantly and clinically meaningfully improved in all treatment dosage groups (low CoE).
- QoL results were mixed between the different studies and dosage groups. There was statistically significant improvement in the 0.1 mg/kg dosage group in the phase 2 study but not the 0.3 mg/kg group. In the phase 3 study, there was statistically significant improvement in the treatment group (0.3 mg/kg) (low CoE). MCID is unknown for the QoL assessment tool used.

Safety

- Most patients experienced an AE, and AEs were more common in treatment groups compared to placebo, though differences were not significant. (moderate CoE). The most common AEs were headache, injection-site reactions, nausea, vomiting, diarrhea, rash, and urinary tract infections.
- SAEs ranged from 0% to 20% and were inconsistent between placebo and different dosages (moderate RoB).

References:

1. Lyon J, Vintro A, Yeddala S, Shaw B, Anderson R. Newer agents for myasthenia gravis. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2025.

2. Antozzi C, Vu T, Ramchandren S, et al. Safety and efficacy of nipocalimab in adults with generalised myasthenia gravis (Vivacity-MG3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. Feb 2025;24(2):105-116. doi:10.1016/S1474-4422(24)00498-8

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
amifampridine phosphate	FIRDAPSE	ORAL	TABLET	N
eculizumab	SOLIRIS	INTRAVEN	VIAL	
eculizumab-aagh	EPYSQLI	INTRAVEN	VIAL	N
eculizumab-aeeb	BKEMV	INTRAVEN	VIAL	N
efgartigimod alfa-fcab	VYVGART	INTRAVEN	VIAL	N
efgartigimod-hyaluronidas-qvfc	VYVGART HYTRULO	SUBCUT	SYRINGE	
efgartigimod-hyaluronidas-qvfc	VYVGART HYTRULO	SUBCUT	VIAL	
inebilizumab-cdon	UPLIZNA	INTRAVEN	VIAL	
nipocalimab-aahu	IMAAVY	INTRAVEN	VIAL	
ravulizumab-cwvz	ULTOMIRIS	INTRAVEN	VIAL	
rozanolixizumab-noli	RYSTIGGO	SUBCUT	VIAL	
zilucoplan sodium	ZILBRYSQ	SUBCUT	SYRINGE	N

Amifampridine

Goal(s):

- Promote safe and effective use of amifampridine in the treatment of LEMS symptoms

Length of Authorization:

- Initial: 14 days
- Renewal: 1 to 3 months

Requires PA:

- Amifampridine

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: Maximum Recommended Dose

Formulation	Minimum age (years)	Weight (kg)	Single Dose Maximum	Cumulative Daily Maximum
Ruzurgi®	≥ 6	< 45	15 mg	50 mg
		≥ 45	30 mg	100 mg
Firdapse®	≥ 6	< 45	15 mg	50 mg
		≥ 45	20 mg	100 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3

Approval Criteria		
3. Is the diagnosis for Lambert-Eaton Myasthenic Syndrome (LEMS)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
~~4. Is the request for a non-preferred product and 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 Committee.~~	~~**Yes:** Inform prescriber of preferred alternatives.~~	~~**No:** Go to #5~~
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there evidence based on chart notes or claims that the patient has a seizure disorder diagnosis or history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Is there evidence based on chart notes or claims that the patient has active brain metastases?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Does the patient have a documented baseline ECG in the past 12 months demonstrating a QT interval < 450 milliseconds?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the amifampridine dose within the appropriate limits? (See **Table 1** in criteria)	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Has the patient been assessed with a baseline quantitative myasthenia gravis (QMG) exam (score>5), 3TUG walking test, or other validated measure of LEMS patient physical functioning?	**Yes:** Go to #10 Document baseline results.	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the patient have follow-up appointments scheduled during weeks 1 and 2 after the proposed therapy initiation date?	**Yes:** Go to #11 Document appointment dates.	**No:** Pass to RPh. Deny; medical appropriateness
11. Will the patient and provider comply with all case management interventions and adherence monitoring requirements required by the Oregon Health Authority?	**Yes:** Approve for 2 weeks	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking amifampridine for ≥1 week AND has there been documented improvement from baseline in ambulation or physical functioning as assessed via the 3TUG, QMG score, or other validated LEMS assessment scale?	**Yes:** Document follow-up assessment scores Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the amifampridine dose within appropriate limits? (See **Table 1** in criteria)	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient experienced any new adverse effects since starting amifampridine therapy (e.g. seizures, arrhythmias)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4

Renewal Criteria		
4. Does the patient have documented evidence of >90% adherence to amifampridine for the previous approval period?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been on >30 days of continuous amifampridine therapy?	**Yes:** Approve for 3 months	**No:** Approve for 30 days; Renewal consideration will require documentation of tolerance, clinical benefit, and adherence.

P&T/DUR Review: 6/26 (SF); 11/19 (DE)
Implementation: TBD; 1/1/2019

Efgartigimod (VYVGART, VYVGART HYTRULO)

Goal(s):

~~Restrict use to OHP-funded conditions.~~

- Promote use that is consistent with medical evidence.

Length of Authorization:

- Up to 12 months

Requires PA:

Efgartigimod alfa-fcab (VYVGART) and efgartigimod alfa-hyaluronidase-qvfc (VYVGART HYTRULO) 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.	
~~2. Is the diagnosis funded by OHP?~~	~~**Yes:** Go to #4~~	~~**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP~~ ~~If eligible for EPSDT review: Go to #3.~~
~~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.~~ 2. Is this an FDA approved indication?	**Yes**: Go to #~~35~~	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #~~46~~
4. Does the patient have an active infection?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #~~57~~
5. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically included hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella. Immunization with live vaccines is not recommended during efgartigimod treatment.	**Yes:** Go to #~~68.~~ Document physician attestation of immunization history	**No:** Pass to RPh. Deny; medical appropriateness. Administer vaccines before initiation of a new treatment cycle of efgartigimod

Approval Criteria		
6. Does the patient have a positive serological test for anti-acetylcholine receptor (AchR) antibodies?	**Yes:** Go to #79	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have a Myasthenia Gravis Foundation of America Clinical Classification of class II, III or IV?	**Yes:** Go to #810	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a myasthenia gravis-specific activities of daily living scale (MG-ADL) total score of 5 points or more?	**Yes:** Go to #911 Record baseline MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient received or is currently receiving two immunosuppressant therapies (as monotherapy or in combination) for at least one year without adequate symptom control or do they have contraindications to these therapies? Example immunosuppressant therapies: - Azathioprine - Cyclosporine - Mycophenolate mofetil - Tacrolimus - Methotrexate - Cyclophosphamide	**Yes:** Go to #102	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of immunosuppressant therapy
10. Is the request for efgartigimod dosing that corresponds to FDA labeling? • ~~10 mg/kg once weekly for 4 weeks~~ • ~~For patients weighing 120 kg or more, the recommended dose is 1200 mg per infusion~~	**Yes:** Approve for up to two cycles. Each cycle is 1 dose/week for 4 weeks. The second cycle should not be administered sooner than 50 days from start of previous cycle.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has it been 50 days or more from the start of the previous efgartigimod treatment cycle?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is this request for the first renewal of efgartigimod?	**Yes**: Go to #3	**No:** Go to #4
3. Has the patient experienced a reduction in symptoms of at least 2 points from MG-ADL total baseline score?	**Yes**: Approve for up to 5 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient maintained a stable MG-ADL score over the last 12 months of efgartigimod therapy?	**Yes**: Approve for up to 7 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/26 (SF); 2/23 (DM); 4/22 (KS)
Implementation: TBD; 4/1/23; 5/1/22

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

Orphan Drug Evaluation: Loargys (pegzilarginase-nbln), intravenous or subcutaneous

Date of Review: June 2026
Generic Name: pegzilarginase-nbln

End Date of Literature Search: 03/19/2026
Brand Name (Manufacturer): Loargys (Immedica Pharma AB)

Dossier Received: No

Purpose for Review:

- Review the evidence for the safety and efficacy for pegzilarginase, recently Food and Drug Administration (FDA)-approved as therapy for hyperargininemia in people aged 2 years and older with Arginase 1 Deficiency (ARG1-D), to establish medically appropriate prior authorization (PA) criteria.
- Wholesale acquisition cost (WAC) per 2 mg vial is $11,469. Dosing is weight based, starting at 0.1 mg/kg/week and dosed based upon plasma arginine levels to a maximum dose of 0.2 mg/kg/week. Price ranges from $357,000 per year for a 2-year-old to over $4 million per year for a 70 kg adult at the maximum dose.

Plain Language Summary:

- Deficiency of the arginase enzyme is a rare condition passed down from the parents that causes the amino acid arginine (a building block of proteins) and ammonia to build up gradually in the blood. Arginine is toxic to the nervous system if levels in the blood become too high.
- Arginase deficiency usually becomes evident by about 3 years of age. It most often appears as stiffness, especially in the legs, caused by abnormal tensing of the muscles (spasticity). Other symptoms may include slower than normal growth, developmental delays and eventual loss of developmental milestones, intellectual disabilities, seizures, tremors, and difficulty with balance and coordination (ataxia).
- People with arginase deficiency are treated by monitoring food (protein) intake, taking certain amino acids supplements, and sometimes taking medicines called nitrogen-scavengers. Nitrogen-scavengers help the body get rid of nitrogen to decrease levels of ammonia in the blood.
- Pegzilarginase is a new medicine that the Food and Drug Administration (FDA) approved to treat people with arginase deficiency. It is given once a week into the veins (intravenously). This medicine must be given by a health care provider in medical setting because this medicine may cause a severe allergic reaction. After 8 weeks of treatment, people can switch to getting this medicine at home, with an injection under the skin (subcutaneously), given by a health care provider.
- In a clinical study that compared intravenous administration of pegzilarginase to placebo (or no active treatment), pegzilarginase reduced blood arginine levels more than people that received placebo. There were no significant changes in the ability to walk a short distance over 2 minutes or the ability to walk, run or jump.
- Side effects with pegzilarginase include vomiting, fever, cough, nausea, and stomach pain.
- The Drug Use Research and Management group recommends that the Oregon Health Authority pay for pegzilarginase in patients with arginase deficiency that is indicated by the FDA after their provider documents medical appropriateness through a process called prior authorization.

Author: Deanna Moretz, PharmD, BCPS

Research Questions:

1. What is the efficacy of pegzilarginase in treating arginine deficiency?
2. What are the harms of pegzilarginase in management of arginine deficiency?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which pegzilarginase is more effective or associated with fewer adverse events?

Conclusions:

- Low-quality evidence shows that pegzilarginase administration resulted in a statistically significant reduction in plasma arginine levels by 71% compared to placebo (95% confidence interval [CI], 89% to -55%; P<0.0001) over 24 weeks.[1] This reduction in plasma arginine did not result in statistically significant improvements in the 2 minute walk test (2MWT) or motor function evaluated by the Gross Motor Function Measure part E (GMFM-E).
- In the clinical trial evaluating the safety of pegzilarginase (n=32), the most frequently reported adverse events with pegzilarginase included vomiting, pyrexia, infusion-associated reactions, constipation, dizziness, and elevated liver function tests.[2]
- The label for pegzilarginase has a black boxed warning regarding the risk of anaphylaxis in patients treated with this drug.[2] Hypersensitivity reactions that were mild to moderate in severity occurred in 13% (6/48) of pegzilarginase-treated patients in clinical trials.[2] The reactions generally occurred with the first few doses but may also occur later in treatment.[2] Pre-medication with antihistamine should be considered when administering pegzilarginase.[2] In patients who have previously developed hypersensitivity reactions to pegzilarginase, corticosteroids can be considered.[2]
- No subgroups of patients based on demographics were identified to show that pegzilarginase is more effective or associated with fewer adverse events in patients 2 years of age and older. Pegzilarginase is currently being evaluated in another Phase 3 clinical trial in pediatric patients less than 2 years of age diagnosed with ARG1-D.

Recommendations:

- Implement clinical PA criteria to ensure pegzilarginase use in appropriate populations that are FDA-approved (**Appendix 2**).

Background:

The urea cycle consists of six consecutive enzymatic reactions that convert waste nitrogen into urea.[3] Arginase is the enzyme involved in the last step of the urea cycle.[3] Hyperargininemia or ARG1-D is a rare inherited metabolic disorder of the urea cycle with an autosomal recessive transmission.[4] It occurs due to a deficiency of the enzyme arginase 1 and causes progressive neurological damage.[4] Unlike other urea cycle disorders, this condition is not generally associated with a hyperammonemic encephalopathy in the neonatal period.[3] The pathophysiologic profile of ARG1-D strongly suggests that elevated arginine, rather than hyperammonemia, plays the key role in development and progression of clinical manifestations.[5] ARG1-D typically presents later in childhood between 2 and 4 years of age with predominantly neurological features.[3] Although increased plasma arginine is the disease hallmark, arginine may not always be exceedingly high.[5] The diagnosis can be confirmed by enzymatic assays (in erythrocytes) or by genetic analysis.[5]

The hallmark feature of ARG1-D is prominent and progressive lower-limb spasticity leading to gait abnormalities, difficulty walking and climbing stairs, and need for assistive devices.[1] The burden of illness is substantial and increases over time as neurologic manifestations progress.[1] Most patients ultimately develop impairment of gross motor function and mobility, potentially becoming non-ambulatory or reliant on a wheelchair.[1] Based on this clinical profile, ARG1-D is uniquely recognized among urea cycle disorders as a clinical mimic of cerebral palsy and hereditary spastic paraplegia.[5] The overall prevalence of ARG1-D is estimated to be of 1:726,000.[6] In the United States, there are an estimated 250 persons diagnosed with ARG1-D.[7] Patients require lifelong treatment and

monitoring, with strict multimodal management regimens.[1] Continued decline into adulthood is associated with significant morbidity and potential early mortality.[1] The age at death for most published ARG1-D cases is less than 50 years.[8]

Treatment of hyperargininemia focuses on dietary protein restriction, supplementation of essential amino acids, symptomatic treatments, and the use of alternative pathways to remove the nitrogen waste.[3] Preventing symptomatic hyperammonemia does not prevent progression or improve long-term outcomes in these patients.[5] Treatment aims at reducing plasma arginine concentrations below 200 µmol/L, to reduce the neurotoxic effects including intellectual disability, developmental delay, and seizures.[5] Lowering plasma arginine levels has the potential to slow disease progression in patients with ARG1-D.[1] Initiation of treatment in younger patients has been described to yield more meaningful neurological benefits.[5] It may take months to years to improve motor function when reductions in plasma arginine are achieved.[5] Significant improvements in spasticity, muscle strength, and mobility—such as the ability to run, climb stairs, and ride a bicycle—have been documented in one patient after 2.5 years of sustained arginine reduction via strict dietary restriction.[5] Due to rare nature of this disease, most clinical evidence to date is largely anecdotal and based on individual cases, familial series, or retrospective case analyses.[5] In the past year (April 2024 to March 2025), 589 patients enrolled in CCOs and Fee-for-Service FFS had a diagnosis of an unspecified type of urea cycle disorder. No patients were identified in the Oregon Medicaid population with the specific diagnosis of ARG1-D (ICD10 code E72.21) during the same time frame.

The National Institute for Health and Care Excellence (NICE) published guidance for the use of pegzilarginase in patients with ARG1-D in March 2026.[9] Usual treatment for arginase-1 deficiency includes dietary protein restrictions, essential amino acid supplementation and ammonia-lowering drugs.[9] Pegzilarginase is the first treatment that specifically treats ARG1-D.[9] Clinical trial evidence shows that pegzilarginase plus usual treatment reduces levels of arginine in the blood compared with placebo plus usual treatment.[9] However, plasma arginine levels do not have a consistent relationship with disease severity.[9] Evidence also suggests improvements in mobility and mental processing, but this is uncertain because the studies were small and short.[9] So, it is unclear how large these benefits are or how long these improvements will last.[9] Long-term outcomes were uncertain because of the lack of a comparator arm in the long-term extension trial and a small number of enrolled participants resulting in underpowered outcomes.[9] The committee also noted the absence of survival data in the company's submission.[9] The clinical experts explained it is plausible that pegzilarginase would extend survival, but this is uncertain.[9] Despite the uncertainties in the clinical and economic evidence, NICE recommended that pegzilarginase can be used, within its marketing authorization, as an option to treat ARG1-D in people 2 years and over.[9]

Drug Information

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Pegzilarginase is a recombinant, cobalt-substituted and pegylated human ARG1 enzyme therapy with increased catalytic activity due to the cobalt-substitution and prolonged half-life.[1] Pegzilarginase provides an exogenous source of the ARG1 enzyme and reduces plasma arginine by converting it to urea and ornithine.[2] Before starting pegzilarginase therapy, baseline plasma arginine concentrations should be obtained and consideration given to pre-medication with antihistamines.[2] It must be administered under the supervision of a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis.[2] After 4 weeks of treatment, plasma arginine levels should be obtained to determine the need for pegzilarginase dose adjustment to maintain plasma arginine levels in normal range (40 to 115 µmol/L).[2] After 8 weeks of once weekly intravenous (IV) pegzilarginase, patients may be switched to once weekly subcutaneous (SC) therapy at the same IV dose.[2]

The FDA initially denied approval of pegzilarginase because there were questions as to whether the drug improved the motor function of enrolled patients. The reduction in plasma arginine was statistically significant, but the mobility scores should not show statistically significant improvements. The manufacturer submitted additional long-term use data to support clinical stabilization of patients with ARG1-D, which led to the FDA-approval. The FDA approved pegzilarginase in February 2026 under the accelerated approval requirements with ongoing approval contingent on confirmatory postmarketing outcomes to verify the benefit of pegzilarginase in patients with ARG1-D.[7]

Clinical Efficacy and Safety:

The clinical trial used to support FDA approval is described and evaluated below in **Table 1.** Noteworthy trial design and patient characteristics include:

- The PEACE (Pegzilarginase Effect on Arginase 1 Clinical Endpoints) trial was designed to investigate efficacy and safety of pegzilarginase in lowering arginine levels and improving clinical outcomes, as compared with placebo, when added to standard-of-care in children and adults with ARG1-D.[1] Standard of care included dietary protein restriction and individualized disease management regimens to manage spasticity, epilepsy, and hyperammonenmia.[1]
- Trial duration: screening period (n=44), 24-week RCT (n=32), followed by open-label long-term extension (LTE) over 150 weeks (n=31).[1]
- Intervention: In the 24-week phase, patients were randomized 2:1 to pegzilarginase or volume-matched placebo administered via 30-minute IV infusion. Patients could be switched to SC injection at any point after the first 8 weeks of the LTE, using the same pegzilarginase formulation and dose level as their last IV dose.[1]
- Key inclusion criteria:
    - Aged 2 years and older
    - Documented ARG1-D diagnosis (as detected through elevated plasma arginine, pathogenic variants in ARG1, and/or diminished erythrocyte ARG1 activity)
    - Plasma arginine ≥250 µmol/L
    - Impairment on any secondary functional mobility assessment
    - On stable medication regimen including ammonia scavengers, anti-epileptic drugs, and/or spasticity medications at least 4 weeks prior to randomization. The investigators did not provide details about concurrent medication regimens for the patients enrolled in this trial.
    - All patients were managed with dietary protein restriction.
- Key exclusion criteria:
    - Symptomatic hyperammonemia (ammonia ≥100 µmol/L) requiring acute care or hospitalization within 6 weeks of first study dose
    - Extreme mobility impairment which did not allow for assessment of improvements in mobility
    - Treatment with botulinum toxin for spasticity-related complications
- Primary outcome: Change from baseline in plasma arginine at week 24 (normal range 40-115 µmol/L).
- Secondary outcomes
    - 2MWT: evaluates distance travelled on a flat surface in 2 minutes (with bracing or assistive devices). In the PEACE trial, a 9% change from baseline in distance travelled was considered clinically significant.[1]
    - GMFM-E: includes 24 tasks involving walking, running, and jumping with a score range of 0-72.[1] Individual tasks are scored as: 0 = does not initiate, 1 = initiates, 2 = partially completes, 3 = completes, or NT = not tested; the total score reflects the sum of all scored tasks.[1] Lower scores indicate greater functional mobility impairment.[1] In the PEACE trial, a score change from level 1 to level 3 was considered clinically significant.[1]
    - Clinically important response thresholds were defined using criteria established for cerebral palsy.[1]
- Baseline disease severity and population characteristics (see **Table 1**):

- Mean age: 10.7 years
  - Pegzilarginase group: 9.6 years
  - Placebo treated group: 12.9 years
- Mean baseline plasma arginine: 402 μmol/L
  - Pegzilarginase group: 365 μmol/L
  - Placebo treated group: 472 μmol/L
- Mean baseline GMFM-E Score: 47.7 points. Anyone scoring < 68 points is considered impaired. More than half of enrolled patients had gross motor functional impairment of GMFCS level ≥ 2 (range 1 to 3).
- Mean baseline 2MWT distance: 105.8 meters

- Magnitude of benefit and clinical relevance of results:
  - In patients treated with pegzilarginase, mean baseline plasma arginine was statistically significantly reduced by 77.9% compared to placebo at week 24 (95% CI, −67.1% to −83.5%; p<0.0001).[2] Arginine plasma levels are a surrogate endpoint that are not consistently correlated with clinical outcomes or functional improvement.
  - Key secondary outcomes showed numeric improvements from baseline to 24 weeks but were not statistically significant per hierarchical testing.[2]
- Safety signals:
  - Adverse events reported with pegzilarginase during the 24-week double blind phase of the PEACE trial included vomiting (29%), pyrexia (19%), cough (19%), increased ammonia (14%), nausea (5%), and abdominal pain (5%).[1] Serious adverse events were reported for 19% on pegzilarginase and 36% on placebo, and consisted of hyperammonemia (pegzilarginase, 10% vs. placebo, 27%), hyperammonemic encephalopathy (pegzilarginase 5% vs. placebo 9%) and vomiting (5%, pegzilarginase only).[2]
  - Transient, generally low-titer anti-drug antibodies (ADAs) were detected in both treatment arms during the double-blind period (pegzilarginase, 19% [n = 4/21]; placebo, 27% [n = 3/11]), including 1 patient in each arm with pre-existing ADAs at baseline.[1]
  - The label for pegzilarginase has a black boxed warning regarding the risk of anaphylaxis in patients treated with this drug.[2] Life-threatening hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with enzyme replacement therapies (ERTs) including pegzilarginase.[2] Hypersensitivity reactions that were mild to moderate in severity occurred in 13% (6/48) of pegzilarginase-treated patients in clinical trials.[2] Hypersensitivity reactions have included facial swelling, rash, flushing and dyspnea.[2] The reactions generally occurred with the first few doses but may also occur later in treatment.[2] Pre-medication with antihistamine should be considered when administering pegzilarginase. In patients who have previously developed hypersensitivity reactions to pegzilarginase, corticosteroids can be considered.[2]

See **Table 1** for major evidence limitations including:
- Short duration of comparative treatment with placebo (24 weeks) for a chronic, progressive, life-long condition.
- Small population enrolled due to rare nature of ARG1-D.
- Differences in baseline demographics (mean plasma arginine level and age) increase the risk of selection bias. It is unclear what impact these differences had on trial results.
- Although primary outcome showed a significant improvement from baseline, secondary outcomes that assessed mobility did not show statistically significant improvements.

Table 1. 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. Russo, RS, et al[1,2] NCT03921541 PEACE trial Phase 3, DB, PC, RCT	1. Pegzilarginase IV once a week via weight-based dosing started at 0.1 mg/kg/week and titrated within a range of 0.05 mg to 0.2 mg/kg as clinically indicated to maintain plasma arginine levels 50 to 150 µmol/L 2. Volume-matched placebo IV once a week Duration of this phase of the trial: 24 weeks	Demographics: -Mean age: 10.7 yo -Male: n=19 (59%) -Race White: 44% Asian: 19% Black: 65 Other: 19% -Age at diagnosis: 3.3 yo -Mean baseline plasma arginine: 402 µmol/L -Baseline GMFM-E score: 47.7 points -Baseline 2MWT distance: 105 meters Key Inclusion Criteria: -Diagnosis of arginase 1 deficiency -Aged ≥2 yo -Plasma arginine ≥250 µmol/L -Impaired mobility -Stabilized on scavenger therapy, anti-epileptic drugs, and/or spasticity medications for at least 4 weeks prior to randomization Key Exclusion Criteria: -Hyperammonemic episode within 6 weeks of study entry -Extreme mobility impairment (unable to complete assessments) --Current treatment with botulinum toxin	ITT: 1. 21 2. 11 PP: 1. 20 2. 11 Attrition: 1. 1 2. 0	Primary Endpoint: Mean percent change in the arginine plasma level from baseline to week 24 1. -74% 2. -3% Treatment difference: -71% 95% CI -89% to -55% P<0.0001 Secondary Endpoints: -Mean change from baseline in 2MWT 1. 7.3 meters 2. 2.7 meters LSMD: 5.5 meters 95% CI -15.6 to 26.7 NS -Mean change from baseline in GMFM-E 1. 4.2 points 2. -0.4 points LSMD: 4.6 points 95% CI -1.1 to 10.2 NS	NA	Any TEAE: 1. 18 (85.7%) 2. 11 (100%) Serious AE: 1. 4 (19%) 2. 4 (36.4%) AE leading to discontinuation: 1. 0 2. 0 Hypersensitivity: 1. 2 (9.5%) 2. 0 (0%) Hyperammonemia episode 1. 3 (14.3%) 2. 4 (36.4%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Randomized 2:1 via a central, computer-generated randomization protocol. Stratified by prior history of hyperammonemia. Mean baseline plasma arginine levels were higher in placebo group vs. treatment group (472 vs. 365 µmol/L) and mean age of treatment group was younger than placebo (9.6 yo vs 12.9 yo) which may bias results in favor of treatment. Other baseline demographics were similar. Performance Bias: Low. Patients, caregivers, and investigators blinded with matching placebo. Detection Bias: Unclear. Outcome assessors blinded to treatment arm. Lab results for arginine may have resulted in unblinding. Investigators were blinded to lab results. Each site had one unblinded physician to manage to protocol-defined dosage adjustments. Attrition Bias: Low. One person in the active treatment arm withdrew from the study for personal reasons. For the primary outcome missing data imputed as change from baseline = 0. No imputation for missing values for secondary outcomes. Reporting Bias: Low. Study protocol available on-line. All prespecified outcomes reported per protocol. Other Bias: High. Funded by the manufacturer. Manufacturer involved in study design, data collection, data analysis, data interpretation and writing of the report. Several authors reported financial support from manufacturer. **Applicability**: Patient: Recruitment limited by the rare prevalence of this condition. The number of people who were on concomitant therapy for hyperammonemia with a nitrogen scavenger was not reported. The average time between diagnosis and treatment was 7 years, and it is unclear if earlier treatment would have more benefit. Intervention: Pegzilarginase dosing assessed in a Phase 2 trial and 90% of people in the treatment group achieved target plasma arginine levels (below 200 µmol/L) and improvements in functional mobility (total n=16). Comparator: Placebo is an appropriate comparator as there are no other approved treatments for arginine deficiency. Outcomes: Plasma arginine levels are a surrogate outcome for treatment efficacy. Improvements in motor function would have been better primary outcomes. 24 weeks may have not been sufficient duration to assess changes in motor function.

								Setting: Conducted at 19 sites in 7 countries: United States, United Kingdom, Canada, Austria, France, Germany, and Italy. 44% of participants were in the US.

Abbreviations: 2MWT = 2 minute walk test; AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; GMFM-E = Gross Motor Function Measure Part E; ITT = intention to treat; IV = intravenous; L = liters; LSMD = least square mean difference; mITT = modified intention to treat; µmol = micromolar; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PC = placebo-controlled; PG = parallel group; PP = per protocol; PEG = polyethylene glycol; RCT = randomized controlled trial; TEAE = treatment emergent adverse events; yo = years old

References:

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7. US FDA has granted accelerated approval of Loargys (pegzilarginase-nbln) for the treatment of hyperargininemia in patients 2 years and older with arginase 1 deficiency (ARG1-D). News release. Immedica Pharma US Inc. February 23, 2026. Accessed February 24, 2026. https://www.prnewswire.com/news-releases/us-fda-has-granted-accelerated-approval-of-loargys-pegzilarginase-nbln-for-the-treatment-of-hyperargininemia-in-patients-2-years-and-older-with-arginase-1-deficiency-arg1-d-302694889.html.
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9. National Institute for Health and Care Excellence. Pegzilarginase for Treating Arginase-1 Deficiency in People 2 years and Over. March 2026. https://www.nice.org.uk/guidance/hst35.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LOARGYS safely and effectively. See full prescribing information for LOARGYS.

LOARGYS (pegzilarginase-nbln) injection, for intravenous or subcutaneous use
Initial U.S. Approval: 2026

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS
See full prescribing information for complete boxed warning

Initiate LOARGYS in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. (5.1)

If a severe hypersensitivity reaction (e.g. anaphylaxis) occurs, discontinue LOARGYS, and immediately initiate appropriate medical treatment, including use of epinephrine. (5.1)

----------INDICATIONS AND USAGE----------
LOARGYS is an arginine specific enzyme indicated for the treatment of hyperargininemia in adult and pediatric patients 2 years of age and older with Arginase 1 Deficiency (ARG1-D), in conjunction with dietary protein restriction. (1)

This indication is approved under accelerated approval based on reduction of plasma arginine. (14) Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

----------DOSAGE AND ADMINISTRATION----------
- Administer LOARGYS under the supervision of a health care provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. (2.1)
- Initiate LOARGYS in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. (2.1)
- Consider pre-medication with antihistamines. (2.1)
- Obtain a baseline plasma arginine concentration prior to initiating treatment. (2.1)
- Recommended starting dosage of LOARGYS is 0.1 mg/kg administered by intravenous infusion once weekly. (2.2)
- Maximum recommended dosage is 0.2 mg/kg once weekly. (2.2)
- See the Full Prescribing Information for recommended titration and maintenance dosage and recommended plasma arginine level testing during treatment. (2.2)
- After eight weeks of once weekly intravenous LOARGYS, patients may be switched to once weekly subcutaneous LOARGYS at the same dosage of intravenous therapy. (2.4)
- See Full Prescribing Information for dosage and administration modifications due to hypersensitivity reactions. (2.5)
- See Full Prescribing Information for instructions on preparation, storage, and administration. (2.7, 2.8, 2.9, 2.10)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 2 mg/0.4 mL and 5 mg/mL in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity: If a severe hypersensitivity reaction occurs, discontinue LOARGYS and immediately initiate appropriate medical treatment, including epinephrine. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>10%) are vomiting, pyrexia, infusion associated reactions and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Immedica at toll-free phone 1-844-627-4687 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2026

Pegzilarginase-nbln (Loargys®) Injection

Goal(s):
- Ensure appropriate utilization of pegzilarginase-nbln in FDA-approved indications.

Length of Authorization: Up to 12 months

Requires PA:
- LOARGYS (pegzilarginase-nbln) for IV or SC administration (pharmacy and provider administered claims)

Covered Populations: FFS and CCO patients beginning 5/1/26

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 a patient with a prior FFS approval for the requested drug?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved age and indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the drug prescribed by or in consultation with a provider with expertise in managing metabolic disorders (i.e., urea cycle disorders)?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for therapy to treat hyperargininemia in a patient with arginase 1 deficiency?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Has the diagnosis been confirmed by genetic testing or documentation of reduced arginase enzyme activity in red blood cells?	**Yes**: Go to #7 Document date and results____ _____	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient prescribed a protein restricted diet (below 1.5 g/kg/day at 2 years of age to 0.83 g/kg/day at 18 years of age per World Health Organization guidance)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there documentation of elevated plasma arginine levels (>200 µmol/L) within the past 3 months?	**Yes:** Go to #9 Document date and results_____	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have symptomatic hyperammonemia (ammonia ≥100 µmol/L)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the patient on a stable medication regimen including ammonia scavengers, anti-epileptic drugs, and/or spasticity medications?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is there a documented plan to evaluate arginine levels within the next 4 weeks to determine need for dose adjustments?	**Yes:** Pass to RPh. Pend; Refer to DMAP for secondary review. Duration: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request to renew therapy for treatment of arginase 1 deficiency?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Have arginine levels decreased by at least 25% from baseline assessment?	**Yes**: Pass to RPh. Pend; Refer to DMAP for secondary review. Duration: Approvals cover up to 12 months. Document results: _____	**No:** Go to #3.
3. Has the provider assessed adherence to treatment and protein restricted diet with a plan to address any identified barriers to care?	**Yes:** Document treatment plan. Pass to RPh. Pend; Refer to DMAP for secondary review. Duration: Approvals cover up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Refer to DMAP for secondary review.

P&T/DUR Review: 6/26 (DM)
Implementation: TBD