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

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

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

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Election of Chair and Vice Chair	R. Citron (OSU)
	D. Approval of Agenda and Minutes	R. Citron (OSU)
	E. Department Update	A. Gibler (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	(Chair)

A. Insulins Literature Scan
B. P & T Methods and Procedures
C. Oncology Prior Authorization Updates
D. Orphan Drug Policy Updates
   1. Public Comment

1:25 PM	III. DUR ACTIVITIES	
	A. Quarterly Utilization Report	R. Citron (OSU)
	B. ProDUR Report	L. Starkweather (Gainwell)
	C. RetroDUR Report	D. Engen (OSU)
	D. Oregon State Drug Review	K. Sentena (OSU)
	1. An Update in Weight Loss Therapies-Including FDA Approved GLP-1 Receptor Agonists	
	2. Prevention of Respiratory Syncytial Virus (RSV) Infection: New Products and Recommendations	

IV. DUR OLD BUSINESS

1:50 PM	A. Spravato® (esketamine) Prior Authorization Update	S. Servid (OSU)
	1. Safety Edit	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

V. DUR NEW BUSINESS

2:05 PM	A. Antipsychotics in Children Policy Evaluation 1. Policy Evaluation/Safety Edit 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
2:25 PM	B. Melatonin Policy Evaluation 1. Policy Evaluation 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Pucik (OSU)
	VI. PREFERRED DRUG LIST NEW BUSINESS	
2:40 PM	A. Lantidra™ (donislecel) New Drug Evaluation 1. New Drug Evaluation 2. Prior Authorization Criteria 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
3:00 PM	B. Maintenance Inhalers for Asthma/COPD 1. Class Update/Prior Authorization criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:15 PM	BREAK	
3:30 PM	C. Duchenne Muscular Dystrophy DERP Report and New Drug Evaluation 1. DERP Report/Prior Authorization Criteria 2. Elevidys (delandistrogene moxeparvovec-rokl) New Drug Evaluation 3. Agamree® (vamorolone) New Drug evaluation 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
3:55 PM	D. Antivirals for SARS-CoV2 Class Review 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
4:10 PM	VII. EXECUTIVE SESSION	
4:50 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS	
	IX. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, December 7th, 2023
1:05 PM - 4:45 PM
Via Zoom webinar

MEETING MINUTES

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

Members Present: Stacy Ramirez, PharmD; Patrick DeMartino, MD; Douglas Carr, MD; Russell Huffman, PMHNP; Caryn Mickelson, PharmD; Robin Moody; William Origer, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Megan Herink, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Lan Starkweather, PharmD; Brandon Wells; Trevor Douglass, DC, MPH; Amanda Parish, LCSW; Jennifer Bowen; Dee Weston, JD; Kyle Hamilton

Audience: Craig Sexton, GSK*; Lynda Finch, Biogen*; Nirmal Ghuman, Janssen*; Basmina Parmakhtiar, Travere Therapeutics*; Mark Kantor, AllCare Health; Philip Santa Maria; Brandon Walker, Servier; Jim Slater, CareOregon; William Lam, Madrigal; Ken Liu, Madrigal; Daria Meleshkina, EOCCO; Rick Dabner; Jason Kniffen; Saghi Maleki; Sami Nasrawi; Jon Buncab, Travere; Susan Lakey Kevo; Kate Ramsay, EOCCO; Cecilia Stewart, EOCCO; Jeffrey Baptista, EOCCO; Amanda Pan, EOCCO; Bill McDougall, Biogen; Melissa Snider, Gilead; Matt Worthy, OHSU; Tiina Andrews, UHA; Brandie Feger, Advanced Health CCO; Lori McDermott, Viking HCS; Georgette Dzwilewski, Indivior; Michele Sabados, Alkermes; Shauna Wick, Trillium; Jeff White, Sumitomo; Lisa Pulver J&J;

(*) Provided verbal testimony

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I. CALL TO ORDER

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

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

C. Approval of Agenda and October 2023 Minutes presented by Roger Citron, RPh
ACTION: Motion to approve, 2nd, all in favor

D. Department Update and recognition of P&T Committee members with terms expiring provided by Trevor Douglass, DC, MPH

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Report

B. Ycanth™ (cantharidin) Abbreviated Drug Review (ADR)
Recommendation:
- Apply Drugs for Non-funded Conditions prior authorization criteria to limit use to funded indications

C. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Aphexda™ (motixafortide); and Ojjaara (momelotinib) to table 1 in the Oncology Agents prior authorization (PA) criteria

D. Orphan Drug Policy Updates
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Rivfloza™ (nedosiran) based on FDA-approved labeling
ACTION: Motion to approve, 2nd, all in favor

III. DUR ACTIVITIES

A. ProDUR Report: Lan Starkweather, PharmD

B. RetroDUR Report: Dave Engen, PharmD

C. Oregon State Drug Review: Kathy Sentena, PharmD
1. **Buprenorphine: Place in Therapy for Chronic Pain**
2. **Update on the Use of SGLT-2 Inhibitors**
3. **2023 Global Initiative for Chronic Obstructive Lung Disease Report: Focus on Revised Recommendations for Inhaler Products**

Oregon Health Authority

OSU Oregon State University College of Pharmacy

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IV. DUR NEW BUSINESS

A. Nexletol® (bempedoic acid) PA Update: Megan Herink, PharmD
Recommendation:
- Update the clinical PA criteria to include coverage for bempedoic acid for high-risk primary prevention in patients with documented statin intolerance already on ezetimibe
ACTION: Motion to approve, 2nd, all in favor

B. Over-the-Counter Policy Proposal: Sarah Servid, PharmD
Recommendations:
- Update operating procedures to clarify policy and process to maintain a list of PDL classes that include covered OTC medications
- Update the OTC list to include new daily contraceptives
ACTION: Motion to approve, 2nd, all in favor

V. PREFERRED DRUG LIST (PDL) NEW BUSINESS

A. Topical Moisturizers Class Review: Sarah Servid, PharmD
Recommendations:
- Cover select topical moisturizers with PA to limit coverage to funded conditions
- Update benefit plan exclusion criteria and review exceptions process
- No PDL recommendations for specific products based on the clinical evidence
- Evaluate costs in executive session
ACTION: The Committee recommended requiring PA only for non-preferred agents
Motion to approve, 2nd, all in favor

B. Erythropoiesis Stimulating Agents (ESA) Literature Scan: Deanna Moretz, PharmD
Recommendations:
- No PDL changes recommended based on the review of recently published evidence
- Retire ESA PA criteria due to limited POS utilization
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

C. Jesduvroq™ (daprodustat) New Drug Evaluation (NDE): Sara Fletcher, PharmD
Recommendations:
- Maintain daprodustat as non-preferred on the PDL
- Implement PA criteria to ensure safe and appropriate use
Public Comment: Craig Sexton, GSK
ACTION: Motion to approve, 2nd, all in favor

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D. Antidepressants Class Update & Zurzuvae™ (zuranolone) NDE: Kathy Sentena, PharmD
Recommendations:
- No PDL changes recommended based on the review of recently published evidence
- Implement safety edit for zuranolone to ensure product use is limited to populations with established safety and efficacy
- Evaluate costs in executive session

Public Comment: Lynda Finch, Biogen; Nirmal Ghuman, Janssen
ACTION: The Committee recommended adding language to permit zuranolone use in moderate to severe post-partum depression when a provider submits the diagnosis of major depressive disorder
Motion to approve, 2nd, all in favor

E. Filspari™ (sparsentan) NDE: Dave Engen, PharmD
Recommendations:
- Make sparsentan non-preferred on the PDL
- Implement PA criteria to ensure safe and appropriate use

Public Comment: Basmina Parmakhtiar, Travere Therapeutics
ACTION: Motion to approve, 2nd, all in favor

F. Oral and Topical Antifungals Class Update & Vivjoya™ (oteseconazole) NDE:
Kathy Sentena, PharmD
Recommendations:
- No PDL changes recommended based on the review of recently published evidence
- Combine the topical and vaginal antifungals agents into one class
- Maintain oteseconazole as non-preferred and subject to PA
- Evaluate costs in executive session

ACTION: The Committee recommended requiring a trial/failure/contraindication to oral fluconazole prior to approval of oteseconazole adding language to permit zuranolone
Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Douglas Carr, MD; Russel Huffman, PMHNP; Caryn Mickelson, PharmD; Robin Moody; William Origer, MD

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

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VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Topical Moisturizers Class Recommendation:

-Cover creams, lotions, ointments. Do not cover other OTC formulations or OTCs costing more than $1 per gram or mL

-Make moisturizers preferred if they cost less than $0.05 per gram or mL. Make all other moisturizers non-preferred

-Until they are reviewed by P&T, new products will be added as non-preferred or non-covered based on current recommendations

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

B. Erythropoiesis Stimulating Agents

Recommendations: Make no changes to the PDL

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

C. Antidepressants Class

Recommendations: Make no changes to the PDL

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

D. Oral and Topical Antifungals

Recommendations: Make no changes to the oral antifungal agents and make terconazole suppositories, butoconazole, miconazole 1 kits and miconazole 3 kits, miconazole suppositories (Miconozole 3) and clotrimazole (Vaginal 3-day) non-preferred. Make other vaginal formulations preferred

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

VIII. ADJOURN

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Drug Class Literature Scan: Insulin Class

Date of Review: February 2024

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

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

Plain Language Summary:

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

Author: Sara Fletcher, PharmD, MPH, BCPS

Conclusions:

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

Recommendations:

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

Summary of Prior Reviews and Current Policy

- Current PDL status available in **Appendix 1**. Non-preferred products are subject to prior authorization (PA).

- The insulin class was last reviewed in 2020 and 2019. Neither review found clinically significant differences in glucose lowering between long-acting insulin products or between short-acting insulin products.
- After executive session in 2020, the prior authorization (PA) for insulin detemir pens (LEVEMIR FLEXTOUCH) was removed. All forms of insulin lispro, except ADMELOG, were designated as preferred.
- The American Rescue Plan (ARP) Act of 2021 included a provision that eliminates the statutory cap on rebates paid to Medicaid by drug manufacturers. Beginning January 1st, 2024, rebates will no longer be capped at 100% of the quarterly average manufacturer price (AMP). This cap previously reduced the amount of rebates paid, particularly for drugs with significant price increases over time. This "AMP CAP" removal has the potential to significantly affect drug rebate amounts. Significant price fluctuations are anticipated in response to this provision, particularly in certain drug classes, including insulins, which have seen large prices increases over time.[6-8]
- Insulin detemir products will be phased out with injection pens being discontinued in April 2024 and vials to be discontinued by the end of 2024. Supply disruptions are anticipated to begin in mid-January 2024. LEVEMIR vials, LEVEMIR FLEXPEN, and LEVEMIR FLEXTOUCH pen are all preferred on the PDL.[9] Insulin glargine (LANTUS vials and LANTUS SOLOSTAR pens) are preferred and available on the market as an alternative long-acting basal insulin.

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

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

New Systematic Reviews:

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

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

- Insulin degludec vs insulin detemir- 2 studies
- Insulin degludec vs insulin glargine- 4 studies

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

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

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

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

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

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

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

certainty evidence), and confirmed nocturnal hypoglycemia (BG < 55 mg/dL) (detemir 13/1000 vs. NPH 40/1000; RR 0.32, 95% CI 0.16 to 0.63; 4 trials, 1718 participants; low-certainty evidence).[2]

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

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

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

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

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

New Guidelines:

High Quality Guidelines:

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

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

Recommendations relevant to the insulin class include:

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

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

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

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

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

Recommendations related to insulin therapy in T1DM include:

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

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

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

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

Recommendations related to insulin therapy in T2DM include:

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

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

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

Additional Guidelines for Clinical Context:

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

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

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

New Formulations:[12]

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

New FDA Safety Alerts:

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

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

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

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Appendix 1: Current Preferred Drug List

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

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

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

Appendix 2: New Comparative Clinical Trials

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

Table 1. Description of Randomized Comparative Clinical Trials.

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

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

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

Abbreviations: ARR = absolute risk reduction; BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CrI = credible interval; DB = double blind; ETD = estimated treatment difference; faster aspart = fast-acting insulin aspart, FIASP; GLA-100 = insulin glargine 100 unit/mL; GLA-300 = insulin glargine 300 unit/mL; HbA1C = glycated hemoglobin; LSM = least squares mean; $iAUC_{0\text{-}2\,h}$ = Incremental area under curve from 0 to 2 h after meals; IAsp = insulin aspart; LGA = large for gestational age; NICU = neonatal intensive care unit; NS = not significant; OL = open label; OR = odds ratio; RCT = randomized clinical trial;

RR = rate ratio; SGLT2-I = sodium-glucose cotransporter 2 inhibitor; SOC-BI = standard of care-basal insulin analogues; TIR = time in range; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; URLi = ultra rapid lispro, LYUMJEV; y = years.

Appendix 3: Abstracts of Comparative Clinical Trials

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 4: Medline Search Strategy

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

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

Appendix 5: Key Inclusion Criteria

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

Insulins

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

Length of Authorization:
- Up to 12 months

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

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

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

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

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

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Review Standards and Methods for Quality Assessment of Evidence
Updated: June 2023

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 preferred drug list (PDL) 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). Provides a summary of new or available literature, and outcomes are not evaluated via the GRADE methodology listed in **Appendix D**.
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 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	Evaluation 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

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 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)

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 • Mitigation strategies (described in the article or journal/organization policies) are documented but could be more robust	• 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 considered for inclusion in SR that are reviewed first by their own author who is on the SR team		• May consider funding sources or conflicts of interest for both the systematic review and the included studies
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: December 2023

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. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs, as well as the ability of Oregonians to access prescriptions that are appropriate for their clinical conditions.
4. 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.
5. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.
6. 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.
7. Guide and approve meeting agendas.

8. 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 pricing information to inform the recommendations regarding inclusion of drugs on the Practitioner-Managed Prescription Drug Plan (PMPDP) or any preferred drug 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: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management). 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: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management).

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:

    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.

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
abiraterone acetate/niraparib tosylate	AKEEGA
capivasertib	TRUQAP
crizotinib	XALKORI
fruquintinib	FRUZAQLA
Melphalan HCl/hepatic delivery kit (HDS)	HEPZATO KIT
nirogacestat hydrobromide	OGSIVEO
repotrectinib	AUGTYRO
toripalimab-tpzi	LOQTORZI

Recommendation:

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

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

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

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

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

Table 1. Oncology agents which apply to this policy (Updated ~~08~~12/29~~31~~/2023)

New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

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

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

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

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

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

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Prior Authorization Criteria Update: Orphan 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 Name	Brand Name
luspatercept-aamt	REBLOZYL
odevixibat	BYLVAY

Recommendation:

- PA was modified to update newly approved indications to existing drugs in policy

Orphan Drugs

Goal(s):

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

Length of Authorization:

- Up to 6 months

Requires PA:

- See Table 1 (pharmacy and physician administered claims)

Covered Alternatives:

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

Table 1. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring
Alpelisib (VIJOICE)	PIK3CA-Related Overgrowth Spectrum (PROS) in those who require systemic therapy	≥ 2 yrs	Pediatric 2 to <18 yrs: • 50 mg once daily • May consider increase to 125 mg once daily if ≥6 years after 24 weeks of treatment • May gradually increase to 250 mg once daily once patient turns 18 Adult: • 250 mg once daily	Baseline Monitoring • Fasting BG, HbA1c Ongoing Monitoring • Fasting BG weekly x 2 weeks, then at least once every 4 weeks, then as clinically indicated • HbA1c every 3 months and as clinically indicated
Avacopan (TAVNEOS)	Severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with glucocorticoids.	≥18 yrs	30 mg (three 10 mg capsules) twice daily, with food	Baseline Monitoring • Liver function tests ALT, AST, ALP, and total bilirubin • Hepatitis B (HBsAg and anti-HBc) Ongoing Monitoring • Liver function tests every 4 wks for 6 months, then as clinically indicated
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH)	XLH ≥ 6 mo TIO	Pediatric <18 yrs: Initial (administered SC every 2 wks): XLH	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated

	FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	≥ 2 yrs	• <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 mg for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max dose 2 mg/kg or 180mg every 2 wks)	• Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only: • Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels • Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Belumosudil (REZUROCK)	Treatment of chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy	≥ 12 yrs	200 mg orally once daily with food 200 mg twice daily when coadministered with strong CYP3A inducers or proton pump inhibitors	Baseline & Ongoing Monitoring • Total bilirubin, AST, ALT at least monthly • Pregnancy test (if childbearing potential)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 yrs	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
Elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2 mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 wks)	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.

	cofactor deficiency (MoCD) Type A		Initial: 0.4mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 wks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥1 yr: 0.9 mg/kg	
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 yrs	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests • Blood homocysteine levels-If homocysteine elevated, assess folate, vitamin B12, and vitamin B6
Leniolisib (JOENJA)	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)	≥ 12 years AND ≥ 45kg	70 mg administered orally twice daily approximately 12 hours apart	Baseline and ongoing monitoring • Pregnancy test (if childbearing potential)
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 mo AND ≥0.39 m^2 BSA	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary and plasma oxalate levels	N/A	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months	N/A

			≥ 20 kg Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions	≥ 18 yr	Initial: 1 mg/kg SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 3 mo	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 380 mcg/kg once daily after 1 week on initial dose, as tolerated	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Mitapivat (PYRUKYND)	Hemolytic anemia in adults with pyruvate kinase (PK) deficiency.	≥ 18 yr	Initial: 5 mg twice daily Titration: If Hb less than normal range or patient required transfusion in previous 8 weeks, then after 4 weeks increase to 20 mg twice daily, and after another 4 weeks increase to 50 mg twice daily.	Baseline/Ongoing Monitoring • Hgb, transfusion requirement

			Max dose: 50 mg twice daily Discontinuation should include down-titration.	
Nedosiran RIVFLOZA	Lower urinary oxalate levels in those with primary hyperoxaluria type 1 (PH1) and relatively preserved renal function, e.g., eGFR ≥ 30 mL/min/1.73 m^2	≥ 9 yr	Weight ≥ 50 kg: 160 mg once monthly Weight <50 kg and age ≥12 yr: 128 mg once monthly Weight <50 kg and age 9 to 11 yr: 3.3 mg/kg once monthly; max 128 mg.	Baseline/Ongoing Monitoring • eGFR
Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3) Cholestatis pruritus in patients with Alagille syndrome (ALGS)	≥ 3 mo ≥ 12 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments Max dose: 120 mcg/kg once daily; not to exceed 6 mg	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Olipudase alfa-rpcp (XENPOZYME)	Non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD)	N/A	Initial: Age based dose escalation table per Package insert Maintenance: 3 mg/kg via IV infusion every 2 weeks Weight: • If BMI ≤ 30, use actual body weight • If BMI > 30, use adjusted body weight Adjusted body weight (kg) = (actual height in M)^2 x 30	Baseline Monitoring • Liver function tests (ALT, AST) within 1 month • Pregnancy test (if childbearing potential) Ongoing Monitoring • Liver function tests (ALT, AST) within 72 hours of infusions during dose escalation, then during routine clinical management once at maintenance dose
Palovarotene, (SOHONOS)	Fibrodysplasia ossificans progressive (FOP)	≥ 8 yr females	≥ 14 years: Daily: 5 mg Flare wk 1-4: 20 mg once daily Flare wk 5-12: 10 mg once daily	Baseline Monitoring • Pregnancy test (if childbearing potential)

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

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

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

Approval Criteria		
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**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?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	**Yes:** Approve for up to 6 months Document benefit	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	**Yes**: Approve for up to 6 months Document benefit and provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/24; 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: TBD; 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

Drug Use Research & Management Program
DHS - Health Systems Division
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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: July 2022 - June 2023

Eligibility	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
Total Members (FFS & Encounter)	1,322,427	1,330,020	1,337,959	1,344,339	1,355,484	1,364,931	1,375,185	1,381,362	1,389,121	1,394,647	1,402,271	1,407,750	1,367,125
FFS Members	115,910	113,720	117,050	118,585	118,506	120,719	124,278	118,766	122,639	122,820	119,962	122,042	119,583
OHP Basic with Medicare	8,606	8,473	8,710	8,899	8,720	8,696	8,865	8,706	8,797	8,863	8,868	8,939	8,762
OHP Basic without Medicare	10,497	10,255	10,368	10,396	10,140	10,077	10,182	9,945	10,050	9,985	9,804	9,895	10,133
ACA	96,807	94,992	97,972	99,290	99,646	101,946	105,231	100,115	103,792	103,972	101,290	103,208	100,688
Encounter Members	1,206,517	1,216,300	1,220,909	1,225,754	1,236,978	1,244,212	1,250,907	1,262,596	1,266,482	1,271,827	1,282,309	1,285,708	1,247,542
OHP Basic with Medicare	94,346	95,446	96,256	97,094	98,309	98,992	99,800	100,627	101,457	102,127	103,362	104,233	99,337
OHP Basic without Medicare	69,022	69,064	68,981	69,116	69,282	69,339	68,751	68,998	68,768	69,036	69,045	68,917	69,027
ACA	1,043,149	1,051,790	1,055,672	1,059,544	1,069,387	1,075,881	1,082,356	1,092,971	1,096,257	1,100,664	1,109,902	1,112,558	1,079,178

Gross Cost Figures for Drugs	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	YTD Sum
Total Amount Paid (FFS & Encounter)	$104,311,244	$117,394,450	$108,880,754	$109,912,531	$111,352,674	$112,682,425	$119,210,483	$110,346,981	$127,060,348	$113,436,416	$126,894,441	$123,187,776	$1,384,670,524
Mental Health Carve-Out Drugs	$11,100,725	$11,884,904	$11,155,872	$11,193,530	$11,310,136	$11,528,343	$12,108,700	$11,202,686	$11,198,645	$9,874,875	$10,904,377	$10,378,235	$133,841,026
OHP Basic with Medicare	$7,612	$3,774	$5,976	$4,972	$2,989	$9,065	$11,372	$5,010	$9,726	$6,346	$6,783	$11,480	$85,103
OHP Basic without Medicare	$3,991,902	$4,330,790	$4,140,126	$4,048,414	$4,092,829	$4,207,837	$4,219,103	$3,926,063	$3,924,318	$3,481,319	$3,901,947	$3,708,124	$47,972,773
ACA	$7,020,871	$7,481,537	$6,947,134	$7,072,877	$7,146,717	$7,245,596	$7,807,115	$7,190,655	$7,185,106	$6,315,368	$6,920,754	$6,578,912	$84,912,642
FFS Physical Health Drugs	$4,812,989	$5,619,157	$5,111,558	$5,323,191	$5,285,073	$5,255,233	$5,931,607	$5,174,656	$6,258,431	$5,471,747	$6,075,581	$5,517,586	$65,836,809
OHP Basic with Medicare	$209,818	$229,505	$199,993	$181,164	$189,778	$200,348	$200,085	$185,599	$220,991	$180,024	$201,360	$188,842	$2,387,507
OHP Basic without Medicare	$976,065	$1,218,034	$1,021,988	$1,224,627	$1,088,762	$1,096,219	$1,286,601	$1,160,119	$1,355,209	$1,200,052	$1,306,615	$1,216,722	$14,151,015
ACA	$3,474,072	$3,998,143	$3,736,815	$3,761,942	$3,805,640	$3,719,781	$4,218,150	$3,576,319	$4,439,343	$3,849,288	$4,348,413	$3,910,568	$46,838,474
FFS Physician Administered Drugs	$1,482,485	$1,286,964	$1,485,908	$1,315,434	$1,009,906	$1,076,644	$2,053,499	$1,687,998	$1,783,457	$1,761,307	$1,902,415	$1,710,449	$18,556,466
OHP Basic with Medicare	$178,424	$129,501	$148,320	$157,790	$140,524	$185,407	$121,540	$101,577	$127,390	$113,639	$80,989	$110,459	$1,595,559
OHP Basic without Medicare	$380,961	$105,425	$522,725	$353,004	$124,435	$158,505	$830,009	$341,711	$161,009	$210,096	$458,645	$358,542	$4,005,067
ACA	$401,444	$485,916	$402,288	$403,208	$367,332	$355,496	$577,708	$665,601	$660,502	$587,055	$609,385	$762,033	$6,277,966
Encounter Physical Health Drugs	$67,148,881	$75,662,435	$70,755,438	$71,160,388	$71,998,900	$73,061,658	$75,677,143	$71,366,771	$81,011,245	$74,139,526	$82,851,101	$81,233,028	$896,066,512
OHP Basic with Medicare	$356,100	$412,658	$378,789	$347,835	$388,427	$363,903	$366,929	$370,307	$427,973	$393,948	$429,997	$418,489	$4,655,355
OHP Basic without Medicare	$16,372,446	$17,925,580	$16,772,704	$17,180,688	$16,858,088	$17,242,631	$17,524,844	$16,476,199	$18,785,570	$16,823,442	$18,983,658	$18,210,045	$209,155,894
ACA	$49,208,903	$55,757,790	$51,995,006	$52,197,117	$53,177,876	$53,757,937	$56,076,231	$52,737,213	$59,708,799	$54,880,126	$61,188,295	$60,428,245	$661,113,537
Encounter Physician Administered Drugs	$19,766,163	$22,940,991	$20,371,979	$20,919,988	$21,748,659	$21,760,549	$23,439,534	$20,914,871	$26,808,571	$22,188,961	$25,160,967	$24,348,478	$270,369,711
OHP Basic with Medicare	$1,100,245	$1,041,001	$912,902	$898,562	$1,180,139	$956,874	$1,228,897	$973,571	$1,354,651	$1,096,477	$1,058,938	$1,149,056	$12,951,313
OHP Basic without Medicare	$4,576,613	$5,248,255	$4,457,749	$4,699,922	$4,894,882	$5,176,864	$5,138,588	$4,476,646	$5,623,378	$4,559,617	$5,210,428	$4,712,203	$58,775,144
ACA	$13,822,814	$16,277,210	$14,646,181	$14,753,110	$15,159,151	$15,063,920	$16,339,901	$15,005,990	$18,899,578	$15,703,876	$18,089,408	$17,732,108	$191,493,248

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: January 18, 2024

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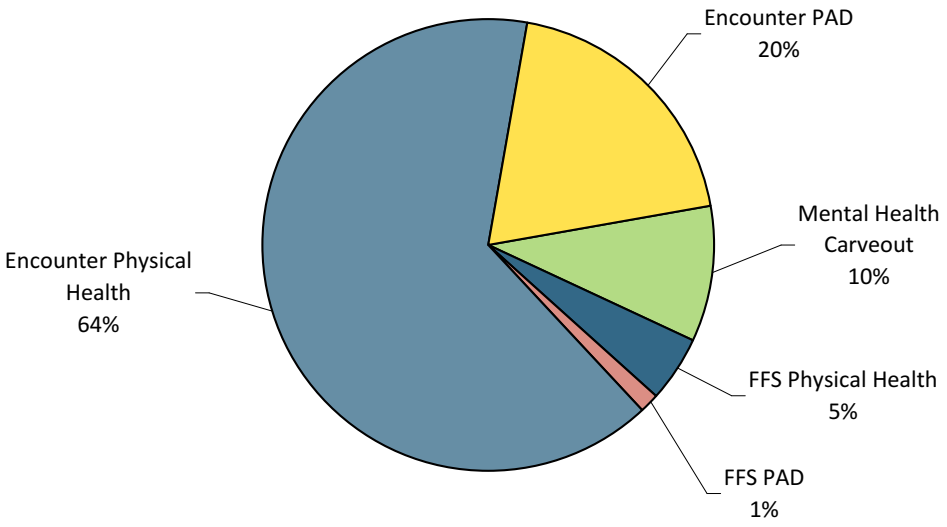
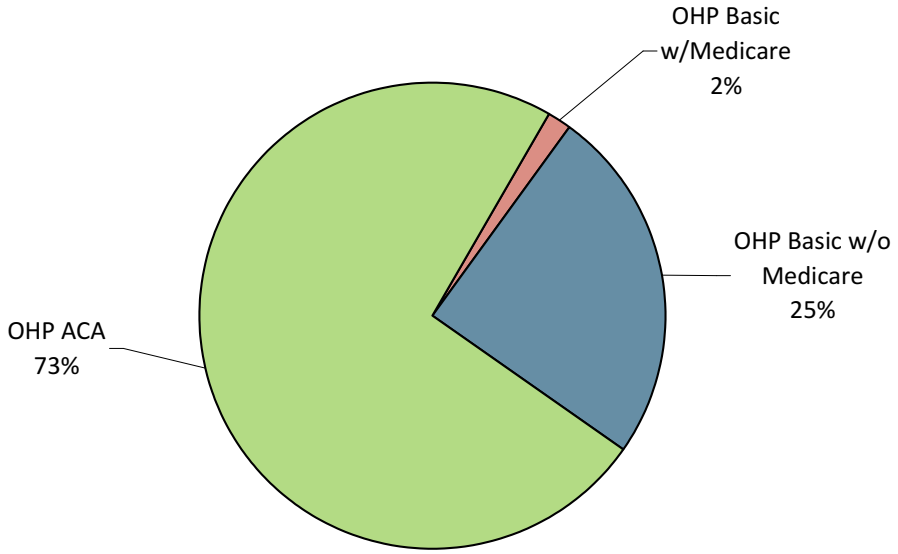
YTD Percent Paid Amounts





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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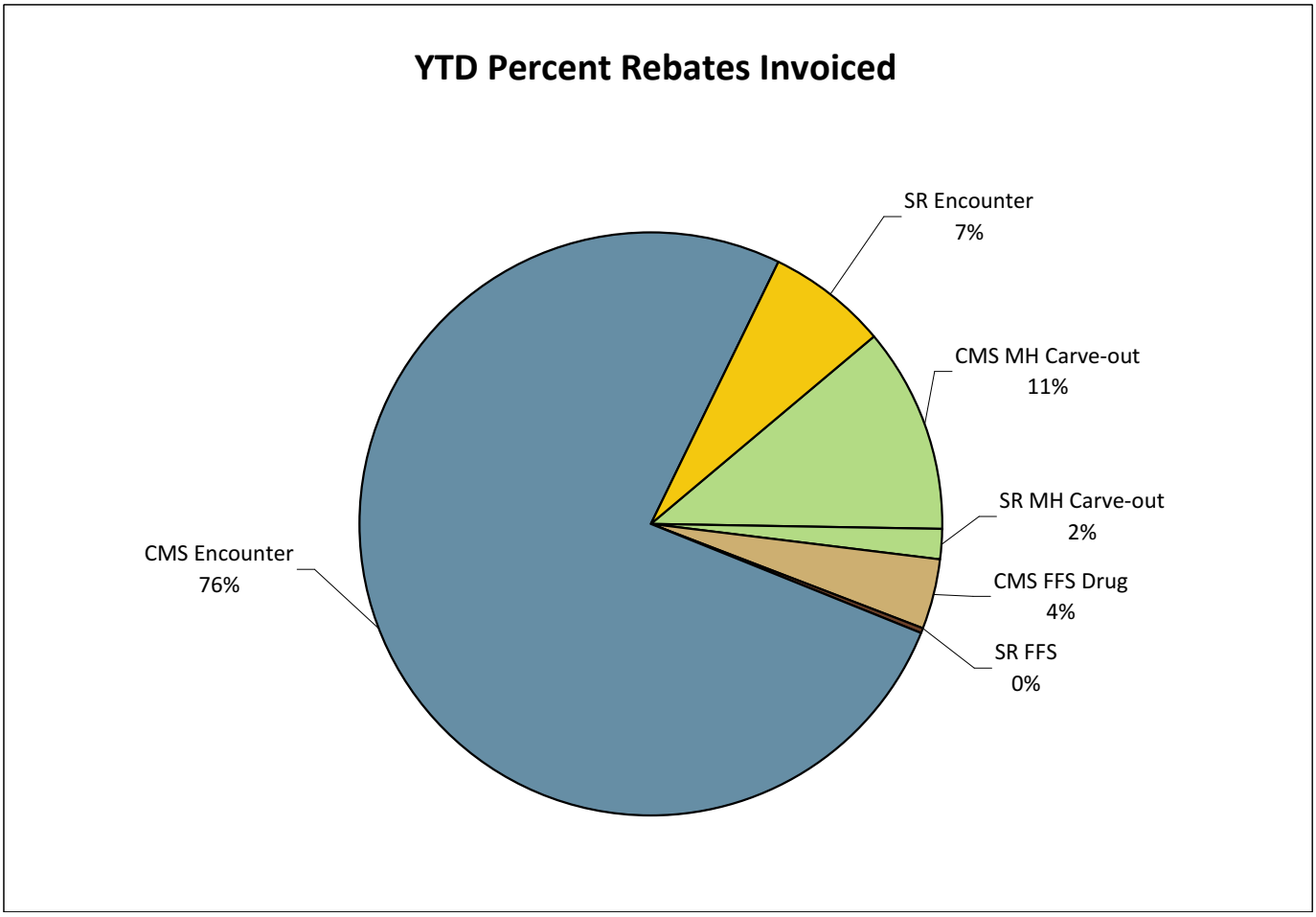
Pharmacy Utilization Summary Report: July 2022 - June 2023

Quarterly Rebates Invoiced	2022-Q3	2022-Q4	2023-Q1	2023-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$120,756,557	$115,576,578	$129,911,059	$143,046,781	$509,290,976
CMS MH Carve-out	$16,615,277	$15,323,997	$15,090,502	$11,213,778	$58,243,554
SR MH Carve-out	$2,206,069	$1,976,038	$1,866,627	$2,361,379	$8,410,113
CMS FFS Drug	$4,523,289	$3,911,477	$5,438,767	$5,503,535	$19,377,068
SR FFS	$557,128	$429,720	$579,671	$536,966	$2,103,485
CMS Encounter	$86,616,033	$85,744,861	$99,575,171	$114,771,319	$386,707,384
SR Encounter	$10,238,761	$8,190,484	$7,360,322	$8,659,804	$34,449,372

Quaterly Net Drug Costs	2022-Q3	2022-Q4	2023-Q1	2023-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$209,829,891	$218,371,052	$226,706,753	$220,471,852	$875,379,549
Mental Health Carve-Out Drugs	$15,320,154	$16,731,973	$17,552,902	$17,582,329	$67,187,358
FFS Phys Health + PAD	$14,718,645	$14,924,284	$16,871,210	$16,398,585	$62,912,723
Encounter Phys Health + PAD	$179,791,092	$186,714,795	$192,282,642	$186,490,938	$745,279,468



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

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Pharmacy Utilization Summary Report: July 2022 - June 2023

Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$78.88	$88.27	$81.38	$81.76	$82.15	$82.56	$86.69	$79.88	$91.47	$81.34	$90.49	$87.51	$84.36
Mental Health Carve-Out Drugs	$8.39	$8.94	$8.34	$8.33	$8.34	$8.45	$8.81	$8.11	$8.06	$7.08	$7.78	$7.37	$8.17
FFS Physical Health Drugs	$41.52	$49.41	$43.67	$44.89	$44.60	$43.53	$47.73	$43.57	$51.03	$44.55	$50.65	$45.21	$45.86
FFS Physician Administered Drugs	$12.79	$11.32	$12.69	$11.09	$8.52	$8.92	$16.52	$14.21	$14.54	$14.34	$15.86	$14.02	$12.90
Encounter Physical Health Drugs	$55.66	$62.21	$57.95	$58.05	$58.21	$58.72	$60.50	$56.52	$63.97	$58.29	$64.61	$63.18	$59.82
Encounter Physician Administered Drugs	$16.38	$18.86	$16.69	$17.07	$17.58	$17.49	$18.74	$16.56	$21.17	$17.45	$19.62	$18.94	$18.05

Claim Counts	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
Total Claim Count (FFS & Encounter)	1,106,008	1,202,993	1,141,967	1,179,219	1,184,623	1,180,869	1,223,411	1,116,649	1,277,819	1,189,404	1,287,183	1,236,032	1,193,848
Mental Health Carve-Out Drugs	189,732	206,349	194,268	196,514	195,984	197,022	210,579	191,974	218,492	204,162	220,533	211,391	203,083
FFS Physical Health Drugs	34,793	36,905	34,841	35,463	35,609	35,287	38,747	35,301	41,633	36,810	39,482	37,405	36,856
FFS Physician Administered Drugs	10,044	10,212	9,855	10,162	10,206	10,077	11,407	10,179	11,192	10,245	10,709	10,563	10,404
Encounter Physical Health Drugs	757,997	828,564	786,733	818,511	826,534	825,342	842,963	767,979	877,971	819,414	891,575	856,810	825,033
Encounter Physician Administered Drugs	113,442	120,963	116,270	118,569	116,290	113,141	119,715	111,216	128,531	118,773	124,884	119,863	118,471

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$94.31	$97.59	$95.34	$93.21	$94.00	$95.42	$97.44	$98.82	$99.44	$95.37	$98.58	$99.66	$96.60
Mental Health Carve-Out Drugs	$58.51	$57.60	$57.43	$56.96	$57.71	$58.51	$57.50	$58.36	$51.25	$48.37	$49.45	$49.09	$55.06
FFS Physical Health Drugs	$138.33	$152.26	$146.71	$150.11	$148.42	$148.93	$153.09	$146.59	$150.32	$148.65	$153.88	$147.51	$148.73
FFS Physician Administered Drugs	$147.60	$126.02	$150.78	$129.45	$98.95	$106.84	$180.02	$165.83	$159.35	$171.92	$177.65	$161.93	$148.03
Encounter Physical Health Drugs	$88.59	$91.32	$89.94	$86.94	$87.11	$88.52	$89.78	$92.93	$92.27	$90.48	$92.93	$94.81	$90.47
Encounter Physician Administered Drugs	$174.24	$189.65	$175.21	$176.44	$187.02	$192.33	$195.79	$188.06	$208.58	$186.82	$201.47	$203.14	$189.90

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$24.45	$24.99	$25.01	$23.64	$23.24	$23.47	$24.00	$24.12	$24.50	$24.18	$24.39	$24.23	$24.18
Mental Health Carve-Out Drugs	$17.21	$17.56	$17.29	$17.35	$17.33	$17.61	$17.83	$17.95	$17.99	$17.68	$17.90	$17.77	$17.62
FFS Physical Health Drugs	$94.81	$103.33	$106.38	$103.97	$105.68	$106.52	$102.89	$97.58	$103.93	$104.69	$107.46	$102.32	$103.30
Encounter Physical Health Drugs	$23.40	$23.73	$23.73	$22.05	$21.46	$21.67	$22.26	$22.60	$22.72	$22.52	$22.65	$22.75	$22.63

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$671.26	$698.50	$644.46	$616.56	$639.26	$673.13	$722.99	$762.26	$755.03	$736.84	$759.46	$760.53	$703.36
Mental Health Carve-Out Drugs	$1,085.19	$1,115.96	$1,147.02	$1,155.25	$1,195.38	$1,233.65	$1,241.11	$1,279.96	$1,289.12	$1,286.57	$1,319.02	$1,306.46	$1,221.22
FFS Physical Health Drugs	$348.53	$400.50	$337.78	$367.86	$355.72	$361.86	$423.95	$416.82	$408.22	$398.86	$420.70	$397.14	$386.50
Encounter Physical Health Drugs	$657.02	$682.86	$625.89	$593.50	$617.19	$651.55	$702.35	$744.75	$744.95	$726.03	$747.78	$752.00	$687.16

Generic Drug Use Percentage	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
Generic Drug Use Percentage	90.7%	90.8%	90.2%	89.9%	90.2%	90.5%	91.2%	91.3%	91.5%	91.6%	91.5%	91.4%	90.9%
Mental Health Carve-Out Drugs	96.1%	96.4%	96.4%	96.5%	96.6%	96.6%	96.8%	96.8%	97.4%	97.6%	97.6%	97.6%	96.9%
FFS Physical Health Drugs	82.8%	83.5%	82.6%	82.5%	82.9%	83.4%	84.4%	84.6%	84.8%	85.1%	85.2%	84.7%	83.9%
Encounter Physical Health Drugs	89.7%	89.7%	89.0%	88.6%	89.0%	89.4%	90.1%	90.3%	90.4%	90.3%	90.3%	90.1%	89.7%

Preferred Drug Use Percentage	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Avg Monthly
Preferred Drug Use Percentage	90.49%	90.42%	90.45%	90.65%	90.48%	90.31%	90.43%	90.35%	90.37%	90.34%	90.25%	90.27%	90.4%
Mental Health Carve-Out Drugs	93.24%	93.13%	93.14%	93.07%	92.87%	92.70%	92.58%	92.51%	92.53%	92.51%	92.39%	92.42%	92.8%
FFS Physical Health Drugs	95.64%	95.77%	95.69%	95.64%	95.79%	95.85%	95.21%	95.24%	95.27%	95.44%	95.36%	95.39%	95.5%
Encounter Physical Health Drugs	89.61%	89.54%	89.59%	89.89%	89.72%	89.54%	89.72%	89.63%	89.64%	89.61%	89.53%	89.56%	89.6%

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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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2023

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	INVEGA SUSTENNA	Antipsychotics, Parenteral	$4,640,488	11.4%	1,898	$2,445	Y
2	VRAYLAR*	Antipsychotics, 2nd Gen	$4,412,791	10.8%	3,608	$1,223	Y
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,538,408	6.2%	1,090	$2,329	Y
4	REXULTI*	Antipsychotics, 2nd Gen	$2,500,370	6.1%	1,974	$1,267	V
5	INVEGA TRINZA	Antipsychotics, Parenteral	$1,166,826	2.9%	157	$7,432	Y
6	CAPLYTA*	Antipsychotics, 2nd Gen	$912,959	2.2%	643	$1,420	V
7	TRINTELLIX	Antidepressants	$859,300	2.1%	2,028	$424	V
8	ARISTADA	Antipsychotics, Parenteral	$805,437	2.0%	345	$2,335	Y
9	SERTRALINE HCL	Antidepressants	$590,724	1.5%	60,413	$10	Y
10	BUPROPION XL	Antidepressants	$584,923	1.4%	48,041	$12	Y
11	DULOXETINE HCL	Antidepressants	$564,702	1.4%	38,716	$15	Y
12	TRAZODONE HCL	Antidepressants	$515,693	1.3%	50,305	$10	
13	LYBALVI*	Antipsychotics, 2nd Gen	$491,624	1.2%	373	$1,318	V
14	ESCITALOPRAM OXALATE	Antidepressants	$488,938	1.2%	45,075	$11	Y
15	FLUOXETINE HCL	Antidepressants	$481,738	1.2%	44,844	$11	Y
16	SPRAVATO*	Antidepressants	$465,614	1.1%	415	$1,122	V
17	TRIKAFTA*	Cystic Fibrosis	$412,070	1.0%	35	$11,773	N
18	BIKTARVY	HIV	$373,692	0.9%	134	$2,789	Y
19	LAMOTRIGINE	Antiepileptics, Outpatient	$331,456	0.8%	30,266	$11	Y
20	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$329,068	0.8%	28,836	$11	
21	INVEGA HAFYERA	Antipsychotics, Parenteral	$303,599	0.7%	19	$15,979	Y
22	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$281,461	0.7%	20,820	$14	Y
23	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$277,202	0.7%	13	$21,323	
24	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$273,906	0.7%	229	$1,196	Y
25	ATOMOXETINE HCL*	ADHD Drugs	$262,656	0.6%	9,264	$28	Y
26	AUVELITY	Antidepressants	$259,340	0.6%	301	$862	V
27	HUMIRA(CF) PEN*	Targeted Immune Modulators	$258,237	0.6%	48	$5,380	Y
28	Elosulfase Alfa, Injection	Physican Administered Drug	$255,084	0.6%	13	$19,622	
29	VENLAFAXINE HCL ER	Antidepressants	$237,757	0.6%	19,186	$12	Y
30	LAMOTRIGINE ER	Antiepileptics, Outpatient	$237,652	0.6%	3,974	$60	V
31	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$233,288	0.6%	20,826	$11	Y
32	BUPROPION XL	Antidepressants	$205,426	0.5%	1,474	$139	V
33	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$205,088	0.5%	20	$10,254	Y
34	Inj Pembrolizumab	Physican Administered Drug	$203,513	0.5%	52	$3,914	
35	QELBREE*	ADHD Drugs	$198,851	0.5%	496	$401	Y
36	LENALIDOMIDE	STC 30 - Antineoplastic	$191,613	0.5%	12	$15,968	
37	VILTEPSO*	Duchenne Muscular Dystrophy	$186,238	0.5%	12	$15,520	
38	CONCERTA*	ADHD Drugs	$181,990	0.4%	531	$343	Y
39	MIRTAZAPINE	Antidepressants	$175,410	0.4%	12,806	$14	Y
40	CITALOPRAM HBR	Antidepressants	$171,082	0.4%	19,082	$9	Y
		Top 40 Aggregate:	**$28,066,211**		**468,374**	**$3,675**	
		All FFS Drugs Totals:	**$40,725,085**		**740,650**	**$667**	

*** 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: January 18, 2024

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2023

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	TRIKAFTA*	Cystic Fibrosis	$412,070	3.8%	35	$11,773	N
2	BIKTARVY	HIV	$373,692	3.5%	134	$2,789	Y
3	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$277,202	2.6%	13	$21,323	
4	HUMIRA(CF) PEN*	Targeted Immune Modulators	$258,237	2.4%	48	$5,380	Y
5	Elosulfase Alfa, Injection	Physican Administered Drug	$255,084	2.4%	13	$19,622	
6	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$205,088	1.9%	20	$10,254	Y
7	Inj Pembrolizumab	Physican Administered Drug	$203,513	1.9%	52	$3,914	
8	LENALIDOMIDE	STC 30 - Antineoplastic	$191,613	1.8%	12	$15,968	
9	VILTEPSO*	Duchenne Muscular Dystrophy	$186,238	1.7%	12	$15,520	
10	CONCERTA*	ADHD Drugs	$181,990	1.7%	531	$343	Y
11	LANTUS SOLOSTAR	Diabetes, Insulins	$154,856	1.4%	398	$389	Y
12	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$149,598	1.4%	79	$1,894	Y
13	TRULICITY*	Diabetes, GLP-1 Receptor Agonists and GIP Thera	$144,507	1.3%	238	$607	Y
14	SPIKEVAX 2023-2024	STC 90 - Biologicals	$142,897	1.3%	903	$158	
15	DAYBUE*	STC 99 - Miscellaneous	$142,461	1.3%	3	$47,487	N
16	PAXLOVID	Coronavirus Antivirals	$128,775	1.2%	108	$1,192	
17	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$115,314	1.1%	7	$16,473	
18	EPIDIOLEX*	Antiepileptics, Outpatient	$111,164	1.0%	56	$1,985	N
19	ELIQUIS	Anticoagulants, Oral and SQ	$110,153	1.0%	294	$375	Y
20	Canakinumab Injection	Physican Administered Drug	$109,524	1.0%	3	$36,508	
21	STELARA*	Targeted Immune Modulators	$106,697	1.0%	16	$6,669	N
22	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$105,169	1.0%	1,460	$72	Y
23	Aflibercept Injection	Physican Administered Drug	$95,969	0.9%	173	$555	
24	Inj. Calaspargase Pegol-Mknl	Physican Administered Drug	$92,164	0.9%	2	$46,082	
25	COMIRNATY 2023-2024	STC 90 - Biologicals	$91,971	0.9%	605	$152	
26	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP Thera	$88,000	0.8%	168	$524	N
27	REVLIMID	STC 30 - Antineoplastic	$87,498	0.8%	1	$87,498	
28	CHOLBAM*	Bile Therapy	$86,917	0.8%	3	$28,972	N
29	Factor Viii Recombinant Nos	Physican Administered Drug	$86,423	0.8%	9	$9,603	
30	JARDIANCE	Diabetes, SGLT-2 Inhibitors	$84,859	0.8%	257	$330	Y
31	SKYRIZI PEN*	Targeted Immune Modulators	$76,354	0.7%	5	$15,271	N
32	VIGABATRIN	Antiepileptics, Outpatient	$75,715	0.7%	3	$25,238	N
33	COSENTYX SENSOREADY (2 PENS)*	Targeted Immune Modulators	$74,821	0.7%	19	$3,938	Y
34	Injection, Nivolumab	Physican Administered Drug	$73,852	0.7%	12	$6,154	
35	Sacituzumab Govitecan-Hziy	Physican Administered Drug	$68,348	0.6%	7	$9,764	
36	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$68,094	0.6%	2,546	$27	Y
37	TAGRISSO*	Antineoplastics, Newer	$64,582	0.6%	4	$16,146	
38	IBRANCE*	Antineoplastics, Newer	$60,355	0.6%	4	$15,089	
39	CREON	Pancreatic Enzymes	$60,182	0.6%	51	$1,180	Y
40	CALQUENCE*	Antineoplastics, Newer	$59,739	0.6%	4	$14,935	
		Top 40 Aggregate:	**$5,461,683**		**8,308**	**$12,554**	
		All FFS Drugs Totals:	**$10,807,583**		**112,304**	**$681**	

*** 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 lo wer, pay Billed Amount, 2) - TPL amount

Last updated: January 18, 2024

ProDUR Report for October through December 2023
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	4	2	0	2	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	1,837	472	0	1,363	1.1%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	8,602	2,620	1	5,975	5.4%	N/A
ER (Early Refill)	**Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)**	**Set alert/Deny claim**	**99,182**	**20,554**	**67**	**78,553**	**63.2%**	**20.7%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	35,229	9,911	8	25,290	22.4%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	832	198	0	634	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	4	4	0	0	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	713	212	0	501	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	425	154	0	271	0.2%	N/A
PA (Drug/Age Precaution)	Products containing Codeine or Tramadol being billed and patient is less than 18 years of age	Set alert/Pay claim	3	0	0	3	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**33**	**29**	**0**	**4**	**0.0%**	**87.9%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	9,965	3,076	0	6,872	6.3%	N/A
		Totals	**156,829**					

ProDUR Report for October through December 2023
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)	7,952	1,533	6,419	80,965	9.8%	19.3%
ER	Lexapro (Escitalopram)	5,833	1,018	4,815	59,790	9.7%	17.5%
ER	Prozac (Fluoxetine)	5,679	1,008	4,671	58,510	9.7%	17.7%
ER	Celexa (Citalopram)	2,047	358	1,689	24,034	8.5%	17.5%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	7,933	1,504	6,429	86,103	9.2%	19.0%
ER	Trazodone	7,258	1,503	5,755	66,947	10.8%	20.7%
ER	Cymbalta (Duloxetine)	5,150	1,083	4,067	49,490	10.3%	21.0%
ER	Effexor (Venlafaxine)	2,985	560	2,425	30,818	9.6%	18.8%
ER	Remeron (Mirtazapine)	1,983	335	1,648	16,784	11.8%	16.9%
ER	Elavil (Amitriptyline)	1,728	341	1,387	18,214	9.4%	19.7%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	4,894	1,213	3,681	34,157	14.3%	24.8%
ER	Abilify (Aripiprazole)	4,107	728	3,379	30,767	13.3%	17.7%
ER	Zyprexa (Olanzapine)	2,723	664	2,059	21,125	12.8%	24.4%
ER	Risperdal (Risperidone)	2,096	457	1,639	13,715	15.2%	21.8%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	3,920	693	3,227	37,820	10.3%	17.7%
ER	Lorazepam	338	118	220	13,283	2.5%	34.9%
ER	Alprazolam	182	42	140	7,259	2.5%	23.1%
ER	Diazepam	70	13	57	3,878	1.8%	18.6%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	6,817	1,394	5,423	48,814	13.9%	20.4%
ER	Intuniv (Guanfacine ER)	1,814	294	1,520	14,090	12.8%	16.2%
ER	Depakote (Divalproex)	1,807	519	1,288	12,550	14.4%	28.7%
ER	Suboxone (Buprenorphine/Naloxone)	138	50	88	2,259	6.0%	36.2%

ProDUR Report for October through December 2023
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	October	4,715	131	268	677	1	3,358	53	0	227
ER	November	4,505	178	240	605	2	3,189	66	0	225
ER	December	4,581	180	240	656	4	3,217	60	4	220
	Total =	**13,801**	**489**	**748**	**1,938**	**7**	**9,764**	**179**	**4**	**672**
	Percentage of total overrides =		**3.5%**	**5.4%**	**14.0%**	**0.1%**	**70.7%**	**1.3%**	**0.0%**	**4.9%**

ProDUR Report for October through December 2023			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
October	DC	3	$319.97
	DD	29	$3,235.86
	ER	58	$7,625.91
	HD	1	$101.99
	ID	35	$6,662.09
	TD	6	$1,309.51
	October Total	**132**	**$19,255.33**
November	DC	2	$585.90
	DD	12	$2,182.89
	ER	94	$16,696.94
	ID	19	$3,591.91
	LR	1	$20.56
	MC	1	$117.99
	TD	5	$439.42
	November Total	**134**	**$23,635.61**
December	ER	10	$834.62
	ID	4	$442.67
	December Total	**14**	**$1,277.29**
		Total 4Q2023 Savings =	**$44,168.23**

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

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	33	12		
		Total Claims Identified	70	12		
		Claims reviewed	16			
		Estimated Savings	$5,240			
	OCC 4 with OCC 2 for different NDC	Total Patients Identified	14	6		
		Total Claims Identified	25	8		
	OCC 4 with OCC 2 for the same NDC	Total Patients Identified	4	1		
		Total Claims Identified	6	1		
	OCC 4 with Primary Payer Rejection Code	Total Patients Identified	5			
		Total Claims Identified	7			

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

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	17	2		
		Unique Patients Identified	17	2		
		Total Faxes Successfully Sent	11			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	4			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$6,059			
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	82	2		
		Unique Patients Identified	82	2		
		Total Faxes Successfully Sent	63	2		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	39			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$16,016			
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	51			
		Unique Patients Identified	52			
		Total Faxes Successfully Sent	39			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	16			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$1,728			

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	RetroDUR Dose Consolidation	Total Claims Identified	4			
		Total Faxes Successfully Sent	3			
		Safety Monitoring Profiles Identified	1			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0			

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

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	794			
		High risk patients identified	5			
		Prescribers successfully notified	4			
		Patients with continued antipsychotic therapy in the following 90 days	4			

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

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	56	5		
		Total prescribers identified	56	5		
		Prescribers successfully notified	55			
		Patients with claims for the same antipsychotic within the next 90 days	29			
		Patients with claims for a different antipsychotic within the next 90 days	2			

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

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	76			
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	30			
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	137			
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	42			
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	14			
		Letters Sent To Providers	4			
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	18			
		Letters Sent To Providers	12			
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	14			
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	19			
		Letters Sent To Providers	2			
	Lock-In	RetroDUR Profiles Reviewed	3			
		Locked In	0			

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

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	13	2		
		Total prescribers identified	13	2		
		Prescribers successfully notified	10			
		Patients with paid claims within next 60 days	6			
		Patients with denied claim within next 60 days	4			

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Retro-DUR Intervention History by Quarter FFY 2023 - 2024

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	98	8		
		Total prescribers identified	98	8		
		Prescribers successfully notified	97			
		Patients with discontinuation of therapy within next 90 days	44	8		
		Patients with new prescription for naloxone within next 90 days	3			
		Average number of sedative drugs dispensed within next 90 days	10	0		
		Average number of sedative prescribers writing prescriptions in next 90 days	10	0		
	Oncology Denials	Total patients identified	2			
		Total prescribers identified	2			
		Prescribers successfully notified	2			
		Patients with claims for the same drug within the next 90 days	2			
		Patients with claims for any oncology agent within the next 90 days	2			
	TCAs in Children	TCA Denials in Children	38	3		
		Total patients identified	18	1		
		Total prescribers identified	18	1		
		Prescribers successfully notified	13			
		Patients with claims for a TCA within the next 90 days	3			

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An Update in Weight Loss Therapies - Including FDA Approved GLP-1 Receptor Agonists

Melissa Yokoyama, Pharm.D and Megan Herink, Pharm.D., Oregon State University Drug Use Research and Management Group

In the past 20 years, the prevalence of obesity in the United States has increased from 30.5% to 41.9% and it is estimated that 1 in 5 children have obesity.[1,2] Obesity is associated with many complications, including cardiovascular disease (CVD), metabolic syndrome, obstructive sleep apnea, type 2 diabetes mellitus (T2DM), osteoarthritis, non-alcoholic fatty liver disease and certain cancers.[1] A comprehensive lifestyle approach, including healthy meal plans, physical activity and behavioral intervention remain the foundation to treating obesity and preventing weight-related complications.[3] For many patients, effectiveness of lifestyle approaches is limited, and pharmacological therapies are needed to achieve weight loss goals. The purpose of this newsletter is to summarize current pharmacologic treatment options for obesity, including the glucagon- like peptide 1 receptor agonist (GLP-1 RA) class.[1,4]

Lifestyle Interventions

A comprehensive lifestyle intervention that combines behavioral, dietary, and physical activity is strongly recommended for all individuals with obesity.[1] Weight loss goals are individualized, and some patients may require larger weight reductions for clinically meaningful benefits. However, a 5-10% weight loss after six months can result in clinically significant benefits on weight associated conditions.[1] There is a dose-response on weight loss with the number and intensity of lifestyle interventions utilized. High-intensity programs have demonstrated 5-10% reductions in weight loss.[5] At one year, lifestyle interventions have also shown to reduce the risk of T2DM.[6] However, intensive lifestyle interventions studied in clinical trials are difficult to replicate in clinical settings.[6] The expense, limited availability, and resources required for implementation contribute to health disparities in access to these interventions.

Pharmacological Therapies for Weight Loss

For patients with obesity (body mass index [BMI] of 30 kg/m^2 or higher) or with a BMI of 27 kg/m^2 or higher with weight-related complications (e.g., hypertension, T2DM, dyslipidemia) who have an inadequate response to lifestyle interventions, guidelines recommend pharmacologic agents **(Tables 1 & 2)**.[3]

The minimal clinically important difference (MCID) for the efficacy of pharmacotherapy in the management of obesity that corresponds to important patient benefits is a mean difference (MD) of 3% total body weight loss (TBWL) between adjunctive pharmacotherapy over lifestyle interventions alone, or an absolute 5% TBWL over baseline.[1] If patients have not lost 5% of their total body weight by 12 weeks of therapy on the maintenance dose, it is generally recommended that medications be discontinued and an alternative medication or treatment be considered.[1]

Table 1: Older Medications for Weight Management[1,3,4]

Drug (Brand name)	Mechanism of Action	%TBWL
Phentermine-topiramate ER (Qysmia)	Sympathomimetic amine-neurostabilizer	MD 8.45% (7.89-9.01%)
Naltrexone-bupropion ER (Contrave)	Opioid antagonist/ dopamine and NE reuptake inhibitor	MD 3.01% (2.47- 3.54%)
Orlistat (Xenical)	Lipase inhibitor	MD 2.78% (2.36 –3.20%)
Phentermine (Adipex)	Sympathomimetic amine	MD 3.63 % (2.97-4.29%)
Diethylpropion (Tenuate)	Sympathomimetic amine	MD 5.36% (3.50– 7.23%)
Abbreviations: ER: extended release; TBWL: total body weight loss, MD: mean difference; NE: norepinephrine		

Phentermine and diethylpropion are FDA-approved for only short-term use (12 weeks). Both medications should be avoided in patients with a history of cardiovascular disease (CVD) or uncontrolled hypertension and are supported by low quality evidence with a limited place in therapy.[1] Despite its FDA approval in 1999, orlistat has limited clinical utility due to its small weight loss benefit and potential for gastrointestinal side effects.[1]

Phentermine-topiramate ER and naltrexone-bupropion ER are FDA-approved for chronic weight loss management.[1] Common side effects include dry mouth, headache, numbness and tingling, and constipation. Topiramate is teratogenic. Women of childbearing potential who take topiramate should be counseled to use effective contraception consistently.[1] Blood pressure and heart rate should be monitored while taking medications with phentermine. The combination of naltrexone-bupropion ER should be avoided in patients with seizure disorders as well as patients taking opioids but may be a consideration in patients with obesity who also need smoking cessation or depression treatment.[1]

Glucagon- Like Peptide 1 Receptor Agonists

Over the past 15 years, GLP-1 RAs have demonstrated beneficial effects on diabetes, renal, CV and weight loss outcomes.[7-10] GLP-1 is an endogenous hormone released by the gastrointestinal (GI) tract in response to the intake of food, resulting in a glucose-dependent release of insulin secretion

(the "incretin" response), delayed gastric emptying, modulation of b-cell proliferation, and improved appetite control, resulting in beneficial effects in glucose levels and body weight.[1]

While all GLP-1 RAs are approved for T2DM, only liraglutide and semaglutide **(Table 2)** are currently FDA-approved for chronic weight management in people with a BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater with at least one weight-related comorbid condition.[11,12] The doses approved for chronic weight management are different from doses approved for T2DM. Both medications are not recommended in pregnancy, and contraindicated in patients with a personal or family history of thyroid carcinoma or multiple endocrine neoplasia syndrome type I.[11,12] They are titrated up slowly at weekly intervals to limit GI side effects. The maximum tolerated dose that achieves the goal weight loss should be continued. If at least 5% weight loss of TBWL is not achieved after 12 weeks at maximum tolerated dose, they should be discontinued.

Table 2: FDA Approved GLP-1 RAs for Chronic Weight Management.[1,11,12]

Generic Name	Brand Name	Target Dose	%TBWL[1]
Liraglutide	Saxenda	3 mg SC daily	MD 4.81% (4.23 - 5.39%)
Semaglutide	Wegovy	2.4 mg SC weekly	MD 10.76% (8.73 -12.8%)

Abbreviations: SC: subcutaneous, MD: mean difference, TBWL: total body weight loss

Liraglutide (Saxenda®)

FDA approval of liraglutide for chronic weight management was based on the results of three, 56-week randomized, double-blind, placebo-controlled trials **(Table 3)**, which were all a part of the Satiety and Clinical Adiposity- Liraglutide Evidence in non-diabetic and diabetic individuals (SCALE) program. Trials randomized patients to liraglutide 3 mg daily or placebo, with dosing starting at 0.6 mg and increasing by 0.6 mg weekly to the target dose.[11]

In the SCALE Maintenance Trial, the effects of liraglutide on weight maintenance was evaluated after an initial run-in period.[13] Patients who lost at least 5% of their initial body weight in the 4- to 12-week low calorie diet run-in period were randomized into the trial. Participants lost a mean of 6.3 kg during the run-in period. After 56 weeks, the liraglutide group achieved greater additional mean weight loss of 6.2% compared to 0.2% with placebo.

The SCALE Obesity and Prediabetes trial stratified according to prediabetes status and BMI (≥30 and <30 kg/m^2).[14] After 56 weeks, patients without T2DM treated with liraglutide lost a mean of 8%±6.7% of their body weight compared to 2.6%±5.7% with placebo. Results were similar regardless of prediabetes status but the liraglutide was less effective in patients with a mean BMI >40.[14] More patients in the placebo group developed T2DM than patients in the liraglutide group (6.2% vs. 1.8%).[14]

The SCALE Diabetes trial included patients with obesity and T2DM.[15] A total of 69.2% of patients on liraglutide achieved an HbA1c less than 7% compared to 27.2% in the placebo group, with reductions in HbA1c of 1.3% and 0.3%, respectively (MD -0.93%; 95% CI -1.08 to -0.78%).[15]

Table 3: Liraglutide Clinical Trials.

Study	Study Population	Mean %TBWL vs Placebo	% patients ≥5% & ≥10% TBWL vs Placebo
SCALE Maintenance Trial[13]	Adults with BMI ≥ 30 or ≥27 with ≥1 weight related condition* without T2DM (n=422)	-6.2% ETD: -6.1% (95% CI -7.5 to -4.6)	50.5% vs. 21.8% ARR 29% /NNT 4 26.1% vs. 6.3% ARR 20% /NNT 5
SCALE Obesity and Prediabetes Trial[14]	Adults with BMI ≥ 30 or ≥27 with ≥1 weight-related condition* without T2DM (n=3731)	-8.0% ETD: -5.4% (95% CI −5.8 to −5)	62.3% vs. 27.1% ARR 20% /NNT 5 33.1% vs.10.6% ARR 23% /NNT 5
SCALE Diabetes Trial[15]	Adults with T2DM, BMI ≥27 and HbA1c 7-10% (n=846)	-6.0% ETD: -4.0% (95% CI -5.1 to -2.9)	54.3% vs. 21.4% ARR 33% /NNT 3 25.2% vs. 6.7% RR 19% /NNT 6

* treated or untreated dyslipidemia or hypertension
Abbreviations: ARR: absolute risk reduction; BMI: body mass index; CI: confidence interval; ETD: estimated treatment difference; HbA1c: hemoglobin A1c; NNT: number needed-to-treat; T2DM: type 2 diabetes mellitus; TBWL: total body weight loss.

All three studies demonstrated a statistically significant reduction in weight compared with placebo after 56 weeks of treatment with liraglutide (**Table 3**). As anticipated, follow-up studies consistently demonstrated weight gain after study medication was stopped, which ranges from 3 to 5%.[1] Therefore, treatment discontinuation needs to be carefully considered in clinical practice and if a clinical response is present, long-term use is expected.

There were more withdrawals due to adverse events with liraglutide compared to placebo (9.8% vs. 4.3%) and the most common adverse effects were GI related, notably nausea (39.3% vs 13.8%), diarrhea (20.9% vs. 9.9%) and constipation (19.4% vs. 8.5%).[1] Most patients reported increased incidence with higher doses and in the first 4-8 weeks of treatment, with decreased reports after week 10.[13-15]

Semaglutide (Wegovy®)

FDA approval of semaglutide for chronic weight management was based off three 68-week, randomized, double-blind, placebo-controlled trials and one 68-week, randomized, double blind, placebo withdrawal trial (**Table 4**), which were a part of the Semaglutide Treatment Effect in People with Obesity (STEP) program.[16-19]

In STEP trials 1-3, semaglutide was titrated to a target dose of 2.4 mg weekly, starting at 0.25 mg weekly for the first 4 weeks, then increased every 4 weeks until week 16.[16,18,19] STEP 4 was a withdrawal trial, evaluating continued semaglutide versus placebo in participants who reached the target 2.4 mg dose in an initial 20-week run-in.[17]

Table 4: Semaglutide Clinical Trials.

Study	Study Population	Mean %TBWL vs Placebo	% patients ≥5% & ≥10% TBWL vs Placebo
STEP 1[19]	Adults with BMI ≥30 or ≥27 with ≥1 condition* without T2DM (n=1961)	-14.9% ETD -12.4% (95% CI -13.4 to -11.5)	86.4% vs. 31.5% ARR 55% /NNT 2 69.1% vs. 12% ARR 41% /NNT 3
STEP 2[16]	Adults with T2DM and BMI ≥27 kg/m^2 with HbA1c 7-10% (n=1210)	-9.6% ETD -6.2% (95% CI -7.3 to -5.2)	68.8% vs. 28.5% ARR 40% /NNT 3 45.6% vs. 8.2% ARR 37% /NNT 3
STEP 3[18]	Adults with BMI ≥30 or ≥27 with ≥1 condition* without T2DM (n=611)	-16.0% ETD -10.3 % (95% CI -12 to -8.6)	86.6% vs. 47.6% ARR 39%/NNT 3 75.3% vs. 27% ARR 48% /NNT 2
STEP 4[17]	Adults with BMI ≥30 or ≥27 with ≥1 condition* without T2DM following run-in period (n=902)	-7.9% ETD -14.8% (95% CI -16 to -13.5)	88.7% vs. 47.6% ARR 41% /NNT 3 79.0% vs. 20.4% ARR 59% /NNT 2

* treated or untreated dyslipidemia, hypertension, obstructive sleep apnea or cardiovascular disease
ARR: absolute risk reduction; BMI: body mass index; ETD: estimated treatment difference, HbA1c: hemoglobin A1c; NNT: number needed to treat, T2DM: type 2 diabetes mellitus.

There was a significant decrease in weight loss from baseline with semaglutide compared to placebo (**Table 4**). In the STEP 1 trial, 84.1% of patients with prediabetes reverted to normoglycemia compared to 47.8% on placebo. A decrease in systolic blood pressure was observed with semaglutide compared to placebo (-6.16 mm Hg vs. -1.06 mm Hg).[19] In the STEP 2 trial, patients with T2DM randomized to semaglutide experienced a mean weight loss of 9.6 kg compared to 3.5 kg with placebo.[16] Furthermore, 67.5% of patients on 2.4 mg of semaglutide achieved an HbA1c less than 6.5% compared to 15.5%.[16] In STEP 3, semaglutide was combined with an intensive behavioral therapy program. STEP 3 resulted in a significant weight reduction compared to placebo (16% vs. 5.7%), and efficacy was consistent with previous studies including less intensive "usual advice".[8]

In the STEP 4 withdrawal trial, patients without T2DM on semaglutide had a mean 10.6% weight loss from baseline during a 20-week run-in period. Following the run-in-period, the mean weight loss with semaglutide was 7.9% compared to a weight gain of 6.9% when patients who were switched to placebo.[17]

Like liraglutide, there was a higher rate of withdrawals due to adverse events (5.7% vs. 3.0%) and GI side effects with semaglutide compared to placebo, including nausea (44% vs. 16%), diarrhea (30% vs. 16%) and vomiting (24% vs. 6%). Most of these adverse events were classified as mild to moderate and decreased or resolved over time. Like liraglutide, there is a significant regain of weight following treatment discontinuation of semaglutide and slow dose titration is important to ensure GI tolerability. The STEP 1 extension study found that patients on average gained two-thirds of prior weight loss after a year of discontinuation.[20]

Phase 3 clinical trials evaluating oral semaglutide for the treatment of obesity are underway and FDA review is expected later this year.

Tirzepatide (Mounjaro®)

Tirzepatide is a once weekly subcutaneous injectable with activity at both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) incretin hormone receptors.[21] While not yet FDA approved, a published phase 3 trial found a mean 20.9% weight reduction with the highest dose of tirzepatide (15 mg) compared to 3.1% with placebo in patients with obesity and without diabetes. There was also a greater reduction in systolic blood pressure (-7.2 mm Hg versus -1.0 mm Hg) and triglycerides (-24.8% versus -5.6%) compared to placebo.[21] A dose-response was observed in both weight reduction and GI side effects. FDA review for possible fast-track approval is currently underway.

Current Policies

Obesity was first recognized as a disease in 2013. Under the Medicaid Drug Rebate Program, weight-loss drugs can be excluded from mandatory coverage, and coverage varies between states. Currently, treatment coverage for obesity through the Oregon Health Plan (OHP) is limited to intensive counseling on nutrition and physical activity with the exceptions below. Intensive counseling visits are covered for an initial 6 months and can be continued for 6 months if there is evidence of continued weight loss. However, access to these covered services can be a barrier for patients. Bariatric surgery is also covered for adults with BMI ≥ 40 kg/m^2 or BMI ≥ 30 kg/m^2 with T2DM or at least 2 other serious obesity-related comorbidities and in adolescents ≥ 13 years old with obesity or significant comorbid conditions. Pharmacological treatments and devices used specifically for weight loss are not currently covered under the OHP Prioritized List of health services, except for specific cases in children and youth under the age of 21 years through the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Program. OHP members with T2DM with or without obesity may also be treated with GLP-1 RAs with prior authorization.

Conclusion

Pharmacological therapy is recommended for patients with obesity (BMI ≥ 30 kg/m^2) or with a BMI of 27 kg/m^2 or greater with weight-related complications who have an inadequate response to lifestyle interventions alone. Newer agents have shown a significant weight loss benefit. Magnitude of efficacy comes with more GI side effects that will need to be considered with each patient and thoughtfully managed with dose titration and education. It remains unclear on optimal duration of risks versus benefits of long-term chronic therapy. Long-term studies are currently underway that will clarify benefit of FDA-approved medications for obesity on long-term clinical outcomes, such as maintenance of weight loss, quality of life, non-alcoholic fatty liver disease, cardiovascular morbidity, and all-cause mortality.

Comprehensive lifestyle interventions currently remain the foundation to treating obesity in individuals on the OHP. With the landscape of obesity treatment rapidly changing, OHP will begin reviewing coverage policies and guidelines in 2024 for possible coverage changes to provide access to cost-effectiveness treatments in Oregon Medicaid.

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Prevention of Respiratory Syncytial Virus (RSV) Infection: New Products and Recommendations

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Respiratory syncytial virus (RSV) causes infections in the respiratory tract of people of all ages.[1] RSV is a seasonal infection that occurs most often between the months of November and April. The COVID-19 pandemic disrupted seasonal RSV infections; however data from the 2022-2023 RSV season suggests that patterns are returning toward pre-pandemic seasonality.[2] Infants, toddlers and those over the age of 65 years are most susceptible to severe infection. In children under the age of 5, RSV infections are responsible for 58,000-80,000 hospitalizations and 100-300 deaths annually.[2] In those 65 years and older RSV is implicated in approximately 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths.[1]

Background

Symptoms of RSV are similar to other respiratory illnesses, such as cough, runny nose, sneezing, and fever. In most healthy individuals, RSV infection is self-limiting and does not cause serious sequelae. Individuals with certain underlying health conditions are most likely to experience complications from RSV including lower respiratory tract disease (LRTD) RSV infections may become serious, such as pneumonia, in adults aged 65 years and over, due to weakened immune systems associated with aging and comorbidities (e.g., diabetes and chronic cardiovascular disease). Children and infants may also suffer severe illness from RSV and develop complications such as bronchiolitis and pneumonia.[3] However, most children will have had an RSV infection by their second birthday without serious sequelae. Infants with certain conditions are at the greatest risk of developing complications, such has pneumonia and hospitalization, from RSV infection (**Figure 1**).

Figure 1. Risk Factors for Severe Illness from RSV in Children

- Premature infants
- Infants 12 months old and younger
- Children under the age of 2 with chronic lung disease or congenital heart disease
- Immunocompromised
- Neuromuscular disorders

RSV Preventative Therapies

Until recently there were no RSV vaccines. Palivizumab (SYNAGIS), a monoclonal antibody, was the only Food and Drug Administration (FDA) approved therapy for the prevention of RSV for use only in high risk infants and children. Within the last year, 3 new options for RSV prevention have been approved: BEYFORTUS, ABRYSVO and AREXVY. Indications and dosing intervals differ between the products and are described in **Table 1**.

Table 1. FDA Approved Products for Respiratory Syncytial Virus Prevention

Drug	Approved Populations*	Dosing∞
SYNAGIS[4] (Palivizumab)	- High risk pediatrics+	- Up to 5 monthly IM injections based on weight throughout RSV season
BEYFORTUS[5] (Nirsevimab)	- Neonates and infants born during or entering their first RSV season - Children up to 24 months who remain vulnerable to severe RSV disease during their second RSV season	- 50 mg IM if less than 5 kg in body weight - 100 mg IM if 5 kg or greater - Children in second RSV season: 200 mg IM
AREXVY[6] (RSVPreF3 vaccine)	- Adults 60 y and older	- 0.5 mL IM
ABRYSVO[7] (RSVpreF vaccine)	- Adults 60 y and older - Pregnant individuals at 32 through 36 weeks gestation	- 0.5 mL IM

Key: * See prescribing information for specific use; + Recommendation for use are based off of American Academy of Pediatric recommendations for high risk infants and children; ∞ Dosing recommendation is for one dose unless indicated
Abbreviations: IM = intramuscular; IV = intravenous; mL = milliliter; OTC = over the counter; PreF = perfusion conformation; SQ = subcutaneous; y = year.

SYNAGIS (Palivizumab)

SYNAGIS was shown to decrease hospitalizations in high risk infants and children.[3] SYNAGIS requires monthly dosing, based on weight, for 5 doses.[4] Palivizumab is approved for pediatric use for the following patients[3]:

- Premature birth (less than or equal to 35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season
- Bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season
- Hemodynamically significant congenital heart disease (CHD) and who are 24 months of age or younger at the beginning of RSV season.

BEYFORTUS (Nirsevimab)

BEYFORTUS is a long-acting RSV F protein-directed fusion inhibitor. It was FDA-approved July 2023 for the prevention of RSV LRTD in all neonates and infants born during or entering their first RSV season, or in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[5] Efficacy was based on 3 clinical trials in term and preterm infants; two phase 2 trials and one phase 3 trial.[5] Two studies were conducted in infants entering their first RSV season. The third trial was done in infants born at less than 35 weeks gestation and infants with chronic lung disease (CLD) or CHD entering their first RSV season and in those infants with CLD or CHD entering their second RSV season. In the phase 3 trial, term and late preterm infants with a gestational age greater than or equal to 35 weeks entering their first RSV season were enrolled. The primary endpoint was the incidence of Medically Attended Respiratory Syncytial Virus Lower Respiratory Tract Infection (MA RSV LRTI) characterized predominantly as bronchiolitis or pneumonia through 150 days after dosing and confirmed by a reverse transcription-polymerase chain reaction (RT-PCR). The number of MA RSV LRTI was 1.2% in the BEYFORTUS group compared to 5.0% in the placebo group (efficacy 74.9%; 95% CI, 50.6 to 87.3; $p < 0.001$).[5] The most common adverse reaction was rash at the injection site.[5]

BEYFORTUS may be given in the second RSV season to those infants who are up to 24 months of age, who remain vulnerable, and received SYNAGIS or BEYFORTUS in their first RSV season.[5] SYNAGIS should not be given to infants who have already received BEYFORTUS in the same season.[5] BEYFORTUS may administered with other age-appropriate vaccines.[8]

ABRYSVO

ABRYSVO is a vaccine that works by facilitating an immune response against RSV pre F that protects against lower respiratory tract disease caused by RSV. Passive Immunization is accomplished by antibodies to RSV antigens from individuals vaccinated in pregnancy transfer transplacentally to protect infants younger than 6 months of age against RSV.[6] ABRYSVO is approved to prevent LRTD caused by RSV in people 60 years and older.[7] In August 2023, ABRYSVO received an additional indication for active immunization of pregnant individuals at 32 through 36 weeks gestation for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.[7]

ABRYSVO was studied in adults 60 years and older. The primary endpoint was relative risk reduction of first episode of RSV-LRTD. Interim analysis of an ongoing phase 3, double-blind, randomized, placebo-controlled trial in those 60 years and older found vaccine efficacy to be 66.7% (95% CI, 28.8 to 85.8) in those with 2 or more symptoms and 85.7% (95% CI, 32.0 to 98.7) in those with 3 or more symptoms who were followed out to 7 months.[7] The most common adverse reactions in those 60 years and older were fatigue, headache, pain at the injection site and muscle pain.

Evidence for the use of ABRYSVO in pregnant individuals was demonstrated in one phase 3, double-blind, randomized controlled trial.[8] RSV-associated LRTD in infants was defined as a medically attended visit with a RT-PCR confirmed RSV illness with one or more of the following respiratory symptoms: tachypnea based on age; SpO2 measured in room air <95%; chest wall indrawing. RSV-associated severe LRTD was a subset defined as meeting the LRTD RSV criteria plus at least one of the following: tachypnea based on protocol. (SpO2 measured in room air <93%; high-flow nasal cannula or mechanical ventilation (invasive or noninvasive), intensive care unit (ICU) admission for >4 hours and/or failure to respond/unconscious.[8] Six infants born to individuals who received ABRYSVO experienced severe LRTD caused by RSV within 90 days of birth compared to 33 infants who received placebo (vaccine efficacy 81.8%; 99.5% CI, 40.6 to 96.3%).[8] At 180 days from birth, 19 infants born to individuals who received ABRYSVO experienced severe LRTD caused by RSV compared to 62 infants who received placebo (vaccine efficacy 69.4%; 97.58% CI, 44.3 to 84.1%).[8] In pregnant individuals, the most common adverse events were pain at the injection site, headache, muscle pain and nausea. Low birth weight and jaundice was associated with the use of ABRYSO in infants born to pregnant individuals.[7]

There is no evidence to support use of SYNAGIS in infants born to individuals who received ABRYSVO. Additionally, the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) advises that there is no evidence to support the use of BEYFORTUS in a baby born to an individual immunized against RSV during their pregnancy; however, BEYFORTUS may be appropriate in rare circumstances if the following occur: a pregnant person has an immunocompromising condition that prevents an adequate immune response or condition associated with a reduced transplacental antibody transfer, infants undergoing cardiopulmonary bypass causing loss of RSV antibodies and those infants at very high risk for severe RSV disease due to comorbidities (e.g., hemodynamically significant heart disease, ICU, requiring oxygen at discharge).[3]

Several clinical implications need to be taken into account when deciding which RSV protection is chosen for infants. **Table 2** presents the risks and benefits of RSV prevention via maternal vaccination (ABRYSVO) compared to infant injection with BEYFORTUS. Additionally, there is limited long-term efficacy and safety data on all the new RSV vaccines and preventative therapy. Evidence on hospitalization reduction and mortality benefits would also help to inform cost-effective evidence-based use.

Table 2. Risks versus Benefit of Maternal RSV vaccination Versus BEYFORTUS Infant Injection[4,6]

Preventative Therapy	Benefits	Risks
ABRYSVO (Maternal RSV vaccine)	- Protection is present upon birth - May be more resistant to virus mutations - Infant does not need to be injected	- Risk of preterm birth - Protection could be reduced due to fewer antibodies produced or are transferred from mother to baby
BEYFORTUS (Nirsevimab)	- Antibodies are given directly to the infant - Antibody levels may wane more slower - No risk of preterm birth	- Supply limitations - Requires infant receives injection

AREXVY

AREXVY (RSV vaccine) was approved in May of 2023 for the prevention of LRTD caused by RSV in those 60 years and older.[6] AREXVY mechanism of action works by eliciting an immune response against RSVpreF3 that protects against LRTD caused by RSV. AREXVY was approved based on a phase 3, randomized, placebo-controlled trial (n=24,960).[6] Results were based on an interim analysis at 6.7 months. The primary endpoint was the prevention of a first episode of confirmed RSV-A and/or B-associated LRTD during the first season. The incidence of infection was 1.0 per 1,000 person-years in those treated with AREXVY compared to 5.8 per 1,000 person-years in those treated with placebo (efficacy 82.6%; 95% CI, 57.9 to 94.1).[6] The most common adverse reactions reported with AREXVY are: injection site pain, fatigue, myalgia, headache and arthralgia.[6]

Guideline Recommendations

The American Academy of Pediatrics (AAP) and the CDC ACIP updated guidance released August 2023, recommended that a single dose of BEYFORTUS be used in all neonates and infants born during or entering their first RSV season, or in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The AAP/ACIP also recommend SYNAGIS be used in those high-risk neonates, infants or children who are not able to access BEYFORTUS.[3,9] If those children who received SYNAGIS initially for the season and less than 5 doses were given, then one dose of BEYFORTUS could be given with no administration of additional doses of SYNAGIS.[9]

In October 2023 the CDC released updated guidance on the use of BEYFORTUS due to supply limitations. They are advising that the 100 mg doses be reserved for the infants that are most vulnerable: young infants (age <6 months) and infants with underlying conditions that place them at highest risk for severe RSV disease. There is no change to the 50 mg dose recommendation. For high-risk children 8-19 months for the 2023-2024 season, the CDC is recommending SYNAGIS, per AAP guidance, instead of BEYFORTUS to conserve supplies. BEYFORTUS is recommended for American Indian and Alaska Native children aged 8–19 months who are not SYNAGIS-eligible due to transporting children with severe RSV who require escalation of medical care since obtaining care is more challenging due to living in remote areas and high rates of RSV in infants and toddlers.

In July 2023 the CDC recommended the RSV vaccine may be given to adults ages 60 and over after discussion with their provider.[3] Such factors as the patient's risk for severe RSV disease and comorbidities (e.g., lung disease, cardiovascular disease, hematologic disorders) associated with an elevated risk should be taken into consideration. RSV vaccines may be given at the same time as other adult vaccines.[2]

Conclusion

There have been recent advances in the prevention of RSV in the most vulnerable populations, such as the very young and elderly. All infants should be protected by receiving an RSV preventative therapy in their first year if protection via maternal vaccination did not occur. However, supply constraints may limit availability to the highest risk infants. Adults 60 years and older should consider a RSV vaccination to protect against LTRD associated with RSV infection. Studies are ongoing to determine if additional doses of vaccines for RSV prevention in adults will be required for protection in subsequent seasons.

Peer Reviewers: Sujeet Govindan, MD, Assistant Professor in Infectious Disease, Department of Medicine, OHSU School of Medicine and Liz Breitenstein, Pharm D, RPh, Antimicrobial Stewardship Pharmacist, Oregon Health Authority

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Prior Authorization Update: Esketamine

Date of Review: February 2024
Generic Name: esketamine
PDL Class: Antidepressants

Date of Last Review: December 2023
Brand Name (Manufacturer): Spravato (Janssen Pharmaceuticals, Inc.)

See **Appendix 1** for Prescribing Information Highlights

Purpose for Class Update:
Evaluate evidence for the effectiveness and safety of esketamine in people with suicidal ideation or behavior to establish a policy for outpatient initiation of therapy in people with depression and acute risk for suicide. This document provides a summary of previous reviews and recent guidelines from the Veterans Administration.

Plain Language Summary:
- Suicide is a common cause of death in the United States. Guidelines recommend risk evaluation for people who have suicidal thoughts or behavior.
- Studies show that some types of talk therapy (like cognitive behavior therapy, dialectical behavior therapy, and/or problem-solving based psychotherapy) decrease risk of suicide. Some medicines also may decrease risk of suicidal thoughts for some groups of people. Medicines with some benefit include:
  - Ketamine infusion for people with depression,
  - Lithium for people with bipolar disorder or depression, and
  - Clozapine for people with psychosis.
- Esketamine is a medicine that the Food and Drug Administration approved for depression in people at risk for suicide. Studies show that esketamine improves depression symptoms but may not change suicide risk compared to placebo (e.g., sugar pill).
- We recommend the Oregon Health Authority pay for esketamine for people with suicidal thoughts and depression when:
  - they have been referred to psychotherapy and
  - the doctor has re-evaluated the medicine they take by mouth for depression.

Research Questions:
1. What is the evidence for esketamine in improving symptoms, function, or quality of life in patients with depression and suicidal ideation?
2. What is the evidence for safety of esketamine in people with depression and suicidal ideation or behavior?
3. Are there specific subpopulations for which esketamine may be specifically indicated, more effective, or associated with less harm?

Author: Sarah Servid, PharmD

Conclusions:

- Guidelines updated in 2019 from the Veterans Administration/Department of Defense (VA/DOD) recommend several treatments with evidence for reduction in suicidal ideation and behavior.[1] Non-pharmacologic treatment includes cognitive behavioral therapy (strong recommendation), a crisis response plan, dialectical behavior therapy, and/or problem-solving based psychotherapy for suicide prevention (weak recommendations).[1] Short-term use of intravenous ketamine was suggested for people with major depressive disorder, lithium was suggested for people with bipolar disorder or unipolar depression, and clozapine was suggested for people with schizophrenia or schizoaffective disorder (weak recommendation for all therapies).[1] Esketamine was approved by the Food and Drug Administration (FDA) after the literature search was completed for this guideline.
- The VA/DOD also recommends management of co-occurring conditions for all people with suicidal ideation or behavior.[1] Evidence shows that patients with psychiatric conditions (e.g., substance use disorder, mood disorders), and psychiatric symptoms (e.g., hopelessness, insomnia, agitation) have increased risk for suicide.[1]
- Two randomized controlled trials (RCTs) evaluated use of esketamine in patients with major depressive disorder (MDD) at high risk for suicide.[2,3] Over 60% of people in these RCTs had a prior suicide attempt, 45-61% were prescribed an oral antidepressant plus oral augmentation therapy, and 67-75% were prescribed a benzodiazepine.[2,3] There is low quality evidence that esketamine does not decrease suicidality, but has a slight improvement in depression symptoms compared to placebo with a mean difference [MD] in the Montgomery-Asberg Depression Rating Scale (MADRS) of -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for each study.[2,3] A 2 point improvement on MADRS may be associated with a clinically significant improvement.[4]
- There is insufficient evidence for other outcomes including suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide.

Recommendations:

- Update the safety edit for esketamine to include outpatient initiation of esketamine for people with suicidal ideation who have optimized alternative treatments for depression.

Summary of Prior Reviews and Current Policy:

- Esketamine was approved by the Food and Drug Administration (FDA) for people with major depressive disorder and acute suicidal ideation or behavior in 2020. Evidence supporting approval for this indication was reviewed by the Pharmacy and Therapeutics Committee in 2021. Esketamine is also FDA-approved as adjunct therapy for treatment-resistant depression.
- The current safety edit for esketamine allows continuation of therapy when esketamine is initiated in a hospital setting for acute suicidal ideation or behavior because studies evaluated for FDA approval were conducted in the inpatient setting.
- Esketamine is carved-out of CCO plans and is paid for by FFS when billed as a pharmacy claims. Medical claims for esketamine are not carved-out and can be covered by CCOs for their members.

Background:

In the United States in 2017, suicide was the 10th leading cause of death (with a death rate of 14 deaths per 100,000 individuals).[5] Epidemiologic studies show that suicidal ideation is higher in women than men, but completed suicides are more common in men.[5] In the United States, the most common means of suicide include use of firearms (for men) and poisoning (for women).[1] Age-adjusted death rates from 2013 to 2015 also indicate that suicide is highest in rural areas and increases with age.[5] Risk factors for suicide include prior suicide attempts, current suicidal ideation, current psychosocial stressors, availability of firearms, prior

psychiatric hospitalization, psychiatric conditions (e.g., substance use disorder, mood disorders), and psychiatric symptoms (e.g., hopelessness, insomnia, agitation).[1]

Recent guidelines from the VA/DOD suggest against the use of a single instrument or method to evaluate suicide risk.[1] Instead, they recommend a comprehensive risk assessment to evaluate risk for suicide based on individual patient factors and circumstances.[1] While risk stratification is routinely done in clinical practice, authors found insufficient information to recommend for or against the use of risk stratification to evaluate the level of suicide risk.[1] Risk stratification usually includes assessment for risk based on intent, preparatory behaviors or a current suicidal plan and the ability of the person to independently maintain their safety with coping skills and social supports.[1,5]

Treatment is generally recommended in the least restrictive setting that is likely to be safe and effective.[5] For people with high acute risk, recommended treatment typically includes psychiatric hospitalization.[1] For people with intermediate acute risk, 2019 VA/DOD guidelines recommend hospitalization if related factors driving risk are responsive to inpatient treatment or intensive outpatient management including frequent contact, regular re-assessment of risk, and a well-articulated safety plan.[1] For people with low acute risk, primary care management is reasonable with outpatient mental health treatment for co-occurring conditions. For all categories of risk, treatment should include management of co-occurring conditions.[1] For people with high chronic risk of suicide, routine mental health follow-up is recommended. These people are considered to be at chronic risk for becoming acutely suicidal, particularly in the context of unpredictable psychosocial changes (e.g., job or relationship loss, relapse on drugs). Routine care should include a well-articulated safety plan, lethal means safety (e.g., no access to guns, limited medication supply), routine suicide risk screening, building coping skills, and management of co-occurring conditions.[1] Similar recommendations are made for people at intermediate chronic risk including routine mental health care, a well-articulated safety plan including lethal means safety, and management of co-occurring conditions.[1] For people at low chronic risk, primary care management or mental health care when needed for successful treatment is usually reasonable.[1]

Goals for people with suicidal ideation or suicide risk include reduction of immediate risk and prevention of recurrent symptoms for people with chronic suicide risk. Goals of treatment for depression typically focus on improvement in symptoms, function, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. Some of the most commonly used rating-scales and thresholds include the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[4] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52). [4] Values associated with remission and minimum clinically important differences for each of these scales vary. A 2 point improvement on MADRS may be associated with a clinical improvement and HAM-D scores of 3 to 7 points may be clinically significant.[4] Typically, a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[4]

Methods:
A Medline literature search for new randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. 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 the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for recent high quality systematic reviews.

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.

Guidelines:
In 2019, the Veterans Administration/Department of Defense updated guidelines for the assessment and management of people at risk for suicide.[1] Recommendations were based on a systematic literature search through April 2018.[1] Literature for esketamine, which was approved by the Food and Drug Administration (FDA) in 2019, was not included. An update of this guideline is currently in progress. Guideline authors used "suggest" to describe recommendations based on weak evidence and "recommend" to describe recommendations with strong evidence. Recommendations were divided into the following categories:

- **Screening**: A validated screening tool, such as the Patient Health questionnaire-9 (PHQ-9), was suggested to identify suicide-related behavior and risk (weak recommendation).[1]
- **Evaluation**: Include an assessment of risk factors as part of a comprehensive evaluation for suicide risk (strong recommendation).[1] They suggest against the use of a single instrument or method to evaluate suicide risk (weak recommendation). While risk stratification is routinely done in clinical practice, authors found insufficient information to recommend for or against the use of risk stratification to evaluate the level of suicide risk.[1]
- **Non-pharmacologic therapy**: Cognitive behavioral therapy for suicide prevention was recommended for people with a recent history of self-directed violence to reduce risk of suicide (strong recommendation).[1] Completion of a crisis response plan is suggested for all patients with suicidal ideation (weak recommendation). Dialectical behavioral therapy was suggested for people with borderline personality disorder or recent self-directed violence (weak recommendation).[1] They suggest offering problem-solving based psychotherapies for people with a history of more than one prior incident of self-directed violence, people with a recent history of self-directed violence, or people with hopelessness and a history of moderate to severe traumatic brain injury (weak recommendation).[1]
- **Pharmacotherapy**: For all patients at risk of suicide, treatment should include management of co-occurring conditions. For people with comorbid major depressive disorder, ketamine infusion was suggested for short-term reduction in suicidal ideation (weak recommendation).[1] Lithium was suggested to reduce the risk of death by suicide as monotherapy in people with bipolar disorder or add-on therapy for people with unipolar depression or bipolar disorder (weak recommendation).[1] For people with comorbid schizophrenia or schizoaffective disorder, clozapine was suggested to reduce risk of death (weak recommendation).[1]
- **Post-acute care:** In addition to usual care after a psychiatric hospitalization, there were weak recommendations to support sending periodic caring communications (e.g., postcards) for 12-24 months, offering home visits to support reengagement for people not presenting for outpatient visits, and offering the World Health Organization brief intervention and contact treatment modality following an ER visit.[1]
- **Technology-based treatments:** There was insufficient evidence to recommend for or against self-directed or provider-driven technology-based, virtual interventions.[1]
- **Population/community-based interventions:** They suggest reducing access to lethal means to decrease suicide rates at a population level (weak recommendation). There was insufficient data to recommend for or against other community-based interventions.[1]

Recommendations for pharmacotherapy were based on the following evidence:

- **Ketamine:** Evidence for this recommendation was based on a meta-analysis of trials evaluating intravenous ketamine infusion which report that 55% of patients at 24 hours post-infusion and 66% of patients at 7 days post-infusion reported no suicidal ideation (moderate quality evidence).[1] Trials were primarily based in the inpatient hospital setting, and there is limited long-term evidence following discharge.[1] Repeated administration is not recommended because of the potential risk of addiction and known dissociative effects which may exacerbate psychotic symptoms.[1] Authors found no data to support ketamine's effect on suicide attempts or deaths.[1]

- **Lithium:** Recommendations for lithium were based on several cohort studies and systematic reviews which demonstrated reduced suicidal behavior and deaths associated with lithium in patients with bipolar depression.[1] Despite these benefits, discontinuations due to adverse events contributed to large variation in adherence across studies.[1] Adverse events related to discontinuations included gastrointestinal effects, polyuria, polydipsia, weight gain, hypothyroidism, and leukocytosis. Lithium has a low therapeutic index and caution is recommended in elderly people and people with comorbidities (e.g, seizure disorders and chronic kidney disease).[1]
- **Clozapine:** Evidence from systemic reviews and meta-analyses show that clozapine can lower death by suicide, suicide attempts, and suicidal behaviors with long-term treatment.[1] While evidence is most favorable for clozapine, evidence suggests that any antipsychotic may protect against suicide risk.[1] Clozapine is only available through a Risk Evaluation and Mitigation Strategy (REMS) program which mandates frequent follow-up visits to monitor for adverse events.[1]

New Indications:
In July 2020, esketamine nasal spray received an expanded indication for depressive symptoms in adults (18-64 years of age) with MDD and acute suicidal ideation or behavior. Esketamine was previously approved for treatment-resistant depression. Approval was based on 2 identical, double-blind, 4-week, multicenter RCTs in adults (ASPIRE I and II).[3] These trials enrolled a total of 456 patients (n=226 in ASPIRE I and n=230 in ASPIRE II) from the United States, Europe, Asia, South Africa, South America, and Canada.[2,3] Participants had a diagnosis of MDD without psychotic features, suicidal ideation within the 24 hours prior to randomization with need for hospitalization due to imminent suicide risk, and a MADRS score greater than 28 indicating at least moderate depression.[2,3] Imminent suicide risk was defined based on affirmative answers to the Mini-International Neuropsychiatric Interview questions B3 ("Did you think about suicide [killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?") upon screening in the emergency department or on inpatient psychiatric admission.[2] Patients received comprehensive standard of care treatment including an initial 5 to 14 day hospitalization in a psychiatric unit.[2,3] Esketamine, administered twice weekly, was initiated upon enrollment with standard antidepressant optimization during the first 2 weeks of each trial.[2,3] Pharmacotherapy standards of care could include either antidepressant monotherapy or an antidepressant plus augmentation therapy (second antidepressant, atypical antipsychotic or mood stabilizer).[2] Patients with clinically significant comorbidities were excluded from the studies (e.g., bipolar disorder, obsessive compulsive disorder [OCD], personality disorder, moderate to severe substance use disorder, psychotic disorder, renal or liver insufficiency, uncontrolled hypertension, history of malignancy, or clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic or metabolic disease).[2,3] The primary endpoint was change in depressive symptom severity evaluated with the MADRS score from baseline to 24 hours.[2,3] The key secondary outcome was symptom severity using the Clinical Global Impression of Severity of Suicidality - Revised scale (CGI-SS-r; range 0 to 6) which is a one-item, clinician-rated assessment of suicide severity.[2,3]

Overall, 78-89% of patients receiving esketamine and 82-83 % of patients receiving placebo completed 4 weeks of treatment, and about 72% of patients in each study completed the 90 day follow-up.[2,3] Baseline mean MADRS score was 40-41 indicating severe depressive symptoms, clinician-rated suicidality based on CGI-SS-r was moderate to extremely suicidal for 90-91% of patients.[2,3] Over 60% of patients in each study had a prior suicide attempt. In ASPIRE I, 28% had a recent attempt in the past month.[2] Common therapy included venlafaxine, escitalopram, duloxetine, quetiapine (as adjunct therapy), mirtazapine, and sertraline.[2,3] On average, an antidepressant plus oral augmentation therapy was prescribed to 45% and 61% of people in ASPIRE I and II, respectively. About 67-75% of patients received concomitant benzodiazepines, though use was not permitted within 8 hours of esketamine dosing.[2,3] Most baseline characteristics were balanced between groups. However, in ASPIRE I, more males were randomized to esketamine compared to placebo (42% vs. 34%) and a slightly higher proportion of patients randomized to esketamine were prescribed antidepressant plus oral augmentation therapy compared to placebo (47% vs. 42%).[2] In ASPRE II, the proportion of patients with a recent suicide attempt within the past 28 days at baseline differed between groups with more patients in the esketamine group

with a recent suicide (31.6%) compared to placebo (21.2%).[3] A prior suicide attempt is a known risk factor for subsequent attempts which may indicate that patients randomized to treatment had more severe suicidality than those given placebo.

There was a substantial difference in MADRS from baseline to 24 hours for both esketamine and placebo groups. Patients given esketamine had mean improvements in MADRS of 16.4 (SD 11.95) and 15.7 (SD 11.56) points while patients randomized to placebo improved by 12.8 (SD 10.73) and 12.4 (SD 10.43) points in each study.[2,3] The mean difference from placebo at 24 hours was -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for ASPIRE I and II, respectively. A 2-point change in MADRS may correspond with clinically meaningful improvements in symptoms. The difference from placebo was maintained at 4 weeks. Both placebo and esketamine groups had a decrease in acute suicidality (median 1 point improvement on CGI-SS-r from baseline to 24 hours), and there was no statistical difference compared to placebo indicating that hospitalization and standard therapy had a greater impact on acute suicidality than esketamine.[2,3] In general, subgroup analyses for the primary outcome based on baseline MADRS score, prior suicide attempts, oral antidepressant therapy, sex and age showed similar treatment effects.[2,3]

The overall rate of suicide attempts during and after the study was low compared to current epidemiological data which authors attribute to the comprehensive clinical care and frequent follow-up required as part of the study. The mean length of hospital stay in ASPIRE II was 21.6 days (SD 20.6) for patients receiving esketamine and 19.1 days (SD 19.6) for placebo indicating that the majority of the trial occurred during an inpatient stay.[3] Hospital duration was not reported in ASPIRE I. Psychotherapy was permitted, but less than 5% of patients received psychotherapy during the 4-week treatment phase.[3]

Nineteen percent (n=21) and 11% (n=13) of patients had a dose reduction due to intolerance in ASPIRE I and II, respectively.[2,3] In total, suicide-related adverse events (including suicidal ideation) occurred in 12 patients in the 4-week treatment period and were generally balanced between groups.[2,3] Eight suicide attempts occurred during therapy (4 in each group) on treatment.[2,3] During the 90 day follow-up period while on standard therapy, 10 patients had suicide attempts (7 with prior esketamine and 3 with prior placebo) during the follow-up period.[2,3] One patient, previously randomized to esketamine, completed suicide.[2] In most cases, patients with a suicide attempt after enrollment also had an attempt prior to enrollment.[2,3]

In these studies, depression symptoms (evaluated with MADRS score) were improved with esketamine compared to placebo. However, there is no evidence to suggest that esketamine decreases suicidal thoughts, suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide. These studies evaluated inpatient initiation of esketamine, and there is limited applicability to outpatient treatment. Both groups had a decrease in acute suicidality with no difference from placebo indicating that standard therapy, including hospitalization and greater clinical follow-up, likely continues to be the most effective treatment for suicidal symptoms.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SPRAVATO® (esketamine) nasal spray, CIII
Initial U.S. Approval: 1970 (ketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)**
- **Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)**
- **SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)**

RECENT MAJOR CHANGES

Indications and Usage (1)	07/2020
Dosage and Administration (2.3, 2.6)	07/2020
Warnings and Precautions (5.1, 5.2, 5.4, 5.6)	07/2020

INDICATIONS AND USAGE

SPRAVATO® is a non-competitive *N*-methyl *D*-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults. (1)
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. (1)

Limitations of Use:

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO. (1)
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

DOSAGE AND ADMINISTRATION

- Administer SPRAVATO intranasally under the supervision of a healthcare provider. (2.1)
- Assess blood pressure prior to and after administration. (2.1)
- *TRD:* Evidence of therapeutic benefit should be evaluated at the end of the 4-week induction phase to determine need for continued treatment. (2.2)
- *Depressive symptoms in MDD with acute suicidal ideation or behavior:* Evidence of therapeutic benefit should be evaluated after 4 weeks to determine need for continued treatment. Treatment beyond 4 weeks has not been systematically evaluated. (2.3)
- See Full Prescribing Information for recommended dosage. (2.2, 2.3)
- See Full Prescribing Information for important administration instructions. (2.4)

DOSAGE FORMS AND STRENGTHS

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3)

CONTRAINDICATIONS

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. (4)
- Intracerebral hemorrhage. (4)
- Hypersensitivity to esketamine, ketamine, or any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- *Increases in Blood Pressure:* Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. (5.6)
- *Cognitive Impairment:* SPRAVATO may impair attention, judgment, thinking, reaction speed and motor skills. (5.7)
- *Impaired Ability to Drive and Operate Machinery:* Do not drive or operate machinery until the next day after a restful sleep. (5.8)
- *Embryo-fetal Toxicity:* May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant):

- TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6)
- Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2020

Appendix 2: Key Inclusion Criteria

Population	People with major depressive disorder and suicidal ideation or behavior
Intervention	Esketamine
Comparator	Placebo, another antidepressant, or standard of care
Outcomes	Symptoms of depression or suicidal ideation, function or quality of life, hospitalizations or urgent care visits, attempted or completed suicides, all-cause mortality
Setting	Outpatient treatment

Appendix 3: Prior Authorization Criteria

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression or suicidal ideation.

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

Covered Alternatives:

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

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 the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
7. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)?	**Yes:** Go to #10	**No:** Go to #8~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.~~
8. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.

Approval Criteria		
9. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
~~8.~~10. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 28 days for induction ~~requested doses~~ (either 56 mg and/or 84 mg for titration) not to exceed 23 units total.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #4
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
4. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 2/24; 12/23 (KS); 2/23, 10/21; 2/21; 7/19
Implementation:1/1/22; 3/1/21; 8/19/19

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Drug Use Evaluation: Antipsychotic Use in Children – 2022 Update

Plain Language Summary:

- Children younger than 18 years can have serious behavior issues related to mental health conditions. Doctors can prescribe medicines called antipsychotics to help manage conditions like bipolar disorder, psychosis, depression, autism, and disruptive behavior.
- Antipsychotic medicines can have a lot of side effects. Many can result in weight gain, movement problems, and changes in hormones. Risk for side effects tend to increase with higher doses and longer length of therapy. Providers should regularly monitor for these side effects, and limit treatment to the shortest duration and lowest dose needed to improve symptoms. Because of these side effects, it is widely recommended that children try other behavioral therapy before taking an antipsychotic medicine to help with symptoms.
- We checked to see how antipsychotic medicine are used in children ages 6-17 years on the Oregon Health Plan (OHP). We found that:
    - Less than 1% of children enrolled in the OHP are prescribed an antipsychotic each month.
    - About 59% of children prescribed an antipsychotic medicine were on them for more than 5 months.
    - About 36% of children on an antipsychotic medicine did not have a condition that has been shown to be treatable with an antipsychotic medicine.
    - Only 57% of children had blood sugar tests, which is recommended for anyone on an antipsychotic medicine.
    - About 79% of children had at least one visit to a behavioral therapist, which is recommended for all children on an antipsychotic medicine.

Research Questions:

- What proportion of Medicaid members aged 6-17 years are prescribed an antipsychotic medication?
- What diagnoses are present in medical claims of members aged 6-17 years that are likely indications for the prescribed antipsychotic medication?
- What proportion of members aged 6-17 years prescribed an antipsychotic have glucose monitoring?
- What proportion of members 6-17 years of age who were prescribed an antipsychotic have claims for psychotherapy?
- How does antipsychotic use, metabolic monitoring, or use of psychotherapy differ in members aged 6-17 years based on member characteristics (member location, age, diagnoses, enrollment in a coordinated care organization [CCO] or prior antipsychotic use), prescriber characteristics (taxonomy), or drug characteristics (drug and duration of therapy)?

Conclusions:

- In 2023, about 0.6% of Medicaid members who were 6 to 17 years of age, were prescribed an antipsychotic each month. **Figure 1** shows a decreasing trend in antipsychotic use for Medicaid members since the start of the COVID pandemic. About 59% of members with claims for an antipsychotic were prescribed long-term therapy for more than 5 out of 6 months.
- Only 50% of members 6-17 years of age had a diagnosis that matched an indication approved by the Food and Drug Administration (FDA) in the 6 months before the first antipsychotic claim (defined as the index event [IE]). The most common FDA-approved diagnoses included autism (25%), major depression (18%), and bipolar disorder (10%). About 14% of members had a compendia-supported diagnosis, and 36% of members did not have a

diagnosis that supports use of an antipsychotic medication. Other common mental health diagnoses included attention deficit hyperactivity disorder (ADHD; 19%), reaction to severe stress and adjustment disorders (15%) and generalized anxiety disorder (10%).

- In members 6 to 17 years of age who were prescribed an antipsychotic, only 57% had glucose monitoring in the 6 months before or after the IE. Various patient, therapy, and prescriber characteristics appeared to influence metabolic monitoring. Compared to the general population, the following groups had lower rates of glucose monitoring:
    - Members with younger age
    - Members living in Oregon's frontier counties
    - Members identifying as male
    - Members who are not in foster care
    - Members with a diagnosis of a developmental disorder
    - Members with shorter durations of therapy (e.g., 1 month vs. ≥5 months)
    - Members with prescriptions from a non-psychiatrist
- The majority of members with claims for an antipsychotic had at least one visit for psychotherapy (78.5%) in the 6 months before or after the antipsychotic claim. For members with psychotherapy visits, the median number of visits was 20 visits (interquartile range 8 to 39) over a 12 month period. Use of psychotherapy was generally consistent across member groups. The following groups had a lower proportion of members with claims for psychotherapy:
    - Members identifying as Asian or Pacific Islander
    - Members enrolled in fee-for-service (FFS) at the time of the IE
    - Members with a diagnosis of a developmental disorder
    - Members with prescriptions written by a general practitioner

Recommendations:

- No policy changes recommended for members over 6 years of age.

Background

Few antipsychotics have been studied in young children, and efficacy and safety has not been established for any antipsychotic in young children less than 5 years of age. Indications with the most evidence of effectiveness in children include use for irritability associated with autistic disorder (including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods). Both risperidone and aripiprazole have an indication for irritability associated with autism for patients at least 5 and 6 years of age, respectively.[1,2] Other antipsychotics have approval for bipolar disorder and schizophrenia in adolescents, but none of them are approved in children under 10 years of age. Current guidelines recommend non-pharmacological therapy as first-line therapy for children prior to prescription of an antipsychotic.[3-5] Antipsychotics can be associated with significant risk of long-term adverse events. Because antipsychotics increase the risk of metabolic syndrome, laboratory monitoring is recommended before starting treatment and routinely during long-term therapy. In Medicaid, several national quality metrics aim to improve use of psychotropic medications in children. The 2023 core set of children's health care quality measures includes metabolic monitoring and use of first-line psychosocial care in children and adolescents taking antipsychotics.[6]

The Pharmacy and Therapeutics committee has previously reviewed evidence for antipsychotics and has recommended several initiatives with the goal of improving appropriate use of antipsychotics in children and adolescents. When compared to placebo, there was evidence that the following therapies have some benefit in children and adolescents:[7]

- Antipsychotics for symptoms of mania in children and adolescents with bipolar disorder in short-term studies (<4 weeks).

- Antipsychotics for symptomatic and functional improvement in children and adolescents with schizophrenia and first-episode psychosis.
- Risperidone and aripiprazole for behavioral symptoms in children and adolescents with irritability associated with autism spectrum disorder.
- Aripiprazole, quetiapine and risperidone for symptomatic and functional improvement in children and adolescents with disruptive behavior disorder.

There is a lack of evidence evaluating whether antipsychotics improve progress in school for any diagnosis or decrease hospitalization or need for acute symptomatic treatment for autism spectrum disorder and disruptive behavior disorders.[7] The utility of antipsychotics is limited by common adverse events including weight gain, metabolic changes, changes in prolactin levels, akathisia, and extrapyramidal symptoms.

Drug compendia also reference several off-label conditions in which antipsychotics have been studied. In this analysis, compendial diagnoses were based on off-label conditions with evidence of efficacy in Micromedex®. Off-label conditions included quetiapine for adults with generalized anxiety disorder, risperidone for people with intellectual disability, aripiprazole for pediatric patients with anorexia nervosa and adults with personality disorder.[8-10] Olanzapine is also recommended as an antiemetic for people with chemotherapy-induced nausea and vomiting. Evidence for off-label intellectual disability, anorexia, and personality disorder was generally based on small trials of short durations.[9,10]

- Quetiapine has been studied in multiple RCTs for adults with generalized anxiety disorder (GAD).[8] There is moderate quality evidence that extended-release (ER) quetiapine improves anxiety symptoms, improves function and induces remission of GAD, as evidenced by statistically significant improvement in Hamilton Anxiety Scale (HAM-A).[8] However, quetiapine is not well tolerated in people with generalized anxiety disorder (GAD), and was associated with more treatment discontinuations due to adverse events compared to placebo.[8]
- Two placebo-controlled RCTs evaluated risperidone in people with intellectual disability over 4-6 weeks.[9] Intellectual disability was defined as borderline intellectual functioning or mild to moderate mental retardation. All trials included people with other comorbid diagnoses such as conduct disorder, oppositional defiant disorder, or disruptive behavior disorder.[9] The average age of children enrolled in these trials was 8-10 years.[9] Compared to placebo, risperidone improved aberrant behavior in adults and severe behavior problems in children.[9] Post-hoc analyses of 2 additional 6-week placebo-controlled studies also identified reduced aggression scores with use of risperidone compared to placebo.[9]
- A small retrospective chart review (n=22) evaluated aripiprazole in adolescents with anorexia nervosa.[10] Participants prescribed aripiprazole had improvement in BMI compared to members not prescribed aripiprazole (BMI percentile on discharge of 36.4% with aripiprazole vs. 28.6% with non-aripiprazole). Mean age of participants in the study was 15 years. [10] Patients in this study were enrolled in an inpatient or partial hospital program, and 2020 from the Canadian practice guidelines recommend use only with consultation from a provider with knowledge aripiprazole only after consultation with an specialist with expertise in the treatment of eating disorders. [10]
- A small 8-week RCT (n=52) evaluated aripiprazole compared to placebo in adults with borderline personality disorder. [10] Patients treated with aripiprazole had a reduction in symptoms compared to placebo. [10] Symptoms were evaluated using a variety of scales and included assessment of anger, impulsivity, and dysregulation. [10]

The Oregon Mental Health Clinical Advisory Group (MHCAG) has published documents related to use of antipsychotics as a first-line treatment option in people with bipolar disorder or schizophrenia and as augmentation in people with major depressive disorder or generalized anxiety who fail to have benefit with alternative therapies. The MHCAG recommends consultation with the Oregon Psychiatric Access Line for several groups of people, including children and young adults and people with co-occurring anxiety disorder, ADHD, or substance use disorder. Bipolar disorder is difficult to accurately diagnose in children and young adults because of a broad differential for symptoms and high rates of comorbid conditions.[11] Because children and adolescents are also more prone to metabolic side effects of medications, MHCAG recommends confirmation of the diagnosis before initiation of medications, use of the lowest effective medication dose, periodic re-assessment to evaluate for dose reductions when appropriate, and frequent monitoring for emergent side effects.[11] MHCAG has also recommended a monitoring schedule for people prescribed second-generation antipsychotic medications, which includes laboratory monitoring for glucose and lipids.[12] Other

routine assessments for adverse effects include evaluations for weight, waist circumference, blood pressure, movement disorders, sexual dysfunction, and treatment adherence.[12]

Ongoing programs for youth that include review of antipsychotics are outlined in **Table 1**. Programs include provider outreach for consultation through the Oregon Psychiatric Access Line (OPAL-K) for children less than 10 years of age prescribed long-term antipsychotics when there is lack of glucose monitoring, non-pharmacologic therapy or FDA-indicated diagnoses identified in claims. Other programs include patient profile review and educational provider letters for youth prescribed multiple mental health drugs or with mental health drug claims from multiple providers. There are also ongoing programs to assist the Department of Human Services and Oregon Youth Authority to provide oversight of mental health drugs prescribed for youth in foster care or in the criminal legal system.

Table 1. Current retrospective and prospective initiatives that aim to improve antipsychotic prescribing in children and adolescents enrolled in the Oregon Health Plan (OHP).

Current programs that include evaluation of antipsychotics	Implementation	Population	Intervention
Foster Care	2010	Members less than 18 years of age in foster care with recent claims for a mental health drug	Review by the Department of Human Services (DHS) is required before starting a new mental health medication. A yearly review is performed by DHS for each member with provider consultation through OPAL-K if needed.
Oregon Youth Authority (OYA)	2018	Members less than 18 years of age in the criminal justice system with recent claims for a metal health drug	Profiles generated every 6 months and sent to OYA for review.
OPAL-K Referrals	2019	Age < 10 years with new start antipsychotic use >6 months and other risk factors (e.g., lack of diagnoses, glucose monitoring, or psychotherapy)	Retrospective provider letter Phone outreach by OPAL-K to provider for optional consultation
Mental Health High-risk Groups	2021	Age <18 years and > 4 mental health drugs for >90 days Age <18 years and > 3 prescribers for mental health drugs Age < 5 years with a mental health drug Any age with combination antipsychotic + stimulant Any age with combination antipsychotics from ≥2 prescribers	Profile review and retrospective provider fax
Antipsychotics in Children <= 5 years of age	2022	Age ≤ 5 years of age with a recent antipsychotic	Retrospective provider fax Prior authorization required after 30 days

The goal of this drug use evaluation is to assess prescribing patterns for antipsychotics in children and adolescents older than 5 and younger than 18 years of age, to evaluate factors that are associated with metabolic monitoring and psychotherapy, and identify opportunities to improve and coordinate care for these members.

Methods:

Members who were 6 to 17 years of age were identified for inclusion in the study based on paid FFS claims for an antipsychotic (defined based on PDL class). The evaluation window for claims was from 10/1/2021 to 09/30/2022 and the first claim in the evaluation window was designated as the IE. For each member the following periods were designated as the baseline and follow-up periods:

- Baseline period: 6 months prior to the IE
- Follow-up period: 6 months following the IE

Inclusion criteria:

- At least one paid FFS claim for an antipsychotic during the evaluation window; AND
- Member aged 6 to 17 years (inclusive) at the time of the IE.

Exclusion criteria:

- Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow-up periods;
- Non-continuous Medicaid eligibility during the baseline or follow-up periods; AND
- Patients with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods. Claims data for these patients may be incomplete. Patients were identified based on the following benefit packages:

Category	Benefit Package	Description
Medicare Part D coverage	BMM BMD MED	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug Oregon Health Plan with Limited Drug Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND CWM SMF SMB	Transplant package Citizenship Waived Emergency Medical Special Low-Income Medicare Beneficiary Only Special Low-Income Medicare Beneficiary Only

Population descriptors included:

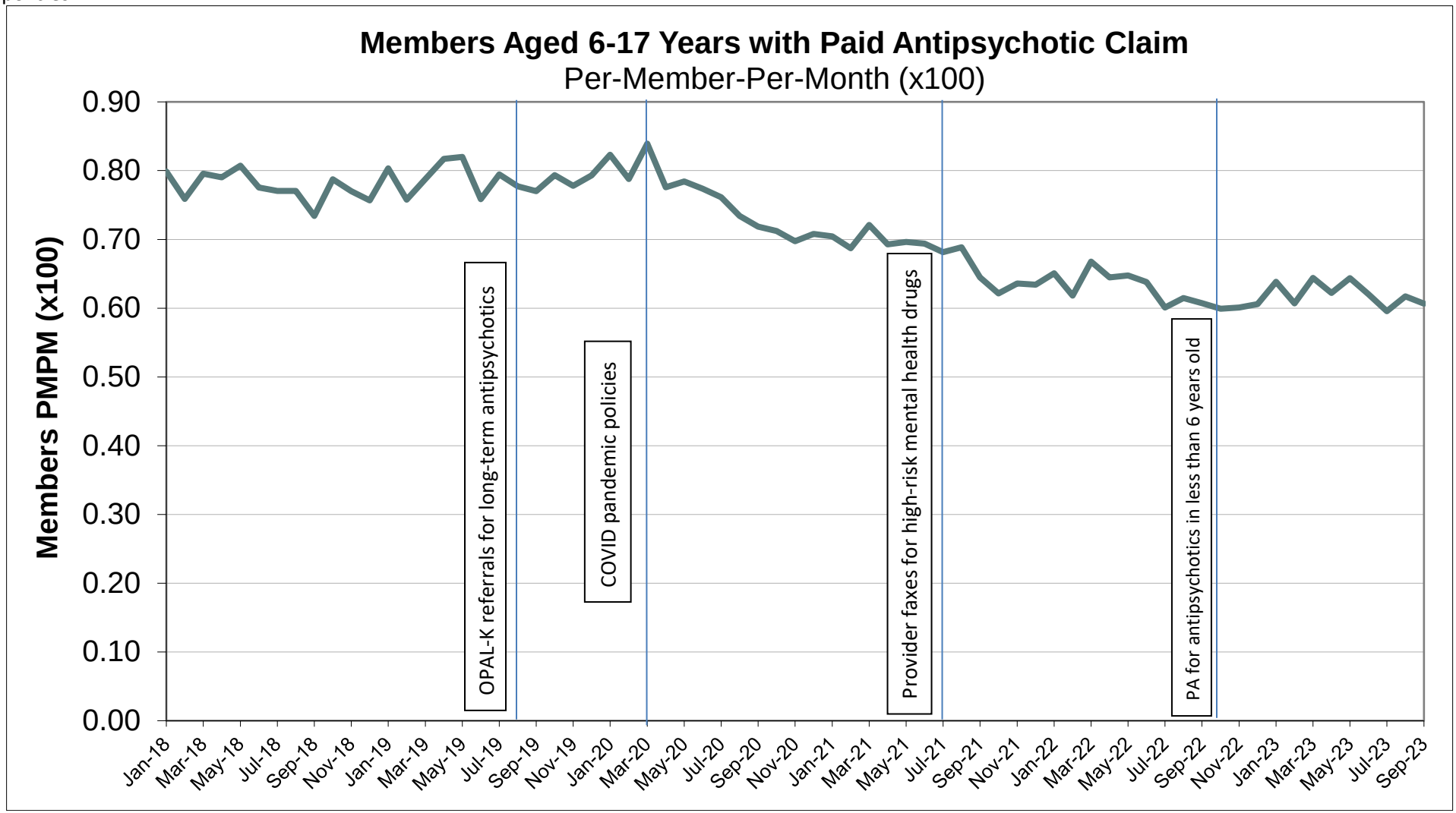
1. Patient characteristics, including:
    a. Demographics evaluated at the time of IE (age, race, CCO enrollment).
    b. Residential area based on member zip code and categorized into rural, urban, or frontier groups based on criteria in **Appendix 1.**[13] Members without an Oregon zip code were categorized as unknown.
    c. Current foster care enrollment or Oregon Youth Authority enrollment.
2. Provider characteristics based on primary prescriber taxonomy for the IE.
3. Drug characteristics, including:
    a. Molecular entity prescribed at the time of the IE.
    b. Duration of therapy for all antipsychotics based on days covered in the 6 months following the IE.
    c. Prior prescription of antipsychotics in the baseline period.

Outcomes evaluated in this analysis included:

1. Proportion of members with claims for metabolic monitoring in the baseline or follow-up period (see **Appendix 1** for medical codes)
2. Proportion of members with claims for psychotherapy in the baseline or follow-up period (see **Appendix 1** for medical codes)
3. Proportion of members with claims for an FDA-approved diagnosis in the baseline period (see **Appendix 1** for ICD-10 codes)

Results:
The proportion of Medicaid members ages 6-17 years of age with paid claims for an antipsychotic has decreased slightly over time. **Figure 1** shows the proportion of members with a paid claim for an antipsychotic compared to total members enrolled in Medicaid who were 6-17 years of age. About 0.6% of members 6-17 years of age had a paid claim for an antipsychotic each month, which is lower than the 0.7% to 0.8% per month rate in 2018. During the coronavirus pandemic, which began in early 2020, eligibility determinations for members on Medicaid were suspended, resulting in an increased number of members enrolled with Medicaid. The number of enrolled members 6 to 17 years of age increased from 268,689 members in March 2020 to 326,997 members in September 2023. The total number of members 6 to 17 years of age prescribed an antipsychotic was 2,255 in March 2020 and 1,983 in September 2023.

Figure 1. Members aged 6-17 years prescribed an antipsychotic per month from 2018 to present. Vertical lines represent implementation dates for various policies.



Numerator: enrolled Medicaid members 6-17 years old with a paid antipsychotic claim. Denominator: enrolled Medicaid members who are 6-17 years old.

Table 2 describes how exclusion criteria affected the population of members eligible for this study. Of members with a paid claim for an antipsychotic during the 1-year evaluation window, 3760 members were 6 to 17 years of age at the time of their first claim. About 20% of these members were excluded because they had other insurance, Medicare, a limited drug benefit, or did not have continuous enrollment during the study period which may make their claims data incomplete. Ultimately, 3,009 members who had a claim for an antipsychotic and were 6 to 17 years of age were included in this analysis.

Table 2. Number of members included in this analysis

	Medicaid Members	
Members with claims for an antipsychotic in the evaluation window	41,254	
After exclusion of members ≤5 or ≥18 years of age at the time of the IE	3,760	100.0%
After exclusion of members with TPL, Medicare, or limited drug benefit	3,219	85.6%
After exclusion of continuous eligibility in baseline/follow-up period	**3,009**	**80.0%**

Demographic information for members with prescriptions for an antipsychotic are outlined in **Table 3**. Most members were over 10 years of age (86%), and the majority were enrolled in a CCO (97%). Approximately 57% of included members identified as male and 54% identified as white. About half of members with claims for an antipsychotic lived in an urban area, and 40% lived in a rural area. Location was classified based on zip code and categorized according to definitions provided by the Oregon Office of Rural Health. Rural areas were defined as locations that were 10 or more miles from a population center of 40,000 people or more. About 4% of members with claims for an antipsychotic were living in a frontier county. Frontier areas were defined as any county with six or fewer people per square mile. Frontier counties include Baker, Gilliam, Grant, Harney, Lake, Malheur, Morrow, Sherman, Wallowa, and Wheeler counties.

Information regarding enrollment in foster care or supervision under the Oregon Youth Authority is only available at a single point in time, and could not be tracked over the course of the evaluation window. However, as of October 2023, about 8% of included members with claims for an antipsychotic were also engaged in foster care or had oversight from the Oregon Youth Authority.

Therapy characteristics are described in **Table 4**. Second-generation oral antipsychotics were prescribed for most patients (98%), and the most commonly prescribed drugs included aripiprazole (40%), risperidone 27%), quetiapine (12%), and olanzapine (10%). Of members included in this analysis, 62% had claims for an antipsychotic in the prior 6 months. Most members (59%) were prescribed long-term antipsychotic therapy and had over 151 days covered by an antipsychotic in the 6-month follow-up period (at least 5 out of 6 months with antipsychotic claims).

Table 3. Baseline demographics at the time of the index event (IE)

	Members with a paid antipsychotic claim	
	3,009	%
Age		
6-9	432	14.4%
10-13	957	31.8%
14-17	1,620	53.8%
Sex		
Female	1,302	43.3%

Male	1,707	56.7%
Race		
White	1,615	53.7%
Unknown	821	27.3%
Native American	262	8.7%
Hispanic	175	5.8%
Black	99	3.3%
Asian or Pacific Islander	37	1.2%
Managed Care Enrollment (as of IE)		
FFS	98	3.3%
CCO	2,911	96.7%
Member Location		
Urban	1,653	54.9%
Rural	1,199	39.8%
Frontier	108	3.6%
Unknown	49	1.6%
Foster Care Enrollment (as of October 2023)	235	7.8%
Oregon Youth Authority (as of October 2023)	14	0.5%

Table 4. Drug Therapy Characteristics

	Members with a paid antipsychotic claim	
	3,009	%
PDL Class on IE		
First-gen	48	1.6%
Second-gen	2,946	97.9%
Parenteral	15	0.5%
Days covered in follow-up period		
<=30	296	9.8%
31-90	412	13.7%
91-150	521	17.3%
>151	1,780	59.2%

Antipsychotic claims in baseline		
New start (no claims)	1,137	37.8%
Prior claim(s)	1,872	62.2%

Top 10 most common IE drugs (by HSN)		
aripiprazole	1,189	39.5%
risperidone	819	27.2%
quetiapine fumarate	345	11.5%
olanzapine	311	10.3%
lurasidone HCl	134	4.5%
ziprasidone HCl	67	2.2%
paliperidone	39	1.3%
chlorpromazine HCl	26	0.9%
cariprazine HCl	19	0.6%
haloperidol	13	0.4%

Table 5 described diagnoses present in medical claims for children and adolescents prescribed antipsychotics. Groups for FDA-approved indications, compendia-supported diagnoses, or no diagnosis are mutually exclusive; if a member has an FDA-approved diagnosis, then they are excluded from the following categories for compendia supported diagnoses. However, members with multiple diagnoses may be counted in more than one group within each of these categories. Only 50% of members with a claim for an antipsychotic had a FDA-approved diagnosis identified in medical claims in the 6 months before the IE. The most common diagnoses included autism (25%), major depression (18%), and bipolar disorder (10%). Diagnoses for schizophrenia (2%), tic disorders (4%) and schizoaffective disorder (1%) were less common. **Table 4** identifies drugs with evidence supporting use for these indications and the proportion of members prescribed one of these agents. For members with a diagnosis of autism, the drugs FDA-approved for autism spectrum disorder (risperidone and aripiprazole) were the most commonly prescribed agents. Risperidone, aripiprazole, However, only 38% of members with tic disorder were prescribed aripiprazole or haloperidone which have FDA indications for tic disorders. Of the 37 members with a diagnosis of schizoaffective disorder, only 5% (n=2) were prescribed paliperidone which is the only antipsychotic with an FDA-approval for this indication.

Risperidone, aripiprazole and quetiapine have off-label, compendia-supported diagnoses for various indications including intellectual and developmental disorders, eating disorders, personality disorders and generalized anxiety disorder (**Table 4**). About 14% of members without an FDA-approved diagnosis had an off-label, compendia-supported diagnoses in the 6 months before the IE. However, in people with generalized anxiety disorder, quetiapine was prescribed for only 39 of 293 members (13%). For 87% of people with a diagnosis of generalized anxiety disorder, a different antipsychotic was prescribed. Risperidone has been studied off-label for people with intellectual disabilities, but of the 88 members with this diagnosis, only 25 (28%) were prescribed risperidone. This may indicate that other antipsychotics are being used off-label for anxiety or intellectual disabilities or may indicate a lack of accurate diagnostic data based on medical claims.

For 36% of members with claims for an antipsychotic, there was no FDA-approved or evidence-supported diagnoses in medical claims in the 6 months before the IE. The most common mental health diagnoses for members with antipsychotic claims included ADHD (19%), reactions to severe stress and adjustment disorders (15%), other anxiety disorders (7%), and conduct disorders (7%).

Table 5. Diagnoses for members with claims for an antipsychotic.

	Members with a paid antipsychotic claim	
	3,009	%
FDA-approved diagnosis	1,516	50.4%
Autism (irritability)	752	25.0%
Risperidone or aripiprazole	563	18.7%
Other drug	189	6.3%
Major Depression (adjunct, for adults)	532	17.7%
Bipolar disorder	294	9.8%
<=9 years	7	0.2%
>=10 years	287	9.5%
Tic disorders (e.g., Tourette's syndrome)	128	4.3%
Aripiprazole or haloperidol	46	1.5%
Other drug	82	2.7%
Schizophrenia	56	1.9%
<=11 years	3	0.1%
>=12 years	53	1.8%
Schizoaffective disorder (for adults)	37	1.2%
Paliperidone	2	0.1%
Other	35	1.2%
Compendia diagnoses where evidence favors efficacy	442	14.7%
Generalized anxiety disorder (for adults)	293	9.7%
Quetiapine	39	1.3%
Other drug	254	8.4%
Intellectual disability (for adults and pediatric)	88	2.9%
Risperidone	25	0.8%
Other drug	63	2.1%

Eating disorders (e.g., anorexia nervosa) (for pediatric)	74	2.5%
Aripiprazole	20	0.7%
Other drug	54	1.8%
Cancer (for adults and pediatric)	25	0.8%
Olanzapine	18	0.6%
Other drug	7	0.2%
Personality disorder (for adults)	12	0.4%
Aripiprazole	8	0.3%
Other drug	4	0.1%
None of the above	1,057	35.1%
Top 10 other mental health diagnoses*		
F90: Attention-deficit hyperactivity disorders	568	18.9%
F43: Reaction to severe stress, and adjustment disorders	446	14.8%
F41: Other anxiety disorders	220	7.3%
F91: Conduct disorders	217	7.2%
F32: Depressive episode	177	5.9%
F34: Persistent mood [affective] disorders	157	5.2%
F98: Other behavioral/emotional disorders with onset usually occuring in childhood & adolescence	67	2.2%
F94: Disorder social with onset specific to childhood & adolescence	46	1.5%
F29: Unspecified psychosis not due to a substance or known physiologic condition	44	1.5%
F88: Other disorders of psychological development	43	1.4%

*Defined as ICD-10 codes beginning with F grouped by first 3 characters of the ICD-10 code

Table 6 describes the proportion of members who had claims for metabolic glucose monitoring and psychotherapy in the baseline and follow-up periods. Only 57% of children and adolescents had claims for glucose monitoring in the 6 months before or 6 months after the IE. For members with a claim, most had a single lab test during the 6 months before or after the IE. About 78% of members with prescriptions for an antipsychotic had claims for psychotherapy. For member with psychotherapy visits, the median number of visit dates was about 20 over the course of the 12-month period (11 visits in the 6 months before the IE and the same number in the 6 months after the IE).

Table 6. Members with metabolic monitoring and non-pharmacologic treatment

	Members with a paid antipsychotic claim		**Median number of service dates per member (for members with a claim) and interquartile range**		
	3,009	%	Q1	Median	Q3

Any metabolic monitoring	1,702	56.6%	1	1	2
Baseline Metabolic Monitoring	1,096	36.4%	1	1	2
Follow-up Metabolic monitoring	1,142	38.0%	1	1	2
Any psychotherapy	2,363	78.5%	8	20	39
Baseline	2,114	70.3%	4	11	21
Follow-up	2,100	69.8%	5	11	21

The proportion of members with claims for metabolic monitoring and psychotherapy was also evaluated by subgroup. The following tables describe how the proportion of members with claims for metabolic monitoring and psychotherapy changed based on patient characteristics (**Table 7**), drug or therapy characteristics (**Table 8**), and prescriber type (**Table 9**).

Glucose monitoring appeared to increase based on patient age and location. Glucose monitoring occurred for 37% of members 6 to 9 years of age, 52% of members 10 to 13 years of age and 64% of members 14 to 17 years of age. Glucose monitoring also varied for members living in urban (58%), rural (55%), and frontier counties (45%). Monitoring was also more common for members identifying as female compared to members identifying as male (65% vs. 50%). Compared to the general population, glucose monitoring was more frequent for members enrolled in foster care (65%). Glucose monitoring appeared to be less common for members with pervasive developmental disorders (51.5%) and developmental disorders of speech and language (48%). In people with less than 30 days of antipsychotic treatment, metabolic monitoring occurred in 48.6% of members. Rates of monitoring increased to 58.6% in people with therapy for more than 150 days (about 5 months) over a 6 month period (**Table 8**). Compared to the general population, risperidone was associated with lower rates of glucose monitoring (45.5%) and members prescribed haloperidol (77%), olanzapine (73%), and paliperidone (72%) had higher rates of glucose monitoring. Members were more likely to have metabolic monitoring if they had prescriptions written by a psychiatrist (63%) compared to other types of mental health providers or general practitioners (53%; **Table 9**).

On average, 78.5% of members with prescriptions for antipsychotics also had a psychotherapy in the 6 months before or after the first claim for an antipsychotic. Comparatively, psychotherapy was identified for 66% of members who were enrolled in FFS at the time of the IE. A relatively small proportion of people identified as Asian or Pacific (1.2%), and psychotherapy was identified for 67% of these members, which was lower than the general population. However, race was unknown for 27% of the population which makes it difficult to identify any potential differences based on race. Psychotherapy did not differ based on age, but was lower than the general population for members with speech and language disorders (66%) and pervasive developmental disorders (70%; **Table 7**). Psychotherapy was generally similar when evaluating various subgroups based on drug characteristics. Members with antipsychotic claims prescribed by a mental health provider more frequently had psychotherapy visits (86%) compared to members with prescriptions written by general practitioners (63%).

In these analyses, age is a confounding factor for drug selection and diagnoses as some drugs such as aripiprazole and risperidone have more evidence in younger populations and mental health diagnoses are likely to change as members get older. In members 6 to 9 years of age, risperidone was prescribed for a larger proportion of members in this age group (50%) compared to members 10-13 or 14-17 years of age (34% and 18% respectively). For example, diagnoses for developmental disorders are more common for younger ages and diagnoses like depression and bipolar disorder are more common for adolescents. This analysis did not account for any of these confounding factors.

Table 7. Outcomes by Patient Characteristics

	Metabolic Monitoring		Psychotherapy		Total
	1,702	56.6%	2,363	78.5%	3,009
Age					
6-9	159	**36.8% ***	318	73.6%	432
10-13	501	**52.4% ***	773	80.8%	957
14-17	1,042	**64.3% ***	1,272	78.5%	1,620
Sex					
Female	842	**64.7% ***	1,091	83.8%	1,302
Male	860	**50.4% ***	1,272	74.5%	1,707
Race					
White	916	56.7%	1,293	80.1%	1,615
Unknown	462	56.3%	633	77.1%	821
Native American	146	55.7%	199	76.0%	262
Hispanic	106	60.6%	132	75.4%	175
Black	51	51.5%	81	81.8%	99
Asian or Pacific Islander	21	56.8%	25	**67.6% ***	37
Managed Care Enrollment (as of IE)					
FFS	50	51.0%	65	66.3%	98
CCO	1,652	56.8%	2,298	78.9%	2,911
Member Location					
Unknown	29	**59.2% ***	39	79.6%	49
Urban	959	**58.0% ***	1,321	79.9%	1,653
Rural	665	**55.5% ***	920	76.7%	1,199
Frontier	49	**45.4% ***	83	76.9%	108
Foster Care Enrollment (as of October 2023)	152	64.7%	196	83.4%	235
Oregon Youth Authority (as of October 2023)	10	71.4%	12	85.7%	14
Top 10 MH diagnoses					
F33: Major depressive disorder, recurrent	398	74.8%	500	94.0%	532
F32: Depressive episode	546	71.5%	708	92.7%	764
F31: Bipolar disorder	208	70.7%	264	89.8%	294
F41: Other anxiety disorders	832	64.2%	1,132	87.3%	1296
F43: Reaction to severe stress, and adjustment disorders	777	63.5%	1,144	93.5%	1223

F34: Persistent mood [affective] disorders	287	63.4%	416	91.8%	453
F91: Conduct disorders	290	54.9%	468	88.6%	528
F90: Attention-deficit hyperactivity disorders	813	54.3%	1,259	84.2%	1496
F84: Pervasive developmental disorders	401	**51.5% ***	546	**70.1% ***	779
F80: Specific developmental disorders of speech and language	117	**48.1% ***	160	**65.8% ***	243

* Designates groups with the largest differences from the general population or notable trends

Table 8. Outcomes by Therapy Characteristics

	Metabolic Monitoring		Psychotherapy		Total
	1,702	56.6%	2,363	78.5%	3,009
PDL Class on IE					
Parenteral	11	73.3%	14	93.3%	15
First-gen	30	62.5%	37	77.1%	48
Second-gen	1,661	56.4%	2,312	78.5%	2,946
Days covered in follow-up period					
<=30	144	**48.6% ***	227	76.7%	296
31-90	226	**54.9% ***	317	76.9%	412
91-150	290	**55.7% ***	407	78.1%	521
>151	1,042	**58.5% ***	1,412	79.3%	1,780
Antipsychotic claims in baseline					
New start (no claims)	656	57.7%	921	81.0%	1,137
Prior claim(s)	1,046	55.9%	1,442	77.0%	1,872
Top 10 most common IE drugs (by HSN)					
haloperidol	10	76.9%	12	92.3%	13
olanzapine	226	**72.7% ***	243	78.1%	311
paliperidone	28	71.8%	32	82.1%	39
ziprasidone HCl	45	67.2%	58	86.6%	67
quetiapine fumarate	217	62.9%	286	82.9%	345
cariprazine HCl	11	57.9%	16	84.2%	19
chlorpromazine HCl	15	57.7%	22	84.6%	26
lurasidone HCl	76	56.7%	112	83.6%	134
aripiprazole	674	56.7%	981	82.5%	1,189
risperidone	373	**45.5% ***	566	**69.1% ***	819

* Designates groups with the largest differences from the general population or notable trends

Table 9. Outcomes by Prescriber Type

	Metabolic Monitoring		Psychotherapy		Total
	1,702	56.6%	2,363	78.5%	3,009
Provider Type on IE					
Psychiatrist	669	**63.2% ***	910	85.9%	1,059
Non-physician mental health provider	534	53.4%	857	85.7%	1,000
All other practitioners	499	52.5%	596	**62.7% ***	950

* Designates groups with the largest differences from the general population or notable trends

Limitations:
As a claims-based analysis, this study has multiple important limitations:

- Diagnostic data are based on claims history which may be incomplete or not accurately reflect true patient diagnoses. It is difficult to determine the intended indication for the drug, particularly when therapy is used off-label or the member has more than one mental health diagnosis.
- About 20% of members identified with paid FFS claims for an antipsychotic were excluded from this analysis. This study assumes that included members are still representative of the entire Medicaid population.
- Information on provider specialty may be inaccurate or incomplete for some providers. Prescribers with multiple specialties or designations may not be identified. Claims data is unable to capture instances where a prescriber consults with an appropriate specialist.
- This analysis relies on claims paid by Medicaid to evaluate duration of therapy which may not be an accurate indicator of what dose the member actually takes. Medical claims for antipsychotics were not included. Thus, the proportion of members prescribed injectable antipsychotics may be underestimated.
- This analysis used common medical codes for psychotherapy to evaluate members accessing non-pharmacologic therapy and may not provide a comprehensive assessment for use of non-pharmacotherapy. Similarly, we were unable to discern the type of psychotherapy provided.
- In this analysis, we used glucose testing as a marker for overall metabolic monitoring. We did not assess how often members had in-person provider visits, and are unable to assess how often physical assessments like weight and waist circumference were performed for members.
- Historical enrollment data for members in foster care or the criminal justice system is unavailable which limits findings from these analyses. Enrollment data from October 2023 was used to categorize patients in this analysis, but the study evaluation period was 10/1/2021 to 09/30/2022. Members who are no longer in foster care would not be accurately categorized.
- The retrospective nature of the study also does not control for confounders which may influence antipsychotic prescribing. Because this analysis does not control for any of these potential confounders, changes in antipsychotic prescribing are difficult to attribute to a single policy decision. Some examples of known confounding factors are listed below.
    - Based on trends in antipsychotic prescribing over time, the COVID pandemic appears to be a significant confounding factor. Between March 2020 and September 2023, the number of members 6 to 17 years of age enrolled in Medicaid increased by over 58,000 members per month. This was associated with a general decrease in the proportion of members prescribed antipsychotics. During this period there were multiple changes related to Medicaid coverage, availability of medical services, family lifestyles, and school routines. It is unknown how these changes may have influenced antipsychotic prescribing.
    - Metabolic monitoring appeared to vary based on age. However, post-hoc analyses showed that drug selection and diagnoses also varied based on member age. Diagnoses like developmental disorders are more common in members 6 to 9 years of age and diagnoses like schizophrenia and bipolar disorder were more common for adolescents.

Discussion:
This policy evaluation provides documentation that overall utilization of antipsychotics for members on Medicaid is not increasing and that many members do have access to some type of psychotherapy within 6 months of being prescribed an antipsychotic. While there are no direct comparisons for antipsychotic prescribing rates between state Medicaid programs, this is consistent with national trends in recent years.[14-16] However, there continues to be opportunities to improve antipsychotic prescribing for appropriate indications. Only 50% of members had an FDA-approved diagnosis present in medical claims. Glucose monitoring was identified in only 57% of members, and monitoring rates varied based on patient, drug therapy and prescriber characteristics. Equitable access

to appropriate evidence-based treatment remains a concern. For example, members living in Oregon's frontier counties appeared to have lower rates of glucose monitoring compared to members in rural or urban areas. Members who identified as Asian or Pacific Islander and members with antipsychotic prescriptions written by a general practitioner also had fewer claims for psychotherapy.

It is difficult to quantify how current retrospective provider educational initiatives impact evidence-based prescribing compared to larger statewide and national policy decisions. Historically, retrospective initiatives have been limited by ability of staff to contact providers. However, this analysis also indicates that ongoing initiatives to improve antipsychotic prescribing may have some benefit. One of the earliest initiatives implemented in the Medicaid program includes oversight of prescribing for members in foster care. This program includes both prospective and retrospective drug reviews conducted by the Department of Health Services. While there are limitations in this review, this analysis identified that members currently enrolled in foster care have slightly higher rates for glucose monitoring and psychotherapy compared to the overall population.

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Appendix 1:

Table A1. PICOS

Population	Medicaid members with a paid FFS claim for antipsychotics in the evaluation window. AND age 6-17 years at the time of the IE AND continuous Medicaid enrollment in the baseline and follow-up periods
Intervention	Initiation of antipsychotic (index event)
Comparators	Age groups Race CCO enrollment Locations (based on zip code) Diagnoses Taxonomy (psychiatrist vs. MHNP vs. non-specialist) Drug type (by generic name) Duration =<30 days vs. 31-119 vs. >=120 Prior antipsyc claims in the baseline period
Outcomes	Metabolic monitoring in the baseline period or follow-up period Psychotherapy in the baseline period or follow-up period Diagnoses

Table A2. ICD-10 codes for FDA-approved or compendia supported mental health diagnoses

ICD-10 Code	Description
F20x	Schizophrenia
F25x	Schizoaffective disorders
F31x	Bipolar disorder
F33x	Major depressive disorder, recurrent
F411x	Generalized anxiety disorder
F60x	Specific personality disorders
F70x-F79x	Intellectual disabilities
F840	Autistic disorder
F50x	Eating disorders including anorexia nervosa
F95x	Tic disorder including tourette's disorder

Table A3. Provider taxonomy groups for mental health providers

Taxonomy	Taxonomy Description	Category
2080P0006X	PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS	Psychiatrist
2080P0008X	PHYSICIAN-PEDIATRICS-NEURODEVELOPMENTAL DISABILITIES	Psychiatrist

2084A0401X	PSYCHIATRY & NEUROLOGY, ADDICTION MEDICINE	Psychiatrist
2084B0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-BARIATRIC MEDICINE	Psychiatrist
2084B0040X	BEHAVIORAL NEUROLOGY & NEUROPSYCHIATRY	Psychiatrist
2084D0003X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-DIAGNOSTIC NEUROIMAGING	Psychiatrist
2084F0202X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-FORENSIC PSYCHIATRY	Psychiatrist
2084H0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-HOSPICE AND PALLIATIVE MEDICINE	Psychiatrist
2084N0008X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROMUSCULAR MEDICINE	Psychiatrist
2084N0400X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY	Psychiatrist
2084N0402X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY WITH SPECIAL QUAL IN CHILD NEUROLO	Psychiatrist
2084N0600X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-CLINICAL NEUROPHYSIOLOGY	Psychiatrist
2084P0005X	PHYSICIAN-PSYCHIATRY&NERUOLOGY-NEURODEVELOPMENTAL DISABILITIES	Psychiatrist
2084P0015X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHOSOMATIC MEDICINE	Psychiatrist
2084P0800X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	Psychiatrist
2084P0802X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-ADDICTION PSYCHIATRY	Psychiatrist
2084P0804X	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	Psychiatrist
2084P0805X	PHYSICIAN-PSYCHIATRY&NEUROLGY-GERIATRIC PSYCHIATRY	Psychiatrist
2084P2900X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PAIN MEDICINE	Psychiatrist
2084S0010X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SPORTS MEDICINE	Psychiatrist
2084S0012X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SLEEP MEDICINE	Psychiatrist
2084V0102X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-VASCULAR NEUROLOGY	Psychiatrist
103T00000X	PSYCHOLOGIST	Non-physician Mental Health Provider
103TA0400X	PSYCHOLOGIST - ADDICTION (SUBSTANCE USE DISORDER)	Non-physician Mental Health Provider
103TC0700X	PSYCHOLOGIST - CLINICAL	Non-physician Mental Health Provider
103TC2200X	PSYCHOLOGIST - CLINICAL CHILD & ADOLESCENT	Non-physician Mental Health Provider
163WP0807X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH	Non-physician Mental Health Provider
163WP0808X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH	Non-physician Mental Health Provider
163WP0809X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH	Non-physician Mental Health Provider
1835P1300X	PHARMACIST - PSYCHIATRIC	Non-physician Mental Health Provider
363LP0808X	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	Non-physician Mental Health Provider
364SP0807X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH	Non-physician Mental Health Provider
364SP0808X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH	Non-physician Mental Health Provider
364SP0809X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH	Non-physician Mental Health Provider

Table A4. CPT codes for metabolic monitoring

CPT Code	Description
80048	Blood Test, Basic Group Of Blood Chemicals (Calcium, Total)
80049	Basic Metabolic Panel
80050	General Health Panel
80053	Blood Test, Comprehensive Group Of Blood Chemicals
80054	Comprehensive Metabolic Panel
80065	Metabolic Panel
81506	Endo Assay Seven Anal
82945	Glucose Other Fluid
82947	Assay Glucose Blood Quant
82948	Reagent Strip/Blood Glucose
82950	Glucose Test
82951	Glucose Tolerance Test (Gtt)
82952	Gtt-Added Samples
82953	Glucose-Tolbutamide Test
82954	Glucose, Urine
82961	Glucose Tolerance Test, Intravenous
82962	Glucose Blood Test
83036	Hemoglobin Glycosylated A1c
83037	Hb Glycosylated A1c Home Dev
95249	Cont Gluc Mntr Pt Prov Eqp
95250	Cont Gluc Mntr Phys/Qhp Eqp
95251	Cont Gluc Mntr Analysis I&R
0403T	Diabetes Prev Standard Curr
3044F	Hg A1c Level Lt 7.0%
3045F	Hg A1c Level 7.0-9.0%
3046F	Hemoglobin A1c Level >9.0%
3047F	Hemoglobin A1c Level = 9.0%
3051F	Hg A1c>Equal 7.0%<8.0%
3052F	Hg A1c>Equal 8.0%<Equal 9.0%
3754F	Screening Tests Dm Done
D0411	Hba1c In Office Testing
D0412	Blood Glucose Level Test
G0096	Basic Metabolic Panel (Carbon Dioxide (B

G0098	Comprehensive Metabolic Panel (Albumin-S
G2089	A1c Level 7 To 9%
G8015	Diabetic Pt W/ Hba1c>9%
G8016	Diabetic Pt W/ Hba1c<Or=9%
G8017	Dm Pt Inelig For Hba1c Measu
G8777	Diabetes Screen
TR200	Tracking Only - Hemoglobin A1c - <7.0
TR201	Tracking Only - Hemoglobin A1c - >7 <8.0
TR202	Tracking Only - Hemoglobin A1c - >8 <9.0
TR203	Tracking Only - Hemoglobin A1c - >9.0

Table A5. CPT codes for psychotherapy

CPT Code	Description
90785	Psychiatric Services Complicated By Communication Factor
90832	Psychotherapy, 30 Minutes
90833	Psychotherapy With Evaluation And Management Visit, 30 Minutes
90834	Psychotherapy, 45 Minutes
90836	Psychotherapy With Evaluation And Management Visit, 45 Minutes
90837	Psychotherapy, 1 Hour
90838	Psychotherapy With Evaluation And Management Visit, 1 Hour
90839	Psychotherapy For Crisis, First Hour
90840	Psychotherapy For Crisis, Each Additional 30 Minutes
90846	Family Psychotherapy Without Patient, 50 Minutes
90847	Family Psychotherapy With Patient, 50 Minutes
90849	Multiple-Family Group Psychotherapy
90853	Group Psychotherapy
90876	Psychophysiological Therapy Incorporating Biofeedback Training With Psychotherapy, 45 Minutes
90899	Other Psychiatric Service Or Procedure
96158	Treatment Of Behavior Impacting Health, Initial 30 Minutes
96159	Treatment Of Behavior Impacting Health, Each Additional 15 Minutes
96167	Treatment Of Behavior Impacting Health With Family And Patient, Initial 30 Minutes
96168	Treatment Of Behavior Impacting Health With Family And Patient, Each Additional 30 Minutes
97153	Adaptive Behavior Treatment By Technician Using An Established Plan, Each 15 Minutes
97154	Adaptive Behavior Treatment By Technician With Multiple Patients Using An Established Plan, Each 15
97155	Adaptive Behavior Treatment By Professional Using An Established Plan, Each 15 Minutes

97156	Adaptive Behavior Treatment By Professional With Family Using An Established Plan, Each 15 Minutes
0362T	Behavior Identification Supporting Assessment For Patient Exhibiting Destructive Behavior, Each 15 M
0373T	Adaptive Behavior Treatment With Protocol Modification For Patient Exhibiting Destructive Behavior,
G0177	Training And Educational Services Related To The Care And Treatment Of Patient'S Disabling Mental He
G0410	Group Psychotherapy Other Than Of A Multiple-Family Group, In A Partial Hospitalization Setting, App
H0004	Behavioral Health Counseling And Therapy, Per 15 Minutes
H0036	Community Psychiatric Supportive Treatment, Face-To-Face, Per 15 Minutes
H0037	Community Psychiatric Supportive Treatment Program, Per Diem
H0038	Self-Help/Peer Services, Per 15 Minutes
H0039	Assertive Community Treatment, Face-To-Face, Per 15 Minutes
H2014	Skills Training And Development, Per 15 Minutes
H2018	Psychosocial Rehabilitation Services, Per Diem
H2027	Psychoeducational Service, Per 15 Minutes
S9480	Intensive Outpatient Psychiatric Services, Per Diem

Table A6. Residential area based on Zip Code. Based on the Oregon Office of Rural Health Geographic Definitions[13]

Zip Code	Designation	Zip Code	Designation	Zip Code	Designation	Zip Code	Designation	Zip Code	Designation
97001	Rural	97018	Rural	97037	Rural	97060	Urban	97103	Rural
97002	Rural	97019	Rural	97038	Rural	97062	Urban	97106	Urban
97003	Urban	97020	Rural	97039	Frontier	97063	Rural	97107	Rural
97004	Rural	97021	Rural	97040	Rural	97064	Rural	97108	Rural
97005	Urban	97022	Rural	97041	Rural	97065	Frontier	97109	Rural
97006	Urban	97023	Rural	97042	Rural	97067	Rural	97110	Rural
97007	Urban	97024	Urban	97044	Rural	97068	Urban	97111	Rural
97008	Urban	97026	Rural	97045	Urban	97070	Urban	97112	Rural
97009	Urban	97027	Urban	97048	Rural	97071	Rural	97113	Urban
97010	Rural	97028	Rural	97049	Rural	97075	Urban	97114	Rural
97011	Rural	97029	Frontier	97050	Frontier	97076	Urban	97115	Rural
97013	Rural	97030	Urban	97051	Rural	97077	Urban	97116	Urban
97014	Rural	97031	Rural	97053	Rural	97078	Urban	97117	Rural
97015	Urban	97032	Rural	97054	Rural	97080	Urban	97118	Rural
97016	Rural	97033	Frontier	97055	Rural	97086	Urban	97119	Rural
97017	Rural	97034	Urban	97056	Rural	97089	Urban	97121	Rural
		97035	Urban	97057	Rural	97101	Rural	97122	Rural
		97036	Urban	97058	Rural	97102	Rural	97123	Urban

97124	Urban	97214	Urban	97290	Urban	97343	Rural	97385	Rural
97125	Rural	97215	Urban	97291	Urban	97344	Rural	97386	Rural
97127	Rural	97216	Urban	97292	Urban	97345	Rural	97388	Rural
97128	Rural	97217	Urban	97293	Urban	97346	Rural	97389	Urban
97130	Rural	97218	Urban	97294	Urban	97347	Rural	97390	Rural
97131	Rural	97219	Urban	97296	Urban	97348	Rural	97391	Rural
97132	Rural	97220	Urban	97298	Urban	97350	Rural	97392	Urban
97133	Rural	97221	Urban	97301	Urban	97351	Urban	97394	Rural
97134	Rural	97222	Urban	97302	Urban	97352	Urban	97396	Rural
97135	Rural	97223	Urban	97303	Urban	97355	Rural	97401	Urban
97136	Rural	97224	Urban	97304	Urban	97357	Rural	97402	Urban
97137	Rural	97225	Urban	97305	Urban	97358	Rural	97403	Urban
97138	Rural	97227	Urban	97306	Urban	97359	Urban	97404	Urban
97140	Urban	97228	Urban	97307	Urban	97360	Rural	97405	Urban
97141	Rural	97229	Urban	97308	Urban	97361	Rural	97406	Rural
97143	Rural	97230	Urban	97309	Urban	97362	Rural	97407	Rural
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97147	Rural	97236	Urban	97321	Urban	97367	Rural	97411	Rural
97148	Rural	97238	Urban	97322	Urban	97368	Rural	97412	Rural
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97202	Urban	97242	Urban	97326	Rural	97371	Urban	97415	Rural
97203	Urban	97256	Urban	97327	Rural	97372	Rural	97416	Rural
97204	Urban	97258	Urban	97329	Rural	97373	Rural	97417	Rural
97205	Urban	97266	Urban	97330	Urban	97374	Rural	97419	Rural
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97207	Urban	97268	Urban	97333	Urban	97376	Rural	97423	Rural
97208	Urban	97269	Urban	97335	Rural	97377	Rural	97424	Rural
97209	Urban	97280	Urban	97336	Rural	97378	Rural	97425	Rural
97210	Urban	97281	Urban	97338	Rural	97380	Rural	97426	Urban
97211	Urban	97282	Urban	97339	Urban	97381	Rural	97428	Rural
97212	Urban	97283	Urban	97341	Rural	97383	Rural	97429	Rural
97213	Urban	97286	Urban	97342	Rural	97384	Rural	97430	Rural

97431	Rural	97470	Rural	97527	Rural	97638	Frontier	97760	Rural
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97461	Rural	97503	Urban	97627	Rural	97750	Frontier	97842	Frontier
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97463	Rural	97520	Rural	97632	Rural	97752	Rural	97844	Frontier
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97467	Rural	97525	Rural	97636	Frontier	97758	Frontier	97850	Rural
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97864	Frontier	97875	Rural	97886	Rural	97908	Frontier	97920	Frontier
97865	Frontier	97876	Rural	97901	Frontier	97909	Frontier		
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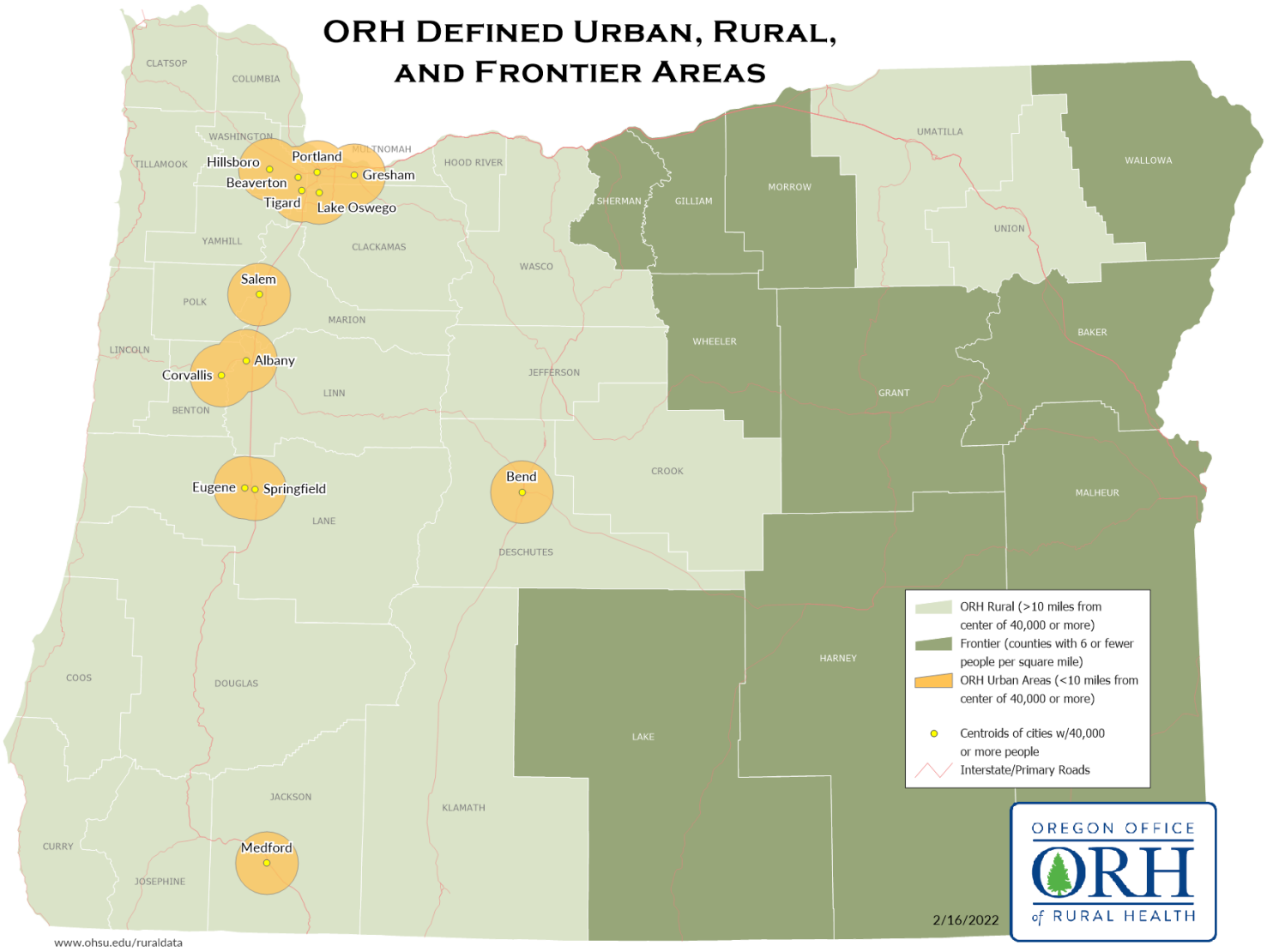
97868	Rural	97880	Rural	97903	Frontier	97911	Frontier		


ORH Defined Urban, Rural, and Frontier Areas
CLATSOP
COLUMBIA
WASHINGTON
TILLAMOOK
MULTNOMAH
Hillsboro
Portland
Beaverton
Gresham
Tigard
Lake Oswego
HOOD RIVER
YAMHILL
CLACKAMAS
Salem
POLK
MARION
LINCOLN
Albany
Corvallis
LINN
BENTON
Eugene
Springfield
LANE
Bend
DESCHUTES
WASCO
JEFFERSON
CROOK
SHERMAN
GILLIAM
MORROW
UMATILLA
WALLOWA
UNION
WHEELER
GRANT
BAKER
MALHEUR
HARNEY
LAKE
COOS
DOUGLAS
JACKSON
KLAMATH
CURRY
JOSEPHINE
Medford
ORH Rural (>10 miles from center of 40,000 or more)
Frontier (counties with 6 or fewer people per square mile)
ORH Urban Areas (<10 miles from center of 40,000 or more)
Centroids of cities w/40,000 or more people
Interstate/Primary Roads
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OREGON OFFICE of RURAL HEALTH
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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

Policy Evaluation: Antipsychotics in Children

Plain Language Summary:

- In children less than 6 years old, providers sometimes prescribe medicines called antipsychotics for serious behavior issues related to developmental disorders.
- Antipsychotics can cause weight gain, movement problems, and changes in hormones. Risk for side effects increases with length of therapy. Providers should regularly monitor for these side effects, and limit use to the shortest duration and lowest dose needed to improve symptoms. Because of these side effects, guidelines suggest people try other behavioral therapy before taking an antipsychotic.
- The Oregon Health Authority requires providers to explain why they are prescribing an antipsychotic to people less than 6 years of age before Oregon Health Plan (OHP) will pay for the medication. We evaluated how this policy is working and found that:
    - Only a small number of people less than 6 years old are prescribed antipsychotics.
    - Antipsychotics were prescribed most often for developmental disorders and challenging behavior.
    - Blood sugar testing occurs for about 40% of young children prescribed an antipsychotic.
    - The policy may decrease the number of people prescribed antipsychotics for longer than 30 days, but more data is needed to confirm these findings.
- We recommend continuing this policy to encourage appropriate antipsychotic use and suggest changes to decrease administrative burden.

Purpose:

The purpose of this policy evaluation is to evaluate administrative burden and changes in antipsychotic prescribing after implementation of a safety edit for children less than 6 years of age.

Research Questions:

1. For members less than 6 years of age prescribed antipsychotics, what diagnoses are present in medical claims that are potential indications for therapy?
2. For members less than 6 years of age, has duration of antipsychotic therapy changed after implementation of the policy?
3. For members less than 6 years of age prescribed antipsychotics, has the proportion of members with metabolic monitoring or with engagement of a mental health specialist changed after implementation of the policy?
4. For members less than 6 years of age prescribed antipsychotics, what proportion of members have denied claims or prior authorization requests?

Conclusions:

- This analysis identified 33 members who were less than 6 years of age and prescribed an antipsychotic in the 6 months after implementation of the policy. In the 6 months before implementation of the safety edit, 31 members were prescribed an antipsychotic. The most common diagnoses for members prescribed antipsychotics included autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and other developmental

disorders. Challenging behavior (e.g., aggressive, combative, explosive, violent or self-harmful behavior) was documented for 42% of members (n=14) during the prior authorization (PA) process.

- The most common antipsychotics prescribed to children less than 6 years of age were risperidone (58%) and aripiprazole (27%). Both risperidone and aripiprazole have an indication for irritability associated with autism for patients at least 5 and 6 years of age, respectively.
- Because of the small number of members and the short follow-up duration, it is difficult to identify whether there were changes in relevant clinical outcomes after implementation of the policy. Preliminary data do not indicate changes in glucose monitoring or the number of prescriptions written by a specialist.
    - In the 6 months before implementation of the policy, 26% of members had antipsychotic prescriptions written by a psychiatrist or neurodevelopmental pediatrician compared to 24% after implementation of the safety edit.
    - In the 6 months before implementation of the policy, 35% of members had claims for glucose monitoring compared to 39% of members in the 6 months after implementation of the safety edit. Profile review identified that 4 members (12%) had glucose monitoring only after the PA requirement.
- This policy was implemented in conjunction with a retrospective provider educational initiative in which providers were faxed information about the new policy when a member had their first paid claim for an antipsychotic. Because automated faxes were successfully sent for only 45% of members, manual efforts were made to call provider offices and send information about the policy.
    - Despite efforts to notify providers about the new policy, about half of members (n=17, 52%) with claims for an antipsychotic had an initial denied claim after implementation of the policy. Some members had subsequent denied claims after short-term approvals or when titrating doses.
- In the 6 months before implementation of the policy, 90% of members had therapy longer than 30 days compared to 73% in the 6 months after implementation of the safety edit.
    - After implementation of the safety edit, PA requests were submitted for 73% of members (n=24). The current policy applies to members less than 6 years of age, and PA was not required for 24% of members because they turned 6 years of age (n=7) before their second antipsychotic claim or had less than 30 days of therapy (n=1). Prior authorization was required, but not submitted for one member (3%).
    - Long-term therapy beyond 90 days was approved for 17 members (52%). For one member (3%) a PA was initially denied. Short-term approvals (up to 90 days) were approved for 6 members (18%). Short-term approvals were intended to avoid interruptions in ongoing care and allow providers additional time to submit information needed to meet PA requirements. Two members had a subsequent denied PA after a short-term approval.

Recommendations:

- Update the safety edit in **Appendix 1** to:
    - include assessment of rapid weight gain for members without glucose monitoring,
    - allow longer initial therapy (up to 90 days) before PA is required to minimize administrative burden, and
    - include members 6 years of age in the policy to provide monitoring for members who are turning 6 years old.
- Continue to improve provider educational initiatives to notify providers about the policy before members have a denied claim.

Background

Few antipsychotics have been studied in young children, and efficacy and safety has not been established for any antipsychotic in young children less than 5 years of age. Prior reviews evaluated by the Pharmacy & Therapeutics Committee have identified evidence that antipsychotics may improve behavior that challenges in children with autism or disruptive behavior disorders.[1] Both risperidone and aripiprazole have an indication for irritability associated with autism

(including symptoms of aggression towards others, deliberate self-injury, temper tantrums, and quickly changing moods) for patients at least 5 and 6 years of age, respectively.[2,3] These drugs also have the most evidence of benefit for disruptive behavior disorders.[1] Lurasidone has been studied in people with autism spectrum disorder, but did not demonstrate symptom improvement compared to placebo, and there is low quality evidence that quetiapine may have symptomatic and functional improvement in people with disruptive behavior disorder.[1]

Current guidelines recommend non-pharmacological therapy as first-line therapy for children prior to prescription of an antipsychotic.[4-6] Antipsychotics can be associated with significant risk of long-term adverse events. Because antipsychotics increase the risk of metabolic syndrome, laboratory monitoring is recommended before starting treatment and routinely during long-term therapy. In Medicaid, several national quality metrics aim to improve use of psychotropic medications in children. The 2023 core set of children's health care quality measures includes metabolic monitoring and use of first-line psychosocial care in children and adolescents on antipsychotics.[7]

In 2021, the Oregon Pharmacy and Therapeutic Committee recommended implementation of a safety edit to support appropriate use of antipsychotics in children 5 years of age or younger. The proposal targeted children after their first prescription in order to accommodate prescribing for urgent or acute symptoms and to avoid interruptions in therapy during transitions of care for patients newly enrolled in Medicaid. Ongoing therapy requires documentation of clinical rationale, metabolic monitoring, use of first-line non-pharmacologic therapy, and specialist consult. Upon their first claim for an antipsychotic, outreach will be conducted for prescribers of the antipsychotic in order to assess appropriateness of care, provide education on evidence-based use of non-pharmacological therapy, and facilitate access to services for appropriate patients.

The goal of this evaluation is to measure the impact on duration of therapy and metabolic monitoring under this policy.

Methods:
Members were identified for inclusion in the study based on paid or denied fee-for-service (FFS) claims for an antipsychotic medication. Antipsychotics were identified for inclusion based on their Preferred Drug List (PDL) class. The evaluation window for antipsychotic claims was from 10/1/2021 to 3/31/2022 for the control period before policy implementation and from 10/1/22 to 3/31/23 for the study period after policy implementation. The index event (IE) was the defined as the first paid or denied antipsychotic claim in the evaluation window. Denied claims were included based on error codes in **Appendix 1**.

For each patient, the baseline and follow-up periods were based on the IE.
- The baseline period was defined as the 90 days prior to the IE (exclusive of the IE).
- The follow-up period was defined as the 60 days following the IE (inclusive of the IE)

Inclusion Criteria:
1. Medicaid members with a paid or denied FFS claim for an antipsychotic in the evaluation window
2. Members less than or equal to 5 years of age at the time of the IE

Exclusion criteria:
1. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow-up period
2. Non-continuous Medicaid eligibility during the baseline period
3. Non-continuous Medicaid eligibility during the follow-up period

4. Patients with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods. Claims data for these patients may be incomplete. Patients were identified based on the following benefit packages:

Category	Benefit Package	Description
Medicare Part D coverage	BMM BMD MED	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug Oregon Health Plan with Limited Drug Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND CWM SMF SMB	Transplant package Citizenship Waived Emergency Medical Special Low-Income Medicare Beneficiary Only Special Low-Income Medicare Beneficiary Only

Population descriptors included:

1. Members with a diagnosis of autism or self-harm in medical claims during the baseline or follow-up period or submitted with a PA
2. Coordinated Care Organization (CCO) enrollment at the time of the IE
3. Drug prescribed at the time of the IE
4. Current foster care enrollment (historical enrollment is unavailable)
5. Race and age

Outcomes that were planned for this analysis included:

1. Proportion of members with claims for metabolic monitoring (see **Appendix 1** for medical codes)
2. Proportion of members with prescriptions from a psychiatrist or developmental pediatrician (see **Appendix 1** for taxonomy codes)
3. Days covered by antipsychotic in the 6 months following the IE categorized as less than or equal to 30 days or more than 30 days

Chart notes submitted with PA requests were also reviewed.

Results:

The number of members included in this analysis are listed in **Table 1**. After exclusion of members with potentially incomplete claims data, there were 31 members in the 6 months before implementation of the PA and 41 members in the 6 months after implementation of the policy. Eight members were excluded from the post-implementation group because they were already included in the pre-implementation group. Baseline characteristics for these members are described in **Table 2**. Because of the small numbers of members, differences between groups are difficult to quantify. Members were primarily 4 or 5 years of age and enrolled in a CCO at the time of the first claim in the evaluation window. Most members identified as male (>70%) and white (>60%). Risperidone (58%) and aripiprazole (27%) accounted for the majority of claims. Five members had claims for olanzapine (15%). In 4 of these members, olanzapine was prescribed as an antiemetic for cancer.

Table 1. Included population of members with paid claims

Number of included patients	Before	After
Age ≤ 5 years with FFS paid or denied antipsychotic claim	32	51
After exclusion of Medicare, TPL, and limited drug eligibility groups	32	46
After exclusion of non-continuous Medicaid enrollment in the 60-day follow-up period	32	44
After exclusion of non-continuous Medicaid enrollment in 90-day baseline period	31	41
After exclusion of members in Post group who were already in the Pre group	**31**	**33**

Table 2. Baseline characteristics

	Before		**After**	
	31	%	33	%
Age				
2	1	3.2%	2	6.1%
3	4	12.9%	3	9.1%
4	7	22.6%	8	24.2%
5	19	61.3%	20	60.6%
Sex				
Female	7	22.6%	9	27.3%
Male	24	77.4%	24	72.7%
Race				
White	19	61.3%	20	60.6%
Unknown	9	29.0%	8	24.2%
American Indian/Alaskan Native	3	9.7%	2	6.1%
Other	0	0.0%	3	9.1%
Foster Care Enrollment (as of May 2023)	2	6.5%	5	15.2%
Managed Care Enrollment (as of IE)				
FFS		0.0%	2	6.1%
CCO	31	100.0%	31	93.9%
IE Drug				
risperidone	18	58.1%	19	57.6%
aripiprazole	7	22.6%	9	27.3%
olanzapine	3	9.7%	5	15.2%
quetiapine fumarate	3	9.7%	0	0.0%

After implementation of the policy, about half of members had an initial denied claim (n=17, 52%). The current policy allows members to fill 30 days without PA, and an initial denial for these members would indicate that they had claims for an antipsychotic in the prior year. Most members with an initial denied claim had subsequent paid claims.

This policy was implemented in conjunction with a retrospective provider educational initiative in which providers were faxed information about the new policy when a member had their first paid claim for an antipsychotic. The intent of this policy was to avoid interruptions in care by notifying providers of the PA requirement before members had a denied claim. Automated, retrospective faxes to providers notifying them about the policy were successfully transmitted for about 45% of members (n=15). Because of the low success rate with initial faxes, manual efforts were made to call provider offices and re-fax information about the policy.

The most common diagnoses present in medical claims were developmental disorders like autism spectrum disorder, ADHD, psychological development disorders, and language disorders (**Table 3**). Members frequently had more than one mental health diagnosis. Diagnoses related to self-harm, hostility, or violence were present for only one member in each group. There was no change in the number of members with prescriptions from a psychiatrist or neurodevelopmental pediatrician and only slight changes in the number of patients with claims for glucose monitoring or therapy beyond 30 days (**Table 4**).

Table 3. Most common mental health diagnoses (ICD-10 codes beginning with F) in medical claims or submitted with PAs

			Before					After	
			31	%				33	%
Top 10 Mental Health Diagnoses (ICD-10 beginning with F)									
1	F902	Attention-deficit hyperactivity disorder, combined type	13	41.9%	**1**	F840	Autistic disorder	14	42.4%
2	F88	Other disorders of psychological development	12	38.7%	**2**	F902	Attention-deficit hyperactivity disorder, combined type	14	42.4%
3	F840	Autistic disorder	9	29.0%	**3**	F88	Other disorders of psychological development	11	33.3%
4	F919	Conduct disorder, unspecified	8	25.8%	**4**	F802	Mixed receptive-expressive language disorder	9	27.3%
5	F802	Mixed receptive-expressive language disorder	8	25.8%	**5**	F419	Anxiety disorder, unspecified	8	24.2%
6	F3481	Disruptive mood dysregulation disorder	7	22.6%	**6**	F919	Conduct disorder, unspecified	7	21.2%
7	F909	Attention-deficit hyperactivity disorder, unspecified type	7	22.6%	**7**	F909	Attention-deficit hyperactivity disorder, unspecified type	6	18.2%
8	F8089	Other developmental disorders of speech and language	6	19.4%	**8**	F4389	Other reactions to severe stress	5	15.2%
9	F913	Oppositional defiant disorder	6	19.4%	**9**	F4310	Post-traumatic stress disorder, unspecified	5	15.2%
10	F419	Anxiety disorder, unspecified	6	19.4%	**10**	F3481	Disruptive mood dysregulation disorder	4	12.1%
10	F4310	Post-traumatic stress disorder, unspecified	6	19.4%	**10**	F411	Generalized anxiety disorder	4	12.1%
10	F918	Other conduct disorders	4	12.9%	**10**	F918	Other conduct disorders	4	12.1%
10	F809	Developmental disorder of speech and language, unspecified	4	12.9%					
10	F4325	Adjustment disorder w/mixed disturb of emotions and conduct	4	12.9%					

Table 4. Clinical Outcomes

	Before		After	
	31	%	33	%
Glucose monitoring in baseline or follow-up period	11	35.5%	13	39.4%
Psychiatrist or neurodevelopmental prescriber specialty	8	25.8%	8	24.2%
Days covered by antipsychotic in the following 6 months				
0 days		0.0%	4	12.1%
1-30 days	3	9.7%	5	15.2%
>30 days	28	90.3%	24	72.7%

Manual review of profiles

Of the 33 members in the study period after implementation of the safety edit, a PA was ultimately submitted for 24 members (73%; **Table 5**). For 51% of members, long-term antipsychotic therapy was approved. For 18% of members (n=6), a short-term approval was authorized for 3 months to avoid interruptions in therapy and allow the prescriber time to submit additional documentation required for longer approval. Subsequent glucose monitoring was conducted for 4 of these members, and one switched to alternate therapy after a denial for longer-term therapy. Eight members (24%) met criteria for a new start of an antipsychotic and had no subsequent PA requirement. Because the current PA criteria apply only to members who were less than or equal to 5 years of age, 7 members turned 6 years of age before a PA was required and one member had less than 30 days of therapy. A PA was initially denied for one member and no PA was submitted for another member. Manual review of submitted chart notes identified 14 members (42%) with explosive, combative, violent, or self-harmful behavior. Diagnoses documented in chart notes included cancer (n=4), autism (n=10), substance exposure as an infant or *in utero* (n=4), and other developmental disorders (n=8). Overall, diagnostic trends were consistent between medical claims and chart notes except for substance exposure and challenging behavior. These diagnoses were apparent in submitted chart notes but were not identified in medical claims.

Table 5. Manual Review of Outcomes of Prior Authorization Status

	Before		After	
Manual review of PA process	31		33	%
Auto-PA for first 30 days (no manual PA requirement)	1	3.2%	8	24.2%
PA Approved > 3 months	1	3.2%	17	51.5%
Short-term PA approval (3 months)	0	0.0%	6	18.2%
No PA submitted and subsequent denied claims	0	0.0%	1	3.0%
Denied PA only	1	3.2%	1	3.0%

Discussion and Limitations:

This analysis is significantly limited by the small numbers of members prescribed antipsychotics. As a claims-based analysis, this evaluation also has several inherent limitations including:

- Before and after study design which is unable to control for potential confounding factors.
- Diagnostic data may be incomplete or not accurately reflect true patient diagnoses. After comparison of diagnoses in medical claims and diagnoses submitted with PAs, we identified that challenging behavior (e.g., aggressive, combative, explosive, violent or self-harmful behavior) was rarely included in medical claims.
- Provider taxonomy, which was used to identify mental health providers, may not actually reflect the true provider specialty or area of practice.
- Use of days' supply on paid claims as a surrogate marker for duration of therapy. Days' supply may not reflect actual member adherence or medication use.
- Use of common codes for psychotherapy and laboratory tests which may not accurately reflect engagement for all types of non-pharmacologic therapies or glucose testing.
- Use of a short follow-up period may result in incomplete data on duration of therapy for some members. In order to maximize the number of people eligible for inclusion, a short follow-up duration (60 days) was chosen. However, based on profile review, members with approval for long-term therapy were inaccurately categorized using this duration. A post-hoc analysis was conducted to evaluate duration of therapy over 6 months instead of 60 days.

The small number of members made it difficult to identify patterns in utilization.

This policy was implemented and designed to avoid interruptions in care for members. Members were allowed to fill 30 days of an antipsychotic without a PA, and a retrospective educational fax was sent at the time of the first claim to notify providers of the PA requirement. If providers requested a PA but did not supply sufficient documentation for long-term approval, 90 days of therapy could be authorized in order to avoid interruptions in care while the provider submitted additional information. During implementation, there were manual efforts to call provider offices and notify providers of the PA requirement. However, despite this, many members still had denied claims for an antipsychotic. It is unclear why providers were unaware of the PA requirement. Potential reasons include:

1. Inaccurate contact information for providers resulting in inability to successfully send a fax notifying the provider of the PA requirement. It is unclear if faxes that were successfully transmitted to a fax number actually reached the provider.
2. Faxes were sent in advance of a denied claim and not at the time of the denial. For members who had intermittent antipsychotic use and had a significant time between their first and second antipsychotic claim, the fax was not temporally associated with the need for a PA request. Retrospective faxes to providers notifying them about the policy were successfully transmitted for about 45% of members (n=15) within the 90 days prior to a denied claim.
3. PA is required for each change in dose or change in drug. In most cases, providers start on a low dose and titrate the antipsychotic if needed to control symptoms. Even when providers submitted an initial PA, subsequent changes in dose or changes in therapy required submission of a new PA.
4. Many PA requests did not include sufficient information to approve long-term therapy. In many cases, a short-term PA was approved in order to give providers time to submit documentation of metabolic monitoring. If providers did not submit this information within 3 months, members may have had subsequent denied claims. Because short-term approval was authorized for most patients, a longer initial treatment duration may be reasonable.

There is insufficient information based on this analysis to determine if the safety edit for antipsychotics in children less than 6 years of age is improving rates of metabolic monitoring, the proportion of providers who consult with a psychiatrist, or the proportion of members who participate in psychotherapy. At the time of this analysis only 3 months of complete follow-up data were available for members in the study, and the small number of people identified for analysis make it difficult to compare differences between groups. However, there were several implementation trends that were apparent after a review of profiles.

- At the time a provider submits a PA, we are unable to distinguish between members in foster care and other Medicaid members. Members in foster care have the same PA requirements as all other Medicaid members (even if the Department of Human Services has already reviewed the medication). The retrospective program is able to incorporate foster care enrollment and can help coordinate care for these members.
- Prior authorizations are typically loaded for a specific drug and dose. Titration of medications or switching between medications because of intolerance or lack of benefit increases the administrative burden for providers.
- Prior authorization criteria were only applied for members younger than 6 years of age. Some members turned 6 years of age before the provider submitted information to support long-term antipsychotic use.
- The current policy uses a one-year lookback period to evaluate previous antipsychotic use. If no claims are identified, then 30 days is authorized to allow the prescriber time to submit information needed for ongoing therapy. However, if members use antipsychotics intermittently with a long period between the first and second claims, then the fax notifying the prescriber about the PA requirement was not temporally related to the member's second denied claim. Over 50% of members in this analysis (n=17) had an initial denied claim, despite efforts to notify prescribers about the PA requirement.
- Review of chart notes documented engagement in a wide variety of non-pharmacological therapies for members prescribed antipsychotics. Therapies included play therapy, occupational therapy, school-based therapies, developmental rehabilitation, attachment-based training, parent-child interaction therapy, and applied behavior analysis. Current criteria for use of antipsychotics do not require only referral for psychotherapy and do not require any particular type of non-pharmacologic therapy.

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Appendix 1: Drug Coding

Table A1. Description of PICOs

Population	Medicaid members with a paid or denied FFS claim for antipsychotics in the evaluation window. AND age <=5 years at the time of the IE AND continuous Medicaid enrollment in the baseline (90 day) and follow-up (60 day) periods
Intervention	Continuation of antipsychotic beyond 30 days
Comparators	Members with antipsychotic claims from 10/1/2021 to 3/31/2022 vs. Members with antipsychotic claims from 10/1/2022 to 3/31/2023
Outcomes	Duration of antipsychotic use Glucose monitoring Specialist oversight Administrative burden of PA process – PAs, denied claims

Table A2. Specific Therapeutic Class for second generation antipsychotics

Specific Therapeutic Class	Generic
H7T	clozapine
H7T	risperidone
H7T	olanzapine
H7T	quetiapine fumarate
H7T	ziprasidone HCl
H7T	paliperidone
H7T	asenapine maleate
H7T	iloperidone
H7T	lurasidone HCl
H7T	asenapine
H7T	lumateperone tosylate
H7T	olanzapine/samidorphan malate
H7X	aripiprazole
H7X	brexpiprazole
H8W	cariprazine HCl
H8Y	pimavanserin tartrate

Table A3. Error codes for denied claims

Error Code	Error Status Description	Criteria for Study
513	RECIPIENT NAME AND NUMBER DISAGREE	Exclude
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE	Exclude
2809	DOB IS INVALID	Exclude
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)	Exclude
628	Other Coverage Reject Code Required for OCC 3	Exclude
503	DATE DISPENSED AFTER BILLING DATE	Exclude
643	INVALID OTHER COVERAGE CODE	Exclude
238	RECIPIENT NAME IS MISSING	Exclude
4999	THIS DRUG IS COVERED BY MEDICARE PART D	Exclude
3002	NDC REQUIRES PA	Include
4025	AGE IS NOT ALLOWED FOR NDC	Include
3000	UNITS EXCEED AUTHORIZED UNITS ON PA MASTER FILE	Include

Table A4. Psychiatrist prescriber taxonomies

Taxonomy	Taxonomy Description
2080P0006X	PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS
2080P0008X	PHYSICIAN-PEDIATRICS-NEURODEVELOPMENTAL DISABILITIES
2084A0401X	PSYCHIATRY & NEUROLOGY, ADDICTION MEDICINE
2084B0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-BARIATRIC MEDICINE
2084B0040X	BEHAVIORAL NEUROLOGY & NEUROPSYCHIATRY
2084D0003X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-DIAGNOSTIC NEUROIMAGING
2084F0202X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-FORENSIC PSYCHIATRY
2084H0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-HOSPICE AND PALLIATIVE MEDICINE
2084N0008X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROMUSCULAR MEDICINE
2084N0400X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY
2084N0402X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY WITH SPECIAL QUAL IN CHILD NEUROLO
2084N0600X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-CLINICAL NEUROPHYSIOLOGY
2084P0005X	PHYSICIAN-PSYCHIATRY&NERUOLOGY-NEURODEVELOPMENTAL DISABILITIES
2084P0015X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHOSOMATIC MEDICINE
2084P0800X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY
2084P0802X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-ADDICTION PSYCHIATRY
2084P0804X	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY
2084P0805X	PHYSICIAN-PSYCHIATRY&NEUROLGY-GERIATRIC PSYCHIATRY
2084P2900X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PAIN MEDICINE
2084S0010X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SPORTS MEDICINE
2084S0012X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SLEEP MEDICINE
2084V0102X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-VASCULAR NEUROLOGY

Table A5. Metabolic monitoring for glucose

CPT Code	Description
80048	Blood Test, Basic Group Of Blood Chemicals (Calcium, Total)
80049	Basic Metabolic Panel
80050	General Health Panel
80053	Blood Test, Comprehensive Group Of Blood Chemicals
80054	Comprehensive Metabolic Panel
80065	Metabolic Panel
81506	Endo Assay Seven Anal
82945	Glucose Other Fluid
82947	Assay Glucose Blood Quant
82948	Reagent Strip/Blood Glucose
82950	Glucose Test
82951	Glucose Tolerance Test (Gtt)
82952	Gtt-Added Samples
82953	Glucose-Tolbutamide Test
82954	Glucose, Urine
82961	Glucose Tolerance Test, Intravenous
82962	Glucose Blood Test
83036	Hemoglobin Glycosylated A1c
83037	Hb Glycosylated A1c Home Dev
95249	Cont Gluc Mntr Pt Prov Eqp
95250	Cont Gluc Mntr Phys/Qhp Eqp
95251	Cont Gluc Mntr Analysis I&R
0403T	Diabetes Prev Standard Curr
3044F	Hg A1c Level Lt 7.0%
3045F	Hg A1c Level 7.0-9.0%
3046F	Hemoglobin A1c Level >9.0%
3047F	Hemoglobin A1c Level = 9.0%
3051F	Hg A1c>Equal 7.0%<8.0%
3052F	Hg A1c>Equal 8.0%<Equal 9.0%
3754F	Screening Tests Dm Done
D0411	Hba1c In Office Testing
D0412	Blood Glucose Level Test
G0096	Basic Metabolic Panel (Carbon Dioxide (B

G0098	Comprehensive Metabolic Panel (Albumin-S
G2089	A1c Level 7 To 9%
G8015	Diabetic Pt W/ Hba1c>9%
G8016	Diabetic Pt W/ Hba1c<Or=9%
G8017	Dm Pt Inelig For Hba1c Measu
G8777	Diabetes Screen
TR200	Tracking Only - Hemoglobin A1c - <7.0
TR201	Tracking Only - Hemoglobin A1c - >7 <8.0
TR202	Tracking Only - Hemoglobin A1c - >8 <9.0
TR203	Tracking Only - Hemoglobin A1c - >9.0

Antipsychotics in Children

Goal(s):

- Ensure safe and appropriate use of antipsychotics in children
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Antipsychotic use beyond ~~30~~ 90 days in children 3-~~5~~ 6 years of age
- All antipsychotic use in children 2 years of age or younger

Note: olanzapine can be automatically approved in patients with a recent cancer diagnosis

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 Indications and Ages for Oral Second-generation Antipsychotics in Children

FDA-Approved Indications and Ages				
Drug	**Schizophrenia**	**Bipolar I disorder**	**Major depressive disorder (adjunct)**	**Other**
aripiprazole	≥13 yrs	≥10 yrs	≥18 yrs	Irritability associated with Autistic Disorder ≥6 yrs Tourette's Disorder ≥6 yrs
asenapine maleate	≥18 yrs	≥10 yrs		
brexpiprazole	≥13 yrs			
lurasidone HCl	≥13 yrs	≥10 yrs		
olanzapine	≥13 yrs	≥13 yrs	≥18 yrs	
paliperidone	≥12 yrs			Schizoaffective disorder ≥18 yrs
quetiapine fumarate	≥13 yrs	≥10 yrs		Bipolar depression ≥18 yrs
risperidone	≥13 yrs	≥10 yrs		Irritability associated with Autistic Disorder ≥5 yrs

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for use of olanzapine as an antiemetic associated with cancer or chemotherapy?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Has the patient been screened for diabetes (blood glucose or A1C) within the last 12 months?	**Yes:** Go to #5	**No:** Go to #4
4. Is there documented clinical rationale for lack of metabolic monitoring (e.g. combative behaviors requiring sedation) OR documentation of patient weight before and after initiation of treatment? Note: Caregivers failing to take patients to the laboratory is not a clinical rationale for lack of monitoring.	**Yes:** Document rationale. Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Annual metabolic screening or consistent evaluation for rapid weight gain is required for chronic use of antipsychotics. Refer denied requests to the OHA for follow-up. ~~A single 90- day continuation of therapy may be granted upon request to allow for laboratory testing.~~
5. Is the patient engaged in, been referred for, or have documented inability to access evidence based first-line non-pharmacological therapy (e.g., applied behavior analysis therapy for autism, parent behavioral therapy, or parent child interaction therapy)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. ~~A single 90- day continuation of therapy may be granted upon request to allow time for engagement.~~

Approval Criteria		
6. Is the drug prescribed by or in consultation with a child psychiatrist or developmental pediatrician?	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Go to #7
7. Is there detailed documentation regarding risk/benefit assessment and the decision to prescribe antipsychotic therapy? A thorough assessment should include ALL the following: a. Multidisciplinary review including a mental health specialist b. Mental health assessment including documentation of diagnoses, symptoms, and disease severity c. Discussion and consideration of first-line non-pharmacological therapies d. Assessment of antipsychotic risks and monitoring strategies e. Specific therapeutic goals of antipsychotic therapy, and for ongoing therapy, discussion of progress toward or achievement of therapeutic goals (or reasons for lack of progress and remediation strategies) f. Anticipated duration of therapy g. Detailed follow-up plan	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. ~~A single 90- day continuation of therapy may be granted upon request to allow for submission of required documentation.~~

P&T/DUR Review: 6/21(SS)
Implementation: 10/1/22

Drug Use Research & Management Program
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Drug Use Evaluation: Melatonin Usage in Pediatric and Adult Members

Research Questions:

1. How have the number of prescriptions for sedative medications (e.g., benzodiazepines, melatonin receptor agonists, non-benzodiazepine hypnotics) changed since the addition of melatonin coverage to the Oregon Health Plan (OHP) fee-for-service (FFS) pharmacy benefit for pediatric members?
2. What proportion of pediatric members receiving prescriptions for melatonin have a diagnosis for insomnia or a comorbid diagnosis predisposing them to insomnia (e.g., depression, anxiety, attention deficit hyperactivity disorder, or autism spectrum disorder), indicating that treatment with melatonin is warranted?
3. Are the daily doses of melatonin for pediatric members appropriate, defined as 3 to 5 mg, as recommended by clinical practice guidelines (e.g., evidence-based dosing)?
4. If insomnia was added as a funded disease state, what proportion of adults have received a prescription for a sedative for longer than 30 days in the past year and could potentially benefit from the coverage of melatonin?
5. If funding of insomnia medications depended on trial of cognitive behavioral therapy (CBT), how many adults would be eligible for such coverage with the documentation of at least one claim for CBT?

Conclusions:

- The total percentage of prescriptions written for melatonin and other sedative medications has remained unchanged since the addition of melatonin to the pharmacy benefit for pediatric members. However, melatonin utilization has improved through a 43.5% increase in paid claims while benzodiazepines paid claims decreased by 41.8%.
- 57.5% of pediatric members have a comorbid diagnosis that predisposes them to insomnia. However, only 21.3% have a diagnosis of insomnia and 36.3% have no diagnosis that supports the use of melatonin.
- Among all age groups of pediatric members, the average daily dose of melatonin when initially prescribed was within the recommended 3-5 mg by clinical guidelines. Members between 13 and 18 years old did have an average daily dose of 4.9 mg, compared to members between 6 and 12 years old who had an average daily dose of 3.5 mg
- Among adults receiving sedative prescriptions, 43% received long-term sedatives (defined as a total of 30 or more days).
- Among adult members receiving a long-term sedative, 49.8% have a least one claim for CBT.

Recommendations:

- No policy changes recommended.

Background:

The consequences of sleep loss on daytime functions are more well documented in adults than in children.[1] However, one comparative study has examined the impact of sleep duration on emotional functioning and cognitive performance in children.[1] The results showed that modest differences, more than one hour

over two weeks, can affect emotional functioning, short-term memory, working memory, attention, and math fluency.[1] Based on these findings, the authors recommend that children experiencing difficulties in any of these areas be screened for sleep problems as a potential cause.[1]

In children, behavioral sleep problems, or behavioral insomnia, are characterized by bedtime refusal or resistance, delayed sleep onset, and prolonged night awakenings requiring parental intervention.[2] This can negatively affect the quality of life for children and carries an increased risk of mood and behavioral problems, academic failure, and worsened health related conditions.[2]

Chronic behavioral insomnia is estimated to occur in 10 to 30 percent of children depending on the exact definition used and the specific age group being studied.[2] Some subgroups of children experience a higher prevalence of insomnia, including those with psychiatric comorbidities, neurodevelopmental disorders, genetic syndromes, and acquired conditions.[2] **Table 1** summaries subgroups of children more likely to experience insomnia.[2]

Table 1. Pediatric Subgroups Predisposed to Insomnia[2]

Psychiatric	Neurodevelopmental	Genetic	Acquired
Depression Anxiety Stress	Attention deficit hyperactivity disorder Autism spectrum disorder	Smith-Magenis Syndrome Angelman Syndrome	Fetal alcohol syndrome

Prior to the initiation of pharmacologic interventions, it may be appropriate to obtain a sleep history by using one of several tools.[2] The BEARS survey, which looks at Bedtime issues, Excessive daytime sleepiness, night Awakenings, Regularity and duration of sleep, and Snoring, or sleep diaries can help clinicians decide the primary problem.[2] Common causes of insomnia include bedtime resistance, difficulty initiating or maintaining sleep, and behavioral disorders.[2] Poor sleep hygiene, including light and screen time before bed, may also be a cause of sleep disruption in children.[3]

The decision to initiate pharmacotherapy for insomnia in children should be based on efficacy, side effects, safety, and ethical considerations.[4] Specific side effects to consider include increased risk of inability to sleep without use of medications and daytime sleepiness associated with prescription sedatives. For some children, despite the previously mentioned considerations, sedatives and hypnotics may deemed appropriate therapy for insomnia.[4] In particular, the use of melatonin has increased in the United States over the past decade as treatment for insomnia in children.[4] This trend may be due to the relative safety of melatonin compared to prescription sedatives. Adverse effects from melatonin include headache, dizziness, nightmares, and excessive daytime sleepiness.[5]

The American Academy of Sleep Medicine clinical practice guideline, based on moderate quality evidence from a singular study, weakly recommends treatment with strategically timed melatonin versus no treatment in children and adolescents with delayed sleep-wake phase disorder.[6] This trial found improved sleep latency with a mean difference ranging from 38.39 minutes to 44.24 minutes depending on the dosage of melatonin given.[6] The clinical guideline proposes the same weak recommendation, based on low quality evidence from two reviewed studies, for treatment in children and adolescents with delayed sleep-wake phase disorder and comorbid psychiatric conditions.[6] A separate systematic review evaluated the effectiveness of pharmacotherapy for sleep disturbances in children with cognitive disabilities.[7] Of the 13 trials included in the review, 12 evaluated the efficacy of oral melatonin.[7] The pooled mean difference for the trials showed a 29.6 minutes increase in sleep time with melatonin, which was statistically significant. However, almost all of the trials had high or unclear risk of bias.[7] Melatonin at dosages ranging from 3-5 mg may be effective in children and adolescents.[6]

In October 2021, the Oregon Health Authority (OHA) added melatonin coverage to the OHP FFS pharmacy benefit for members 18 years of age or younger. All other sleep drugs still require a prior authorization (PA), including benzodiazepines which are only approved for an initial 30 days. In addition, melatonin is not covered for adult members and insomnia remains an unfunded condition. This drug use evaluation examines utilization of melatonin in pediatric OHP members, including appropriate dosage and indication, as well as associated costs due to the addition of melatonin to the pharmacy benefit plan. Furthermore, this drug use evaluation will provide insight into overall melatonin utilization in adults OHP members.

Methods:

Melatonin Coverage in Children Policy Evaluation

To evaluate changes in utilization, members 18 years of age or younger with a paid or denied FFS claim for melatonin or other sedatives (**Appendix 1**) from 10/01/2020 to 12/31/2022 were included.

The index event (IE) was defined as the first paid or denied FFS claim for a new start melatonin or other sedative (members without a history of melatonin or other sedative use in the past three months) in the evaluation window. If members had a paid and denied claim on the same day, the claim was classified as paid. For each member, the baseline and follow-up periods were defined based on the IE:

- The baseline period was defined as 6 months prior to the IE (exclusion of the IE).

Members were categorized into the following groups based on the IE.

(1) First claim for melatonin or sedative medication from October 1, 2020 to September 30, 2021 (pre-policy change)
(2) First claim for melatonin or sedative medication from January 1, 2022 to December 31, 2022 (post-policy change)

Average daily dose was collected and categorized into dosing groups (< 3 mg, 3-5 mg, > 5 mg) based on the IE dosage.

Inclusion Criteria:

- Paid or denied FFS claim for melatonin or other sedatives (**Appendix 1**). Denied claims were included if they were associated with error codes of 3002 “NDC requires PA”, 4002 “No coverage for billed NDC”, 3022 “Non-Preferred Drug, PA Required”, 1017 “Non-rebatable eligible indicator”, or 1016 “Non-participating manufacturer” without any of the error codes listed in **Appendix 1.**

Exclusion criteria:

- Patients with Medicare Part D coverage or limited or no Medicaid drug benefit in the baseline period.

Category	Benefit Package	Description
Medicare Part D coverage	BMM BMD MED	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug Oregon Health Plan with Limited Drug Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND CWM	Transplant package Citizenship Waived Emergency Medical Special Low-Income Medicare Beneficiary Only

	SMF SMB	Special Low-Income Medicare Beneficiary Only

- Patients with primary insurance coverage (i.e., third party liability [TPL]) in the baseline period
- Patients with non-continuous Medicaid enrollment in the baseline period
- Patients with Coordinated Care Organization (CCO) enrollment on the IE date
- Patients identified in both pre- and post-policy groups will be excluded from the post-policy change group

Outcomes:

- Proportion of members prescribed melatonin or other sedative who have a diagnosis of insomnia, delayed sleep-wake phase disorder, depression, anxiety, attention deficit hyperactivity disorder, or autism spectrum disorder based on medical claims in the baseline period (**Appendix 1**).
- Proportion of members who have a paid or denied FFS claim for melatonin and the dosage prescribed.

<u>Sedative Coverage in Adults</u>

Inclusion Criteria:

- Members > 18 years old with a paid FFS claim for a sedative medication from 01/01/2022 to 12/31/2022 will be identified.

The IE was defined as the first paid FFS claim for sedative in the evaluation window. For each member, the baseline and follow-up periods were defined based on the IE:

- The baseline period was defined as 6 months prior to the IE (exclusion of the IE).
- The follow-up period was defined as the 45 days following the IE (inclusive of the IE).

Exclusion Criteria:

- Patients with Medicare Part D coverage or limited or no Medicaid drug benefit in the baseline period

Category	Benefit Package	Description
Medicare Part D coverage	BMM BMD MED	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug Oregon Health Plan with Limited Drug Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND CWM SMF SMB	Transplant package Citizenship Waived Emergency Medical Special Low-Income Medicare Beneficiary Only Special Low-Income Medicare Beneficiary Only

- Patients with primary insurance coverage (i.e., third party liability [TPL]) in the baseline period
- Patients with non-continuous Medicaid enrollment in the baseline period
- Patients with non-continuous FFS enrollment in the follow-up period
- Patients with CCO coverage during the follow-up period

Outcomes:

- Proportion of adult members who have an FFS paid claim for long-term sedative medications (30 days based on day supply)
- Documentation of any visits for CBT during the baseline period. Documentation of CBT was identified using medical service codes (**Appendix 1**).

Results:
In OHP FFS, 1,669 pediatric members during the pre-policy time period and 1,610 in the post-policy time period were identified as having a paid or denied claim for melatonin or other sedative medication. After all the exclusion criteria were applied, 126 pediatric members from the pre-policy period and 80 from the post-policy period were included for analysis. For adults, 32,716 members were identified as having an FFS claim for melatonin or other sedative; however, only 762 were included for analysis after the exclusion criteria was applied. Details regarding the number of patients included from the analysis can be found below in **Tables 1A and 1B**.

Table 1A: Population of included pediatric patients

	Pre-Policy		Post-Policy	
Number of included pediatric patients	#	%	#	%
Pediatric paid or denied claim for melatonin or sedative medication	1,669		1,610	
After exclusion of Medicare Part D, limited benefit plans, and TPL	1,310	78.5%	1,315	81.7%
After exclusion of non-continuous Medicaid enrollment in the baseline period	1,242	74.4%	1,245	77.3%
After exclusion of patients enrolled in a CCO on the index date	126	7.5%	93	5.8%
After exclusion of members in Post group who were already in the Pre group	**126**	**7.5%**	**80**	**5.0%**

Table 1B: Population of included adult patients

Number of included adult patients	#	%
Adult paid FFS claim for melatonin or sedative medication	32,716	
After exclusion of Medicare Part D, limited benefit plans, and TPL	30,715	93.9%
After exclusion of non-continuous Medicaid enrollment in the baseline period	28,535	87.2%
After exclusion of non-continuous FFS enrollment in the follow-up period	**762**	2.3%

Table 3: New start sedative prescriptions in pediatric patients

	Before						After					
	Paid Claim		Denied Claim		Total		Paid Claim		Denied Claim		Total	
	59	%	67	%	126	%	69	%	11	%	80	%
Benzodiazepines	58	98.3%	8	11.9%	66	52.4%	39	56.5%	6	54.5%	45	56.3%
Melatonin-receptor agonists		0.0%		0.0%		0.0%		0.0%		0.0%		0.0%
Non-benzodiazepine hypnotics	1	1.7%		0.0%	1	0.8%		0.0%	1	9.1%	1	1.3%
Melatonin		0.0%	59	88.1%	59	46.8%	30	43.5%	4	36.4%	34	42.5%
Received benzodiazepine in 90 days after melatonin		0.0%		0.0%		0.0%	1	1.4%		0.0%	1	1.3%

During the pre-policy time period all information on melatonin dosages came from denied claims. Among those denied claims, 13.6 percent were for a daily dose less than 3 mg, 45.8 percent was for 3 to 5 mg, and 40.7 was for a dose greater than 5 mg. The average daily dose of these claims was 3.2 mg for pediatric members 0 to 5 years old, 5 mg for 6 to 12 years old, and 5.2 mg for 13 to 18 years old.

Following the policy change, the statistics for melatonin prescriptions is based on both paid and denied claims. Among the claims for melatonin 8.8 percent were for a daily dose less than 3 mg, 61.8 percent were for 3 to 5 mg, and 29.4 percent were for a dose greater than 5 mg. The average daily dose of these claims was 3.0 for pediatric patients 0 to 5 years old, 3.5 mg for 6 to 12 years old, 4.9 for 13 to 18 years old. All of this information can be found below in **Table 4**.

Table 4. Melatonin prescription statistics

	Before						After					
	Paid Claim		Denied Claim		Total		Paid Claim		Denied Claim		Total	
	0	%	59	%	59	%	30	%	4	%	34	%
Daily Dose of Melatonin at IE												
< 3 mg		0.0%	8	13.6%	8	13.6%	3	10.0%		0.0%	3	8.8%
3-5 mg		0.0%	27	45.8%	27	45.8%	20	66.7%	1	25.0%	21	61.8%
> 5 mg		0.0%	24	40.7%	24	40.7%	7	23.3%	3	75.0%	10	29.4%
Average Daily Dose of Melatonin at IE by Age												
0-5			3.2		3.2		3.0				3.0	
6-12			5.0		5.0		3.0		5.0		3.5	
13-18			5.2		5.2		4.3		10.0		4.9	

During the pre-policy period, 22.2 percent of claims were for insomnia with no claims for delayed sleep-wake phase disorder. For comorbidities contributing to insomnia, 36.5 percent of pediatric members had a diagnosis of depression, 33.3 percent had anxiety, 27 percent had ADHD, and 4 percent had autism. Among all diagnoses, 57.1 percent of pediatric members had any comorbid diagnosis and 34.9 percent had no diagnosis (neither insomnia nor a comorbid diagnosis).

In the post-policy period, 1.3 percent of claims were for a sleep disorder and 20 percent were for insomnia. In terms of comorbidities related to insomnia, 30 percent of pediatric members had a diagnosis of depression, 37.5 percent had anxiety, 26.3 percent had ADHD, and 11.3 percent had autism. Of those diagnoses, 57.5 percent of pediatric members had any comorbid diagnosis and 36.6 percent had no diagnosis. Information on the proportions of paid and denied claims for the diagnoses can be found below in **Table 5**.

Table 5: Pediatric patient diagnoses in the 6 months before the index event

	Before						After					
	Paid Claim		Denied Claim		Total		Paid Claim		Denied Claim		Total	
	59	%	67	%	126	%	69	%	11	%	80	%
Evidence-supported diagnoses												
Sleep disorder		0.0%		0.0%		0.0%	1	1.4%		0.0%	1	1.3%
Insomnia	13	22.0%	15	22.4%	28	22.2%	15	21.7%	1	9.1%	16	20.0%
Delayed sleep-wake phase disorder		0.0%		0.0%		0.0%		0.0%		0.0%		0.0%
Comorbidities contributing to insomnia												
Depression	12	20.3%	34	50.7%	46	36.5%	20	29.0%	4	36.4%	24	30.0%
Anxiety	17	28.8%	25	37.3%	42	33.3%	27	39.1%	3	27.3%	30	37.5%
ADHD	7	11.9%	27	40.3%	34	27.0%	19	27.5%	2	18.2%	21	26.3%
Childhood Autism	4	6.8%	1	1.5%	5	4.0%	7	10.1%	2	18.2%	9	11.3%
Any comorbid Dx	23	39.0%	49	73.1%	72	57.1%	40	58.0%	6	54.5%	46	57.5%
No diagnosis (neither evidence-supported or comorbid)	29	49.2%	15	22.4%	44	34.9%	24	34.8%	5	45.5%	29	36.3%

Among the adult members with a prescription for sedative medications, 328 met the defined criteria for having long-term sedative prescriptions. Of these members, 92.1 percent of long-term sedative medications prescribed were benzodiazepines. In addition, only 27.7 percent of patients with sedative prescriptions and 32.0 percent of those long-term sedative prescriptions have documentation of CBT. More information on sedative prescriptions in adult members can be found below in **Table 6**.

Table 6: Adult patients with long-term sedative prescriptions

	All		With History of CBT	
Adult Patients with sedative prescriptions	762	%	211	%
Adult Patients with *long-term* sedative prescriptions	328	43.0%	105	49.8%
Benzodiazepines	302	39.6%	97	46.0%
Melatonin-receptor agonists	1	0.1%		0.0%
Non-benzodiazepine hypnotics	25	3.3%	8	3.8%
Melatonin		0.0%		0.0%

Discussion:

The addition of melatonin to the OHP FFS pharmacy benefit increased utilization and access for pediatric members. However, there was no evidence of impact to benzodiazepines or other sedative prescriptions from opening access to melatonin. While the proportion of paid claims for benzodiazepines did decrease, there were no additional policy changes to explain why this may have occurred. A potential benefit to benzodiazepines usage may be seen in the fact that only one member received a prescription for benzodiazepines 90 days after starting melatonin. Further studies will be needed to determine if requiring trial of melatonin could prevent new starts of benzodiazepines.

Sixty-five percent of pediatric members had insomnia or comorbidity predisposing them to insomnia. While it represents a minority, the 21 percent of members without any diagnosis remains concerning. These patients may benefit from deprescribing if they are receiving a sedative without a corresponding indication.

Many claims for melatonin were for dosages consistent with clinical practice guidelines. Average higher daily doses were seen in older adolescents, which could coincide with weight-based dosing. Based on the average doses seen in pediatric members, there are no concerns for adding quantity limits to melatonin at this time.

In adults, 43 percent of sedative prescriptions were for long-term sedatives defined as a total of more than 30 days. Among adults on long-term sedative prescriptions, only 32 percent had documentation of CBT. It is difficult to determine if coverage of insomnia would benefit many adult members since only a minority of sedative prescriptions are for long-term use, and an unknown number of prescriptions are being used for insomnia. In addition, if documentation of CBT is required for payment of insomnia medications, even fewer adult members will benefit from the additional coverage.

Limitations:

- Medicaid includes a significant proportion of members who are only transiently enrolled in FFS. Often members are quickly enrolled into a CCO upon eligibility for Medicaid and remain in FFS for only a few months. In order to accurately capture data from this population in the analysis, a baseline period of 6 months was required. However, this limitation led to several assumptions when identifying pediatric members who were starting melatonin or a sedative. Members were assumed to not be receiving a new start if they met the following criteria: had prior claims for melatonin or other sedatives paid by Medicaid. However, there is a limitation to this definition, and it is possible that members were previously paying out of pocket for sedative medication or purchasing melatonin over-the-counter.

- A significant proportion of pediatric patients were excluded because they had partially incomplete claims data due to other primary insurance or were not eligible for Medicaid for the required 6-month baseline period. After all exclusion criteria, about 7.5% of pediatric members in the pre-policy group and 5% in the post policy group were included for analysis. This study assumes that included members would still be representative of most pediatric patients prescribed melatonin or other sedatives in Medicaid.
- In order to fairly assess if the policy change had any impact on melatonin and other sedative use in pediatric members, a 3-month gap period was left between the end of the pre-policy evaluation period and the beginning of the post-policy evaluation period. It was assumed that 3 months would be long enough for providers to adjust their prescribing patterns; however, it may not have allowed for enough for such changes to occur.
- This analysis relied on evidence-supported diagnoses and conditions that have been shown to predispose children to insomnia. However, any diagnoses that are commonly accepted in clinical practice without being documented in current literature would have been excluded.
- This analysis defined long-term sedative use in adults as 30 days, based on total days' supply. This definition assumes that prescriptions totaling less than 30 days' supply are not considered long-term, regardless of the quantity or how long the prescription may last. However, it is possible that members are not taking the medication as frequently as their prescriber has allowed. In this scenario, members could be sporadically using sedative medications for many months, but would not have been included in this analysis.
- In order to find claims data for CBT, this analysis relied on a list of medical service codes. The list was based on common service codes found during preliminary research. Since the research for services codes occurred through online resources, without the consultation of a clinician or subject matter expert, it is possible that some service codes were unintentionally omitted. As such, a higher proportion of adults on long-term sedative medications may be documentation of CBT than the number portrayed in this study.
- This analysis included benzodiazepines for treatment of insomnia and other sleep disorders. However, benzodiazepines are commonly prescribed for other indications not related to sleep, including medical and dental procedures.

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Appendix 1. Data Coding

Table A1. Melatonin GSN codes

GSN	Form	Generic	Type
026076	Tablet	Melatonin	Extended-release
071898	Tablet	Melatonin	Extended-release
076846	Tablet	Melatonin	Extended-release
077022	Tablet	Melatonin	Extended-release
024665	Tablet	Melatonin	Immediate-release
039195	Tablet	Melatonin	Immediate-release
041568	Tablet	Melatonin	Immediate-release
063960	Tablet	Melatonin	Immediate-release
069202	Tablet	Melatonin	Immediate-release
081048	Tablet	Melatonin	Immediate-release
068895	Tablet Rapid	Melatonin	Immediate-release
070353	Tablet Rapid	Melatonin	Immediate-release
071356	Tablet Rapid	Melatonin	Immediate-release
075697	Tablet Rapid	Melatonin	Immediate-release
080947	Tablet Rapid	Melatonin	Immediate-release
081652	Tablet Rapid	Melatonin	Immediate-release
070234	Tablet Chew	Melatonin	Immediate-release
073498	Tablet Chew	Melatonin	Immediate-release
079871	Tablet Chew	Melatonin	Immediate-release
082032	Tablet Chew	Melatonin	Immediate-release
048015	Tablet Sublingual	Melatonin	Immediate-release
070888	Tablet Sublingual	Melatonin	Immediate-release
073509	Tablet Sublingual	Melatonin	Immediate-release
080957	Lozenge	Melatonin	Immediate-release
053232	Drops	Melatonin	Immediate-release
083165	Drops	Melatonin	Immediate-release
061740	Liquid	Melatonin	Immediate-release
071047	Liquid	Melatonin	Immediate-release
032584	Capsule	Melatonin	Immediate-release
040954	Capsule	Melatonin	Immediate-release
061738	Capsule	Melatonin	Immediate-release

Table A2. Diagnosis codes

Condition	ICD-10 Diagnosis Code
Sleep Disorders	
Behavioral insomnia of children	Z73.819
Insomnia	G47X, F51X
Delayed Sleep-Wake Phase Disorder	G47.21X
Depression	
Depressive Episode	F32X
Recurrent Depressive Disorder	F33X
Persistent Mood Affective Disorders	F34X
Anxiety	
Other Anxiety Disorders	F41X
Attention Deficit Hyperactivity Disorder	F90X
Childhood Autism	F840

Table A3. Medical service codes for CBT

Code	Description
90785	Psytx complex interactive
90791	Psytx diagnostic evaluation
90792	Psytx diagnostic evaluation with medication services
90832	Psytx with patient 30 minutes
90833	Psytx with patient with evaluation and management 30 minutes
90834	Psytx with patient 45 minutes
90836	Psytx with patient with evaluation and management 45 minutes
90837	Psytx with patient 60 minutes
90838	Psytx with patient with evaluation and management 60 minutes
90839	Psytx crisis initial 60 minutes
90840	Psytx crisis each additional 30 minutes
90845	Psychoanalysis
90847	Family psytx with patient 50 minutes
90853	Group psychotherapy
90899	Psychiatric service/therapy
9615X	Health and behavior assessment

Table A4. Error codes associated with denied claims that are excluded from the analysis

Error Code	Description
4999	THIS DRUG IS COVERED BY MEDICARE PART D
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER
513	RECIPIENT NAME AND NUMBER DISAGREE
503	DATE DISPENSED AFTER BILLING DATE
628	Other Coverage Reject Code Required for OCC 3
205	PRESCRIBING PROVIDER ID MISSING
502	DATE DISPENSED EARLIER THAN DATE PRESCRIBED
214	DATE PRESCRIBED IS INVALID
268	BILLED AMOUNT MISSING
271	HEADER TOTAL BILLED AMOUNT INVALID
269	DETAIL BILLED AMOUNT INVALID
500	DATE PRESCRIBED AFTER BILLING DATE
222	DAYS SUPPLY INVALID
221	DAYS SUPPLY MISSING
238	RECIPIENT NAME IS MISSING
1040	PRESCRIBING PHYSICIAN NOT ENROLLED
1026	PRESCRIBING PHYSICIAN ID NOT ON FILE
1001	BILLING PROV HAS NO CONTRACTS FOR DOS
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
2809	DOB IS INVALID
2804	CASE NUMBER NOT ON FILE
4014	NO PRICING SEGMENT ON FILE

Table A5. Drug definitions for other sedative drugs

Drug Category	Generic Drug Name	HSN
Benzodiazepines	Alprazolam	001617
	Chlordiazepoxide HCl	001610
	Clonazepam	001894
	Diazepam	001615
	Lorazepam	004846
	Midazolam	001619
	Oxazepam	001616
	Temazepam	001592
	Triazolam	001594
Melatonin Receptor Agonists	Ramelteon	033126
	Tamsimelteon	072007
Non-Benzodiazepine Hypnotics	Eszopiclone	026791
	Zaleplon	020347
	Zolpidem tartrate	007842

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

New Drug Evaluation: donislecel (LANTIDRA)

Date of Review: February 2024
Generic Name: donislecel-jujn

End Date of Literature Search: 12/10/23
Brand Name (Manufacturer): Lantidra (CellTrans Inc)
Dossier Received: no

Plain Language Summary:

- Type 1 diabetes mellitus (T1DM) occurs when the body does not make insulin. People who have T1DM need to inject insulin into the skin multiple times each day. Insulin helps the body absorb and use sugar from food. Without insulin, humans would not be able to survive. But, too much insulin can cause low blood sugars, called hypoglycemia, which can be dangerous. Low blood sugars can lead to confusion and even death.
- Donislecel is the first cell transplant for people with T1DM. Donislecel is made from pancreas cells that are donated from other people. These healthy pancreas cells make insulin so that people no longer need injections. Seventy percent of the 30 people that were treated with donislecel were able to stop taking their insulin when evaluated at 1 year.
- The Food and Drug Administration (FDA) only recommends donislecel for people who are not able to reach normal blood sugar levels because of repeated episodes of severe low blood sugar, even with education and efforts to control blood sugar levels.
- People that receive donislecel also have to take other medicines, called immunosuppressants, so that their body tolerates the injected treatments. These immunosuppressants are associated with a risk of side effects, such as infection and cancer.
- The Drug Use Research and Management Group recommends that the Oregon Health Authority only pay for this treatment when people aren't able to obtain normal blood sugar values and experience repeated severe low blood sugars.

Research Questions:

1. In patients with T1DM, what is the efficacy evidence for pancreatic islet cell transplant with donislecel based on important outcomes (e.g., insulin independence, hemoglobin A1c [HbA1c])?
2. In patients with T1DM, what is the evidence for harms for donislecel, related to transplant and immunosuppressive therapy?
3. Are there subpopulations of patients with T1DM for which donislecel is likely to be more or less successful?

Conclusions:

- Evidence for the efficacy of donislecel is from 2 unpublished, non-randomized, single-arm studies enrolling a total of 30 patients with T1DM.[1]
- A total of 21 patients (70%) from a combination of both studies did not require insulin for one year or longer after receiving donislecel. Eleven patients (37%) were insulin independent for 1-5 years and 10 patients (30%) did not require insulin for over 5 years.[1,2]
- At least one serious adverse reactions occurred in 90% of patients. The most common severe adverse reactions, infection and malignancy, were related to immunosuppressive therapy.

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- The Food and Drug Administration agreed that 4-5 years of insulin independence represents a clinically meaningful treatment benefit.
- There were no subpopulations that were identified as having better or worse outcomes with donislecel. The enrolled population was comprised of 100% White patients and 80% were female. The small sample size limits the ability to draw strong conclusions regarding subpopulations.

Recommendations:

- Require prior authorization (PA) for donislecel to ensure that it is used in patients in which the benefits outweigh the risks of transplant (e.g., those with T1DM with severe hypoglycemia despite intensive management and education).

Background:

The pathophysiology of T1DM is from autoimmune destruction of pancreatic islet cells. Pancreatic islet cells contain the β-cells responsible for production of insulin. Without insulin, patients suffer from hyperglycemia. If left untreated, hypoglycemia can become fatal. Managing blood glucose level in patients with T1DM is important to avoid short-term complications such as diabetic ketoacidosis as well as long-term complications such as retinopathy, nephropathy and cardiovascular disease.[3] It is important to optimize glucose control without precipitating severe hypoglycemic events (SHE). A SHE is characterized by requiring the active assistance from another person to administer carbohydrates, glucagon or take other corrective action.[2] Hypoglycemia can become unrecognized by patients who have had diabetes for an extended duration and can be masked by medications. Some individuals lose the ability to detect hypoglycemia warning signs, such as blurred vision and inability to concentrate, which can lead to more severe sequelae.[3]

The only treatment for T1DM is lifelong intensive management with the use of exogenous insulin via insulin pumps or subcutaneous injection and coordinating frequent blood glucose monitoring.[2,3] There are no available cell-based therapies for patients with T1DM other than donislecel.

Important outcomes in the management of patients with T1DM are to obtain normalized glucose levels, as measured by hemoglobin A1c (HbA1c), to prevent long-term complications associated with hyperglycemia (e.g., heart disease, renal disease, retinopathy). In the case of islet cell transplant, insulin independence is the desired outcome. Obtaining normalization of glucose levels without significant hypoglycemia is also important. The hypoglycemic (HYPO) score is an objective measure of severity of hypoglycemia comprised of the frequency, severity, and degree of unawareness of the hypoglycemia. A score of 1,047 or more is indicative of a serious problem with hypoglycemia, a score of 423 to 1,046 represents moderate problems and scores of 423 or less demonstrate less serious problems.[2]

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:

Donislecel is a cell-based therapy made from deceased allogeneic donor pancreatic islets of Langerhans (cluster of cells within the pancreas) for the treatment of T1DM in adults who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.[1] The suspension of cells help to maintain blood glucose levels through secretion of hormones in response to glucose stimulation. This is available through the Organ Procurement and Transplantation Network (OPTN) and currently only administered at the University of Illinois Hospital.[1] Each dose is from a single donor, and additional doses are derived from a different deceased donor pancreas. The strength of donislecel is dependent on the total number of islets packaged for infusion. The recommended minimum dose is 5,000 Equivalent Islet Number (EIN) per kg of body weight for initial infusion into the hepatic portal

vein.[1] Subsequent infusions, up to the 3 total, should be 4,500 EIN/kg.[1] A patient is a candidate for a second and/or third infusion, if after each infusion they are unable to achieve independence from exogenous insulin within one year of the infusion or within one year after losing independence from exogenous insulin after a previous infusion. Infusion of estimated tissue volume should not exceed 10 cc per transplant infusion.[1] The incidence of panel reactive antibody (PRA) went up, from baseline Class I PRA <20% to ≥20% after infusion, with each additional infusion, 11% of patients with one infusion, 25% of patients with two infusions, and 29% of patients with 3 infusions. Donislecel is used in conjunction with immunosuppression.

Donislecel was studied in 2 non-randomized, single-arm studies in a total of 30 adult participants. Studies are not published, and information from these trials is reported based on FDA Clinical Review.[2] Eligible participants had to have T1DM for more than 5 years with one of these additional factors:

1. Were hypoglycemic unaware, defined by plasma glucose levels of < 54 mg/dL (3 mmol/l) with the absence of adequate autonomic symptoms (patient reported)
2. Metabolic lability/instability, characterized by two or more episodes of documented severe hypoglycemia, OR two or more hospital visits for diabetic ketoacidosis over the last year
3. Complications of diabetes, despite adequate glucose control (e.g., retinopathy, nephropathy, neuropathy)

Patients enrolled in the study were a median age of 46.5 years (range of 21-67 years), 100% white and 80% female.[1] Glucose variability was measured by continuous glucose monitoring (CGM). At baseline, only 1 patient (5.5%) had a HYPO score of ≥1,047 indicating a serious problem with hypoglycemia. Three patients (16.7%) had moderate problems with hypoglycemia and 14 (77.8%) had less serious problems with hypoglycemia.[2] The median dose of islet number per infusion was 399,178 EIN.[1] In the studies, 37% of patients had 1 transplant, 40% of patients had 2 transplants and 23% of patients had 3 transplants. The primary endpoint was proportion of patients with an HbA1c of less than or equal to 6.5% and free of SHE for at least 1 year after the first and 1 year after the last islet cell infusion.[2] If the patient used insulin within a year of their last transplant and required insulin for a period not exceeding a total of 14 days, due to intercurrent illness (e.g., illness occurring during the progress of another disease) or other event, they were still considered a success. Therefore, insulin independence from 2 weeks up to each point of evaluation during the 1-year follow-up after transplant was deemed a success. Partial success was defined when each point of evaluation had all of the following during the 1-year follow-up after transplant:

- a reduction in insulin requirement that was at least 50% relative to baseline
- were present with a reduction in HbA1c that was at least a 0.3% absolute decrease from baseline, or alternatively a HbA1c ≤ 6.5%
- a reduction in hypoglycemic (HYPO) score that was no less than 50% relative to baseline or a HYPO score being 0 for the duration of evaluation

Transplant failure was defined as inadequate insulin secretion or failure of a graft to achieve full or partial success (e.g., reduction in insulin requirement, HbA1c levels, HYPO score).[2] Patients who do not achieve “success” or “partial success”, but still presented with detectable C-peptide production (e.g., any patient with basal C-peptide levels less than 0.3 ng/ml for two consecutive follow-up visits after last transplant) were considered a failure. Secondary endpoints were measurement of insulin independence, hypoglycemic episodes and glucose variability (measured by continuous glucose monitoring). Patients were followed for 52-weeks post-transplant and were asked to continue follow-up evaluations every three months for 5 to 10 years for safety and efficacy monitoring.[2]

Donislecel was used in combination with immunosuppressive therapy (**Table 2).** Immunosuppression should be continued unless life-threatening infection develops, pregnancy, or cancer requires that immunosuppression should not be used. Immunosuppression should be discontinued if the patient is dependent on exogenous insulin for 2 years after their last infusion, unless team determines that it should be continued. Exenatide (5 mcg twice daily) was also given within 60 minutes before the infusion and continued a total of 6 months after each transplant. Exenatide was found to enhance insulin secretion by the transplanted islet cells; however, 15 subjects did not receive exenatide, or received a lower dose of exenatide than specified in the protocol, so there is insufficient evidence for the use of exenatide with donislecel.[1]

Table 2. Other Drugs Administered with Donislecel in Studies 1 and 2[2]

Concomitant Medications	Study 1	Study 2
	All Patients (N=10)	All Patients (N=20)
Anakinra	1 (10%)	0 (0%)
Daclizumab	10 (100%	5 (24%)
Basiliximab	5 (10%)	19 (95%)
Mycophenolate mofetil	6 (60%)	5 (24%)
Etanercept	6 (60%)	20 (100%)
Everolimus	1 (10%)	2 (10%)
Sirolimus	10 (100%)	20 (100%)
Tacrolimus	10 (100%)	20 (100%)
Cyclosporine	1 (10%)	3 (15%)
Anti-thymocyte immunoglobulin	1 (10%)	4 (20%)
Exenatide	6 (60%)	20 (100%)

At 1 year, 20 patients (70%) experienced insulin independence (**Table 6**).[2] Combined data from both studies found 83.3% of patients were insulin independent (for any duration) (**Table 3**).[1,2] There were a total of 5 patients (17%) from a combination of both studies who did not experience insulin independence at any time point.[2] Four patients (13%) experienced insulin independence for less than one year, 36.7% of patients had 1-5 years of insulin independence and 33.3% had more than 5 years of insulin independence.[2] The duration of insulin independence did not correlate with the number of transplants received. The FDA did not identify any baseline factors that influenced the duration of insulin independence.[2] After transplant, the duration of follow-up of was the following:

- 1-5 years: 50% of patients
- 5-10 years: 40% of patients
- >10 years: 10% of patients

The mean follow-up after transplant was 3 years (0.3 to 14.5 years).

Table 3. Duration of Glycemic Control After Donislecel Infusion[1]

Total Duration Insulin Independent (years)	Patient Number	Mean	Standard Deviation	Minimum	Maximum
Study 1	10	5.1	4.2	0.2	12.8
Study 2	20	3.2	3.1	0	9.9

Clinical Safety:

Common adverse events associated with donislecel transplantation and immunosuppression are displayed in **Table 4**. Donislecel is associated with a high number of serious adverse reactions with 90% of participants having at least one.[1] Severe adverse reactions due to infusion (during and after) were: liver laceration/hematoma, hemorrhage, and intra-abdominal bleeding (13%) and elevation of portal pressure (7%). The most common severe adverse reactions related to immunosuppression were: infection (87%) and malignancy (37%).[1] Additional adverse events associated with immunosuppression are severe

infections including opportunistic infections, malignancy, and severe anemia. Graft rejection occurred more often in participants with positive T- and B-cell crossmatch between recipient serum and donor lymphocytes.[2] Due to the risk of severe infections, donislecel should be administered with pneumocystis jirovecii pneumonia (PCP) and cytomegalovirus (CMV) prophylaxis.[1] Panel Reactive Antibodies (PRA) may be increased with donislecel, which may prevent eligibility for any future renal transplant. Donislecel should not be given to people that are pregnant or have concomitant diseases or conditions that contraindicate the infusion procedure or immunosuppression.[1] Patients should be counseled on risk of teratogenicity associated with immunosuppressants and need to avoid pregnancy before committing to transplant.

Table 4. Some Common Adverse Reactions Occurring in ≥20% of Patients from Initial Transplant through 1 Year after Final Transplant[2]

Adverse Event	Patients (n=30)
Anemia	80%
Diarrhea	80%
Nausea	83%
Abnormal weight loss	73%
Headache	67%

Females of reproductive potential should have a pregnancy test prior to infusion of donislecel due to risk of fetal malformations with required concomitant medications, such as immunosuppressants.[1]

Limitations to the evidence are small, non-randomized studies in predominately female populations. Important baseline data (e.g., HbA1c and SHE) were missing which limits the ability to interpret outcome findings after transplant. There is insufficient evidence for use beyond 3 infusions.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Insulin independence
2) HbA1c level
3) Severe hypoglycemic events
4) Serious adverse events

Primary Study Endpoint:
1) Insulin independence

Table 5. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	The primary mechanism of action of is believed to be secretion of insulin by infused (transplanted) pancreatic β- cells.
Oral Bioavailability	N/A
Distribution and Protein Binding	N/A N/A
Elimination	N/A
Half-Life	N/A
Metabolism	N/A

Abbreviations: N/A = not applicable

Table 6 . Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints (Combined Results for Study 1 and Study 2)	ARR/ NNT	Safety Outcomes (Combined Results for Study 1 and Study 2)	ARR/ NNH	Risk of Bias/ Applicability
1. Study 1[2] Open-label, single-arm, Phase 1/2	1. Donislecel (1-4 allogenic pancreatic islet transplants) Follow-up: 52 weeks post transplantation	Demographics: Female: 90% Age: 46.4 years White: 100% Non-Hispanic: 100% BMI: 22 kg/m^2 HbA1c: 7.3% Mean time since diagnosis: 28 years Mean HYPO Score at baseline: 88.2 (n= 7) Key Inclusion Criteria: - Age 18-65 years - T1DM for more than 5 years and at least one of the following despite intensive insulin management: 1. Reduced awareness of hypoglycemia was defined as the absence of adequate autonomic symptoms at plasma glucose levels of <54 mg/dL reported by patient 2. Metabolic lability/instability defined as 2 or more episodes of documented severe hypoglycemia or 2 or more hospital visits for diabetic ketoacidosis over the last year 3. Secondary complications of diabetes: retinopathy, nephropathy, or neuropathy Key Exclusion Criteria: - HbA1c >12% - cardiac disease - active alcohol or substance abuse, including cigarette smoking - psychiatric disorders - non-adherence - previous transplant - Hepatitis C, hepatitis B or HIV - Other uncontrolled disease states - Anticoagulant therapy (excluding low dose aspirin after transplant)	ITT: 1. 10 PP: 1. 10 Attrition: 0	Primary Endpoint: Insulin independence from 2 weeks after the last transplant based on a composite endpoint with an HbA1c of ≤6.5% and absence of SHE through 1 year (without insulin): 1. 21 (70%) Secondary Endpoint: HbA1c >6.5% at 1 year: 1. 5 (16.7%) Any SHE at 1 year: 1. 7 (23.3%)	N/A	Anemia: 1. 24 (80%) Diarrhea: 1. 24 (80%) Discontinuations: 1. 2 (7%) Severe Hypoglycemia: 1. 1 (3%)	N/A	**Risk of Bias (low/high/unclear)**: Studies were not published and risk of bias could not be fully assessed. Selection Bias: (high) not randomized. Performance Bias: (high) Open-label design. Baseline SHE values were missing for 83.3% of participants and 20% of baseline HbA1c values were missing (combined study population). Detection Bias: (high) Analysis of data was not blinded. Analysis was not described. Attrition Bias: (low) There was little to no attrition. Reporting Bias: (low) Data was reported by the FDA. **Applicability**: Patient: Results are most applicable to women with T1DM who are in their 4th decade of life who are White and non-Hispanic. Exclusion criteria limit applicability in people with any comorbid conditions. Intervention: Doses were appropriate based on previous studies. Comparator: Comparison to insulin would be helpful to contextualize HbA1c changes and hypoglycemia rates. Outcomes: Insulin independence is an appropriate outcome. Setting: Single-center at University of Illinois at Chicago.

2. Study 2[2] Open-label, single-arm, Phase 3	1. Donislecel (1-4 allogenic pancreatic islet transplants) delivered via the portal vein with a target total of 10,000 IE/kg (up to 3 injections could have been administered if insulin independence, or other glycemic goals were not achieved by the fourth week after each infusion) Follow-up: 52 weeks post transplantation	Demographics: Female: 75% Age: 47 years White: 100% Non-Hispanic: 95% BMI: 24 kg/m^2 HbA1c: 7.4% Mean time since diagnosis: 29.4 years HYPO Score at baseline: 428.5 (n=12) Key Inclusion Criteria: - Age 18-75 years - T1DM for more than 5 years and at least one of the following despite intensive insulin management: 1. At least 1 episode of severe hypoglycemia in the past 3 years* 2. Reduced awareness of hypoglycemia, as defined as the absence of adequate autonomic symptoms at plasma glucose levels of <54 mg/dL reported by patient Key Exclusion Criteria: - HbA1c >12% - cardiac disease - active alcohol or substance abuse, including cigarette smoking - psychiatric disorders - non-adherence - Hepatitis C, hepatitis B or HIV - Other uncontrolled disease states - Current smoker	ITT: 1. 20 PP: 1. 18 Attrition: 1. 2	See study above	N/A	See study above	N/A	**Risk of Bias (low/high/unclear)**: See study above.

Key: * Severe hypoglycemia as symptoms compatible with hypoglycemia in which the patient required the assistance of another person and was associated with either a blood glucose level of <50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.
Abbreviations [alphabetical order]: ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; EIN = equivalent islet number; FDA = Food and Drug Administration; HbA1c = hemoglobin A1c; HYPO = hypoglycemia; ITT = intention to treat; kg = kilogram; mITT = modified intention to treat; N = number of subjects; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; SHE = severe hypoglycemia event; T1DM = type 1 diabetes mellitus.

References:

1. Lantidra (donislecel-juju) [prescribing information]. Chicago, IL; Cell Trans Inc. June 2023.

2. Food and Drug Administration. Clinical Review Memo - Lantidra. Available at: https://www.fda.gov/media/170827/download?attachment. Accessed on November 26, 2023.

3. ElSayed N, Allepo G, Aroda V, et al. Pharmacological Approaches to Glycemic Treatment: Standards of Care in Diabetes - 2023. Diabetes Care 2023;46: S140-S157.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LANTIDRA (donislecel-jujn) Allogeneic Pancreatic Islet Cellular Suspension for hepatic portal vein infusion
Initial US Approval: 2023

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

LANTIDRA is an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. Use in conjunction with concomitant immunosuppression. (1)

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

For infusion into the hepatic portal vein only.

- Do not irradiate.
- Do not use leukodepleting filters.
- Do not use if product time exceeds 6-hours post product release or if temperature is not maintained between 15 and 25° C
- The recommended minimum dose is 5,000 equivalent islet number (EIN) per kg patient body weight for initial infusion (transplant) and 4,500 EIN/kg for subsequent infusions (same recipient). (2.1)
- Administer cells through the hepatic portal vein (2.3). The estimated tissue volume should not exceed 10 cc per transplant infusion. (2.1)

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

The dosage form is a cellular suspension. Dosage strength depends on the total number of islets packaged for infusion, which is reported on the container label and associated documents. (3)

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

LANTIDRA is contraindicated in patients for whom immunosuppression is contraindicated. (4)

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

- Risks from Concomitant Immunosuppression: Increased risk of severe infections including opportunistic infections, malignancy, and severe anemia. Monitor closely. Administer PCP and CMV prophylaxis. (5.1)
- Procedural Complications: Liver laceration and hemorrhage have occurred. Monitor for bleeding, portal hypertension, and portal vein thrombosis during and immediately following infusion. (5.2)
- Increased Risk of Graft Rejection: Patients with a positive T- and B-cell crossmatch between recipient serum and donor lymphocytes may be at increased risk for graft rejection. (5.3)
- Transmission of Donor-Derived Infections: Monitor for signs of infection following infusion and treat accordingly. (5.4)
- Panel Reactive Antibodies (PRA): Product administration may elevate PRA and negatively impact candidacy for renal transplant. (5.5)

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

Ninety percent (90%) of subjects had at least one serious adverse reaction. (6.1)
The major causes are attributed to:

- Infusion procedure
  - liver laceration/hematoma, hemorrhage, and intra-abdominal bleeding (13%)
  - elevation of portal pressure (7%)
- Immunosuppression
  - Infection (87%)
  - Malignancy (37%)

To report SUSPECTED ADVERSE REACTIONS, contact CellTrans at 1-800-500-1617 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 06/2023

Lantidra (donislecel)

Goal(s):

- To ensure appropriate use of donislecel in patients with T1DM.

Length of Authorization:

1. Up to 3 infusions

Covered Alternatives:

- There are no other approved allogenic pancreatic islet cellular therapies.

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.
3. Is the patient 18 years or older and less than 65 years of age?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Does the patient have a diagnosis of type 1 diabetes mellitus (T1DM)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the patient unable to meet HbA1c goal due to current repeated episodes* of severe hypoglycemia (e.g., symptoms consistent with hypoglycemia which required assistance of another person and was associated with a blood glucose of <50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration) despite intensive diabetes management (e.g., self-monitoring of glucose values no less than a mean of 3 times a day averaged over each week and by administration of 3 or more insulin injections each day or insulin pump therapy) and education?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been informed that they will not be a candidate for future transplants (e.g., kidney) after receiving donislecel?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; inform patient of risk.
7. Has the patient received 3 prior infusions of donislecel?	**Yes:** Pass to RPh. Deny; medical appropriateness. Labeling recommends a maximum of 3 infusions.	**No:** Approve for up to 3 infusions Document number of infusions.

* Current repeated episodes identifies a patient population at risk for severe hypoglycemic events on an ongoing basis.

P&T/DUR Review: 2/24 (KS)
Implementation: TBD

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

Drug Class Update: Inhalers for Asthma and COPD

Date of Review: February 2024

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

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

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

Plain Language Summary:

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

Research Questions:

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

Conclusions:

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

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

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

Recommendations:

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

Summary of Prior Reviews and Current Policy:

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

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

Background:

Asthma

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

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

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

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

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

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

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

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

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

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

Chronic Obstructive Pulmonary Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

COPD Findings

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

New Guidelines:

<u>Global Initiative for Asthma - 2023 Update</u>

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

Asthma Medication Terminology

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

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

Treatment Recommendations

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

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

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

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

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

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

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

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

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

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

Summary of GINA 2023 Medication Recommendations and Strength of Evidence

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

Global Initiative for Chronic Obstructive Lung Disease – 2023 Update

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

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

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

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

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

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

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

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

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

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

Summary of GOLD 2023 Recommendations:
Bronchodilators in COPD

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

Anti-inflammatory Therapy in Stable COPD

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

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

New Formulations or Indications:

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

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

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

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

Table 10. Description of Randomized Comparative Clinical Trials.

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

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

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

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

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

				95% CI 0.58 to 0.87 P=0.001	

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

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Appendix 1: Current Preferred Drug List

Long-Acting Muscarinic Antagonists (LAMA)

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

Beta-Agonists, Inhaled Long Acting (LABA)

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

Beta-Agonists, Inhaled Short-Acting (SABA)

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

Corticosteroids, Inhaled (ICS)

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

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

Corticosteroids/SABA & LABA Combinations, Inhaled

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

LAMA/LABA Combination, Inhalers

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

Appendix 2: Abstracts of Comparative Clinical Trials

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 3: Medline Search Strategy

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

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

Appendix 4: Key Inclusion Criteria

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

Inhaled Corticosteroids (ICS)

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

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred ICS products

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

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

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

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

Long-acting Beta-agonists (LABA)

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

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred LABA products

Covered Alternatives:

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

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

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

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

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- All non-preferred LAMA/LABA and LAMA/LABA/ICS products

Covered Alternatives:

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

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

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

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

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

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Drug Class Update with New Drug Evaluation: Drugs for Duchenne Muscular Dystrophy

Date of Review: February 2024

Date of Last Review: August 2021
Dates of Literature Search: 01/01/2021 – 11/20/2023

Generic Name: delandistrogene moxeparvovec-rokl
vamorolone

Brand Name (Manufacturer): Elevidys (Sarepta Therapeutics, Inc.)
Agamree (Santhera Pharmaceuticals)

Dossier Received: yes

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

Purpose for Class Update:
The purpose of this update is to review place in therapy for 2 agents that were recently approved by the Food and Drug Administration (FDA).

Plain Language Summary:

- People who have Duchenne muscular dystrophy (DMD) slowly loose muscle strength and ability to walk over time.
- Steroids are a type of medicine that can extend the time people are able to walk and delay the need for a wheelchair.
- Prednisone, deflazacort, and vamorolone are 3 steroids that providers can prescribe for people with DMD. Studies do not show that one steroid improves muscle function better than another. All steroids have long-term side effects, and it is difficult to estimate how often these side effects occur. But, some studies show that the amount of people who have a side effect varies based on the medicine.
    - Deflazacort may cause less weight gain than prednisone.
    - Deflazacort may cause more vision problems than prednisone.
    - Vamorolone and prednisone appear to have similar side effects after about 6 months. We need more long-term data to verify if these medicines have different side effects.
- In controlled studies, other medicines have not shown that they improve symptoms or change the course of the disease.
- The Food and Drug Administration (FDA) recently approved a new medicine called a gene therapy for people with DMD. The goal of this medicine is to delay worsening muscle symptoms for people with DMD. However, people who took this medicine had similar muscle function compared to those who did not get the treatment after about 1 year.
- The FFS Oregon Health Plan will currently pay for prednisone. Before Oregon FFS Medicaid will pay for other medicines in people with DMD, the provider must send in additional information to the Oregon Health Authority. This process is called prior authorization (PA).
- We recommend adding new medicines for DMD to this policy.

Author: Sarah Servid, PharmD

Research Questions:

1. What is the comparative efficacy or effectiveness of therapies for Duchenne muscular dystrophy (DMD) based on symptom improvement, muscle or pulmonary function, quality of life, or disease progression?
2. What is the comparative safety of therapies for people with DMD?
3. What is the efficacy and safety of vamorolone compared to other corticosteroids for the treatment of people with DMD?
4. What is the evidence evaluating efficacy and safety of delandistrogene moxeparvovec for people with DMD?
5. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from drugs for DMD?

Conclusions:

- This class update includes one systematic review, evaluations of 2 new drugs, and one comparative randomized controlled trial (RCT).
- The systematic review identified insufficient evidence that exon skipping therapies improve muscle or pulmonary function compared to standard of care.[1] Evidence was limited by lack of controlled trials. Confirmatory, randomized placebo-controlled trials for exon skipping therapies have not been completed.
- A new corticosteroid, vamorolone, was approved by the Food and Drug Administration (FDA) for DMD based on a single, placebo-controlled, active-comparator RCT.
    - Compared to placebo at 24 weeks, vamorolone 6 mg/kg/day improved multiple motor function tests including the time to stand from a supine position (difference in velocity of 0.06 rises/second; 95% CI 0.02 to 0.10; p=0.002) and the distance walked in 6 minutes (mean difference 41.6 meters; 95% CI 14.2 to 68.9) and mean time to run or walk 10 meters (mean difference of 0.4 miles/hour or 0.24 meters/second; 95% CI 0.09 to 0.39; p=0.002) based on low quality evidence.[2] These differences achieved values thought to be related to minimum clinically important changes referenced in the literature.
    - Compared to prednisone, vamorolone had similar motor function changes in people with DMD over 24 weeks based on low quality evidence.[2] Vamorolone has similar safety concerns as other corticosteroids.[2,3] Safety concerns include immunosuppression, alterations in endocrine, cardiac and renal function, behavior and mood disturbances, effects on bone, delays in growth, and ophthalmic effects.[4] There is insufficient information to evaluate whether vamorolone and prednisone have different effects on risk of fracture, growth, or development in people with DMD.[3]
- A trial evaluating use of corticosteroids in people with DMD given daily deflazacort and prednisone given daily have comparable muscle and pulmonary function after 3 years.[5] Daily corticosteroid regimens were better at preserving muscle function than intermittent prednisone use.[5]
- There is insufficient evidence that the gene therapy, delandistrogene moxeparvovec, improves muscle function in ambulatory patients 4 to 7 years of age with DMD over 48 weeks compared to placebo.[6] There was no statistical difference in the North Star Ambulatory Assessment (NSAA) score at 48 weeks with delandistrogene moxeparvovec compared to placebo (change from baseline of 1.7 vs. 0.9 points; least square mean difference [LSMD] 0.8; 95% confidence interval [CI] -1.03 to 2.67; p=0.37).[6] Secondary timed motor function tests were also no different between groups.[6] FDA approval was based on a post-hoc, subgroup analysis in people 4-5 years of age.
- Safety concerns identified with this gene therapy include acute liver injury, thrombocytopenia, immune-mediated myositis, and myocarditis.[7] Prednisone 1 to 1.5 mg/kg/day is administered one day prior to treatment and for 60 days post-treatment to decrease the risk of an immune response.[7] Therapy is contraindicated in patients with deletions involving exon 8 or 9, and patients with deletions in exons 1 to 17 or exons 59 to 71 of the DMD gene may be at increased risk for myositis.[7] Patients administered delandistrogene moxeparvovec also demonstrated a persistent immune response to the viral capsid which is expected to cross-react with other vectors of different serotypes and could preclude use of any future gene therapy.[8]

Recommendations:

- Implement prior authorization criteria for delandistrogene moxeparvovec to limit use to the FDA approved indication.
- Update prior authorization criteria to include all non-preferred corticosteroids for DMD.
- No changes to the preferred drug list (PDL) are recommended for corticosteroids based on clinical evidence. Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

Therapies approved by the United States (US) Food and Drug Administration (FDA) for treatment of DMD were last reviewed by the Pharmacy and Therapeutics (P&T) Committee in February and August 2021.

- Corticosteroids are recommended as a first-line treatment for patients with DMD. Prior reviews have identified insufficient evidence to determine differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions.[9,10] Evidence was limited by small sample sizes, high or unclear risk of bias, incomplete outcome reporting, and inadequate data in a population of US patients.[9,10]
- Exon-skipping treatments were approved by the FDA based on changes in dystrophin protein from baseline, and confirmatory studies have not been completed. Current evidence demonstrates no difference in motor function outcomes for exon-skipping therapies (e.g., casimersen, eteplirsen, golodirsen, viltolarsen) compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes.
- Prior authorization (PA) is currently required for deflazacort and all target therapies for DMD to ensure medically appropriate use (see **Appendix 2**). Prednisone is available without PA.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. DMD primarily affects males and is the most common type of muscular dystrophy with an estimated worldwide prevalence of 1.7 to 4.2 in 100,000 patients.[11] In the US, it is estimated that Duchenne and Becker muscular dystrophies may affect 1.4 to 2 in 10,000 males ages 5 to 9 years,[11,12] and the estimated incidence of new DMD patients is 1 in approximately 5000 male births.[13] Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Disease progression varies considerably based on individual factors, and patients with Becker muscular dystrophy generally have less severe symptoms than people with DMD. Long-term complications for people with DMD include respiratory failure, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death at an early age.[11] In a recent systematic review assessing median survival of patients with DMD, improved trends in survival over time were identified which was attributed to improvements in supportive care, including use of ventilator support, leading to a decrease in respiratory-associated deaths in this population.[14] Age of death in patients in earlier decades (e.g., 1960s-1970s), was significantly earlier than age of death for patients who died in more recent decades.[14] The pooled median survival was 29.9 years (95% CI 26.5 to 30.8) in patients with ventilator support compared to 19 years (95% CI 18 to 20.9) in patients without ventilator support.[14]

There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Non-pharmacological therapies are often essential in disease management, and include physical therapy and use of support devices such as braces and wheelchairs.[11] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[11] Available drug treatments include corticosteroids and exon-skipping therapies. Guidelines from the American Academy of Neurology recommend initiation of corticosteroids, either deflazacort or prednisone, as first-line treatment for ambulatory children with a decline in motor function to delay loss of ambulation, preserve pulmonary function, and reduce risk of scoliosis.[11,15] Corticosteroids are often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.[11] Some of the most common steroid regimens include prednisone 0.75 mg/kg/day, deflazacort 0.9 mg/kg/day, or intermittent prednisone 0.75 mg/kg for 10 day on and 10 days off for people unable to tolerate daily dosing.[5]

Exon-skipping therapies have been approved based on changes in dystrophin protein. The theoretical goal of these therapies is to modify mRNA splicing and increase the amount of dystrophin protein in cells, thereby correcting the underlying disease process. Using this mechanism, a truncated dystrophin protein is formed. While preclinical animal studies indicate truncated dystrophin can be functional, the level of function associated with the truncated protein is unknown and may vary depending on the inherited mutation.[16] Each therapy is intended to target a specific mutation. Eteplirsen was approved in 2016 for DMD with mutations amenable to exon 51 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.[17] In 2019 and 2020, golodirsen and viltolarsen were approved for patients with mutations amenable to exon 53 skipping (thought to represent about 8% of the DMD population or approximately 1200 patients in the US).[18] Most recently, casimersen was approved for patients with mutations amenable to exon 45 skipping. All therapies have the same mechanism of action and are administered as weekly intravenous infusions.

While eteplirsen and golodirsen have shown a slight increase in dystrophin (with increased dystrophin levels remaining at less than 1% of normal), the impact of these therapies on clinical outcomes had not been demonstrated in randomized controlled trials.[19,20] In the trial used for eteplirsen approval (n=12), there was no difference observed in the 6-minute walk test (6MWT) at 24 or 48 weeks compared to placebo. Similarly, there are no published, placebo-controlled studies evaluating functional outcomes with golodirsen or casimersen, and FDA review of available clinical outcomes identified no substantial difference from natural history data.[18] While subsequent follow-up studies have evaluated pulmonary, cardiac, and muscle function in this population, they are limited by their single-arm observational design, small sample size, and lack of comparator groups or comparison to historical control.[21-24] Because natural history studies have shown that disease progression with DMD varies significantly based on a variety of individual patient factors, these uncontrolled or historical-controlled studies have limited utility in evaluating drug efficacy.[8] Without adequate randomization, studies cannot control for unknown confounding factors which may impact disease progression. Similarly, risk of performance and detection bias is increased for unblinded and uncontrolled studies that evaluate motor function tests since results are highly dependent on procedure (method of administration) and motivation of the patient. Data from open-label studies generally show greater improvement than data from blinded studies because open-label studies are unable to control for differences in test administration and patient effort.[8] Confirmatory post-marketing, randomized trials have not been completed for any exon skipping therapies.

There is currently no consensus on the minimum change in dystrophin level that may result in a clinical improvement, and available thresholds cited in the literature are currently based on expert opinion. In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[25] Experts suggest that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[25] Some experts suggest that very minimal improvements in dystrophin level may constitute a beneficial change while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[25,26] In patients with Becker muscular dystrophy, a less severe form of muscular dystrophy, dystrophin protein levels are on average 80% of normal.[25] An FDA analysis evaluating the change in 6MWT per year and dystrophin level changes associated with golodirsen failed to demonstrate a positive correlation (R=0.14), indicating that small increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.[18]

Clinically important outcomes in DMD include morbidity, mortality, disease progression, motor function, and improvements in motor, pulmonary, or cardiac symptoms. There are multiple methods used assess motor function and strength in patients with DMD including timed functional tests scoring tools. For example, the North Star Ambulatory Assessment (NSAA) is a 17-item scale designed for patients able to ambulate at least 10 meters (total score range 0 to 34).[27,28] It evaluates various functional assessments including standing, hopping, climbing stairs, and rising from the floor. Individual items are rated on a 0 to 2 scale based on ability to perform the test normally (2), able to perform the test with modifications or assistance (1), and inability to perform the test (0). The minimum clinically important difference in NSAA score has not been established. In people with DMD, natural history studies have shown that, with standard of

care alone, muscle function usually continues to improve in patients who are 4 to 6 years of age.[8] In 395 patients identified from the North Star Clinical Network database, NSAA scores increased by about 3 points per year until an average of 6.3 years (peaking at an NSAA score of 26) and declined by about 3 points per year for subsequent years.[8] However, there was significant heterogeneity among patients. In people with DMD, NSAA scores had decreased to less than or equal to 5 points in about 25% of people by age 10, in 35% of people by age 12, in 21% of people by age 14, and scores remained greater than 5 points in 19% of people beyond 15 years of age.[8]

Other standard timed functional tests include time to climb 4 stairs, time to walk 10 meters, time required to stand from a supine position, and the 6MWT which evaluates distance traveled in 6 minutes.[29] One publication, with notable potential conflicts of interest with a drug manufacturer, correlated clinician-rated scores of disease severity to changes in timed functional tests to define minimum clinically important differences (MCID) for ambulatory patients with DMD.[30] Authors use data from natural history studies to compare times on these functional tests to differences of at least one point on the Vignos lower extremity scale.[30] The Vignos scale is a validated 8 item clinician-rated score which evaluates a patient's ability to walk, rise from a chair, and climb stairs with or without assistance. Scores range from one (walks and climbs stairs without assistance) to 4 (walks unassisted and rises from chair but cannot climb stairs) to 8 (participant is in bed at all times).[30] They concluded that in the 10 meter walk test, a decline of 0.21 meters/second corresponded to a one point change in the Vignos scale over 12 months.[30] Similarly minimum differences of 0.023 rises/second in the time to stand from supine and 0.035 tasks/second in the time required to climb 4 stairs corresponded to one point change on the Vignos scale over 12 months for patients with DMD who are ambulatory.[30] However, these MCID values may vary depending on the baseline ambulatory function of a population. In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.[24,31,32] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[29] NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.[28] The NSAA is generally considered a more comprehensive measure of functional status compared to other functional outcomes. Like all motor function assessments, NSAA score is often very dependent on motivation.[25]

Pulmonary function is often evaluated during clinical trials using spirometry. In patients with DMD, current evidence demonstrates a gradual decline in pulmonary function tests beginning around 5 years of age (about 4-7% per year of percent predicted forced vital capacity [FVC] and peak expiratory flow [PEF]).[33,34] However, there is currently only limited data to correlate decline in percent predicted FVC or PEF to clinical outcomes such as need for mechanical ventilation or airway clearance.[33]

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

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

Systematic Reviews:
A 2022 DERP systematic review evaluated exon-skipping therapies for DMD.[1] The review evaluated evidence from RCTs, uncontrolled interventional studies and cohort studies with at least 20 participants published through February 2022. Clinical outcomes in interest included adverse events, mortality, and tests for cardiac, pulmonary and motor function. The review identified 11 studies evaluating eteplirsen (n=6), golodirsen (N=1), viltolarsen (N=3), and casimersen (n=1).[1] Most of the data was from non-randomized and uncontrolled studies or studies with only a historical control. Only one placebo-controlled RCT was identified for each drug, and only one RCT (for eteplirsen) evaluated clinical outcomes of interest compared to placebo. Evidence was graded as insufficient for all safety and efficacy outcomes reflecting substantial uncertainty in the treatment effects.[1]

- Motor function:
  - In the single RCT evaluating effectiveness of eteplirsen compared to placebo, motor function (assessed with the 6MWT) declined from baseline with no difference compared to placebo.[1]
  - In uncontrolled studies for eteplirsen and golodirsen, motor function declined from baseline with no comparable control group to determine if decline was slower with treatment.[1]
  - In uncontrolled studies of viltolarsen, there were mixed results for motor function. In one study, motor function improved or remained stable at 25 weeks, and motor function declined over 24 weeks in another study.[1] There were differences in age between participants enrolled in these trials, which may explain some of the observed variability in motor function.
  - No identified studies evaluated motor function for casimersen.[1]
- Pulmonary function:
  - In 5 uncontrolled studies of eteplirsen, pulmonary function declined from baseline with no comparable control group to determine if decline was slower with eteplirsen.[1] Similar decline was observed in one uncontrolled study of golodirsen.[1]
  - No identified studies evaluated pulmonary function for viltolarsen or casimersen.
- Adverse events:
  - In the single RCT evaluating eteplirsen compared to placebo, there was no difference in adverse events between groups.[1]
  - In uncontrolled studies, most participants experienced at least one adverse event, but few serious adverse events were reported.[1]
  - There were no deaths reported during these studies.[1]

New Guidelines:
No new high-quality guidelines were identified since the last review.

New Formulations or Indications:
No new formulations or expanded indications were identified since the last review.

New FDA Safety Alerts:
FDA labeling for casimersen (Amondys 45®) was updated in March 2023 to include risk of hypersensitivity reactions including angioedema and anaphylaxis based on post-marketing reports.[35] Similar language is also included in FDA labeling for eteplirsen (Exondys 51®).[19]

Randomized Controlled Trials:

A total of 40 citations were manually reviewed from the initial literature search. After further review, all except one RCT was excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). This trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Guglieri, et al. 2022.[5] NCT01603407 DB, PG, RCT N=196 Duration: 3 years	1. Prednisone 0.75 mg/kg daily 2. Deflazacort 0.9 mg/kg daily 3. Prednisone 0.75 mg/kg intermittent (10 days on/10 days off)	Genetically confirmed DMD, age 4 to 7 years, who were treatment-naïve to corticosteroids Jan 2013 to Oct 2019 32 clinics in 5 countries (Canada, Germany, Italy, the UK, and the US). 42% were from the US.	Composite of: • Rise from floor velocity • FVC • Participant/ parent TSQM global satisfaction score Values were averaged for all follow-up visits through 36 months. Follow-up visits occurred at 3 months, 6 months, then every 6 months until 3 years.	Rise from floor (rises/s) 1. 0.236 (95% CI 0.219 to 0.253) 2. 0.240 (95% CI 0.223 to 0.258) 3. 0.180 (95% CI 0.163 to 0.197) 1 vs. 2: MD−0.004 (95% CI −0.03 to 0.02); NS 1 vs. 3: MD 0.06 (95% CI 0.03 to 0.08); p=0.003 2 vs. 3: MD 0.06 (95% CI 0.03 to 0.09); p=0.017 FVC (liters) 1. 1.44 (95% CI 1.38 to 1.50) 2. 1.40 (95% CI 1.34 to 1.46) 3. 1.46 (95% CI 1.40 to 1.52) 1 vs. 2: MD 0.04 (95% CI −0.06 to 0.14); NS 1 vs. 3: MD −0.02 (95% CI −0.12 to 0.08); NS 2 vs. 3: MD −0.06 (95% CI −0.16 to 0.04); NS TSQM global satisfaction score (range 0-100) 1. 71.2 (95% CI 66.8 to 75.7) 2. 67.8 (95% CI 63.2 to 72.4) 3. 65.1 (95% CI 60.6 to 69.5) 1 vs. 2: MD 3.5 (95% CI −3.7 to 10.6); NS 1 vs. 3: MD 6.2 (95% CI −0.9 to 13.2); NS 2 vs. 3: MD 2.7 (95% CI −4.4 to 9.8); NS Secondary motor function outcomes (6MWT, 10m run/walk time, NSAA score) were not different for daily regimens, but were improved with daily regimens compared to intermittent dosing.	*There was no difference in primary or secondary motor outcomes for daily deflazacort or prednisone. Participants on daily regimens had improved motor outcomes compared to intermittent prednisone dosing.* Attrition was similar between groups (14%). Medication supply issues necessitated a temporary switch to prednisone for 74 people in 2017 and unblinding of 4 participants in the intermittent prednisone group. Of 229 people screened, 196 were randomized. Most common reason for ineligibility was inability to maintain reproducible FVC (10%). Most participants (74-90%) in each group identified as White. 14-21% identified as Hispanic; other races were underrepresented. AEs that were ≥5% more frequent with daily prednisone vs. deflazacort: URI, abdominal pain, weight gain, influenza, skin papilloma. AEs that were ≥5% more frequent with daily deflazacort vs. daily prednisone: musculoskeletal pain, sleep disturbance, limb injury, joint pain, cataracts.

Abbreviations: 6MWT = 6-minute walk test; AE = adverse events; CI = confidence interval; DB = double blind; DMD = Duchenne muscular dystrophy; FVC = forced vital capacity; m = meter; MD = mean difference; NSAA = North Star Ambulatory Assessment; PG = parallel group; RCT = randomized controlled trial; s = second; TSQM = treatment satisfaction questionnaire for medication; UK = United Kingdom; URI = upper respiratory infection; US = United States

NEW DRUG EVALUATION: Vamorolone

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

Clinical Efficacy:
Vamorolone is a corticosteroid which was FDA approved for the treatment Duchenne muscular dystrophy in people at least 2 years of age.[4] The recommended maintenance dose is 6 mg/kg/day which can be titrated down based on tolerability. The primary trial used for FDA approval was a multicenter phase 2b trial evaluating vamorolone 6 or 2 mg/kg/day compared to prednisone 0.75 mg/kg/day or placebo over 24 weeks (**Table 4**).[2] Enrolled patients (n=121) were 4 to 7 years of age and identified primarily as White and non-Hispanic.[2] Pharmacology data from an open-label study was used to support FDA-approval down to 2 years of age.[3] Enrolled patients had to be able to walk unassisted and stand from a supine position in less than 10 seconds. People were excluded if they had a variety of comorbid conditions including symptomatic cardiomyopathy, immunosuppression, diabetes, or history of systemic fungal/viral infections.[2]

The trial used adequate methods for randomization and allocation concealment, but groups were small and had imbalances in baseline characteristics which could impact results. In particular, patients randomized to prednisone had better motor function tests than those randomized to vamorolone.[2] There were also clinically important differences in the 6MWT for patients randomized to placebo compared to vamorolone groups (placebo 355 m vs. vamorolone 313 m), and mean values for other motor function tests were slightly better than vamorolone 6 mg/kg group, though the exact impact of these differences is unknown.[2] The trial used a double dummy design, but the specific methods used to blind treatments was not reported making risk for performance and detection bias unclear. Accommodations were also made during the COVID pandemic in order to collect some tests remotely. About 10% of 24-week assessments for time to stand from a supine position were conducted remotely by family and video recorded for assessment by providers.[2] Secondary outcomes were not collected during the pandemic for 15% (n=17) of 6MWT and 12% (n=14) of assessments for time to run/walk 10 meters.[2] Imputation methods for missing data were not reported leading to unclear risk for attrition bias for secondary outcome measures. However, attrition rates were similar between groups and multiple sensitivity analyses to assess the impact of missing data confirmed the results from the primary analyses.[3]

The primary outcome was the time to stand from supine with vamorolone 6 mg/kg/day compared to placebo (measured in velocity [rises per second]). A variety of other motor function tests were evaluated in the study including the 6MWT, time to run or walk 10 meters, NSAA, and time to climb 3 stairs. Strength assessments and parent-reported outcomes were also evaluated. Secondary outcomes were analyzed in a hierarchical testing method. At 24 weeks, the time to stand from a supine position was improved with vamorolone 6 mg/kg/day (mean change of 0.05 rises/s) compared to placebo (mean change of -0.01 rises/s; difference 0.06 rises/s; 95% CI 0.02 to 0.10; p=0.002).[2] Similar improvement was observed for 2 mg/kg/day compared to placebo. The 6MWT was improved with both vamorolone doses compared to placebo with mean differences of 41.6 m (95% CI 14.2 to 68.9) and 37.1 (95% CI 9.6 to 64.7) for 6 and 2 mg/kg/day, respectively.[2] These results meet thresholds for clinically important differences that are referenced for the 6MWT (MCID of 30 m) and time to stand from supine (MCID 0.02 rises/s), but differences in baseline motor function assessments decrease certainty that these differences are due to treatment alone. Vamorolone 6 mg/kg/day also had improved time to run/walk 10 meters compared to placebo (mean difference of 0.4 miles/hr or 0.24 m/s; 95% CI 0.09 to 0.39; p=0.002), but

results for the 2 mg/kg/day group were not statistically significant compared to placebo.[2] Other motor function outcomes were considered exploratory based on the hierarchical testing pattern. Changes in motor function tests were apparent after 6 weeks of treatment and continued to improve over 24 weeks.[2] Subgroup analyses based on age, race, country, and baseline time to stand from supine were generally consistent with the overall treatment effects for motor outcomes.[3]

Specific results for motor function tests were not reported for prednisone, but were described as no different than vamorolone 6 mg/kg/day.[2] Vamorolone 2 mg/kg/day was less effective than prednisone 0.75 mg/kg/day for time to run/walk 10 meters and time to climb 3 steps, but had similar outcomes for time to stand from supine, 6MWT, and NSAA scores.[2]

Limitations in the evidence include lack of long-term efficacy data and lack of data for patients with lower functional scores. Corticosteroids are generally recommended as a first-line treatment option for patients with DMD to prevent disease progression and preserve motor function. This study only included participants who were 4 to 7 years of age, and the efficacy of vamorolone in people with more progressive disease is unknown. Prednisone and deflazacort are the most common corticosteroids used in people with DMD and there are no direct comparisons to deflazacort. Specific results for prednisone were not analyzed in this study and comparisons were described only generally. People who identified with a non-White racial group were underrepresented in this study.

Clinical Safety:
Vamorolone has many of same adverse events and safety concerns as other corticosteroids. Warnings and precautions for all corticosteroids include alterations in endocrine function (e.g., Cushing's syndrome, hyperglycemia and adrenal insufficiency with withdrawal), immunosuppression and effects on vaccine efficacy and safety, behavior and mood disturbances, effects on bones, ophthalmic effects, delayed growth and development, changes in cardiovascular and renal function, gastrointestinal perforations, Kaposi's sarcoma, myopathy, and thromboembolic events.[4] *In vitro* studies have suggested that vamorolone has some activity as a mineralocorticoid antagonist. However, there is insufficient data from clinical studies to demonstrate that risk for cardiovascular or renal adverse effects differ with vamorolone compared to other corticosteroids.[3]

The phase 2b trial also evaluated laboratory markers of bone turnover. These markers indicate that, like other corticosteroids, vamorolone is associated with increased risk of bone turnover and fracture risk in a dose dependent manner.[3] This is supported by data from open-label extension studies in which bone fractures occurred in 2% (n=2) of patients receiving vamorolone 2 mg/kg/day and 7% (n=7) of patients receiving 6 mg/kg/day.[3] Two patients (2%) treated with vamorolone 6 mg/kg/day had spinal compression fractures in the study extension period.[3] Compared to prednisone, patients treated with vamorolone had a lower rate of bone turnover markers and improved height percentile for their age.[3] However, imbalances in baseline height percentile increase risk of selection bias.[2] Height percentile for age was 23% for vamorolone 6 mg/kg/day, 30% for vamorolone 2 mg/kg/day, 37% for prednisone, and 33% for placebo.[2] Studies were also conducted only over a short period, were not powered to detect differences between groups, and were not designed to control for multiplicity for these outcomes. Furthermore, the association of these bone turnover markers on fracture risk is unknown, and additional data are needed to quantify comparative fracture risk with different corticosteroids.

In clinical trials, the most common adverse events occurring in more than 10% of patients and more common than placebo included Cushingoid features, psychiatric disorders, vomiting, weight increases, vitamin D deficiency (**Table 2**).[4] Compared to prednisone, vamorolone has similar adverse effects.

Table 2. Adverse events occurring in more than 5% of patients and more common than placebo[4]

	Vamorolone 2 mg/kg/day (%)	Vamorolone 6 mg/kg/day (%)	Prednisone 0.75 mg/kg/day (%)[3]	Placebo (%)

Cushingoid features	7	29	23	0
Psychiatric disorders Irritability[3]	7 0	21 11	32 3	14 0
Vomiting	17	14	3	7
Fall[3]	7	11	13	3
Weight increased	0	11	13	3
Vitamin D deficiency	7	11	3	0
Cough	10	7	10	3
Headache	7	7	3	3
Diarrhea	3	7	7	3
Increased appetite	3	7	3	3
Rhinitis	3	7	0	3

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Functional ability or symptom improvement (motor, pulmonary, or cardiovascular)
2) Disease progression
3) Quality of life
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Time to stand from a supine position (motor function)

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Corticosteroid which binds to the glucocorticoid receptor to cause anti-inflammatory and immunosuppressive effects.
Oral Bioavailability	After administration with food, the median Tmax is ~2 hours. A high fat or high calorie meal reduces Cmax by 18% and AUC by 13%, and delays Tmax by about 1 hour.
Distribution and Protein Binding	Vd = 162 L for a patient with DMD weighing 20 kg Protein binding 81% *in vitro* with a blood to plasma ratio of 0.87.
Elimination	Clearance of 58L/hr in a person with DMD who is 20 kg. Excreted 30% in feces (15% as metabolites), 48% in urine (>99% as metabolites).
Half-Life	2 hours
Metabolism	Metabolized via CYP3A4/5, CYP2C8, UGT1A3, UGT2B7, UGT2B17.

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; DMD = Duchenne muscular dystrophy; hr = hour; kg = kilogram; L = liter; Tmax = time to maximum concentration; Vd = volume of distribution

Table 4. Comparative Evidence Table for Vamorolone.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Guglieri, et al. 2022.[2] Phase IIb, AC, DB, double-dummy, PC, cross-over, RCT NCT03439670	1. Vamorolone 6 mg/kg/day suspension 2. Vamorolone 2 mg/kg/day suspension 3. Prednisone tablets 0.75 mg/kg/day 4. Placebo tablets Period 1: 24 wks Period 2: 24 wks In period 2, people receiving prednisone or placebo switched to vamorolone	Demographics: - Mean age: 5 yrs - BMI: 16.2-16.8 mg/kg - TTSTAND velocity: 0.18-0.22 rises/s - 6MWT: 313-355 m - TTRW 10 m velocity: 1.6-1.9 m/s - NSAA: 17-21 - Mean height percentile: 23% (vamorolone 6 mg/kg) to 37% (prednisone) Key Inclusion Criteria: - DMD gene loss-of-function variation or lack of muscle dystrophin - Age: 4-6 years (inclusive) - Time to stand from supine < 10 s without assistance - Ability to walk independently - Weight 13-39.9kg - Chicken pox immunity - Normal clinical laboratory testing Key Exclusion Criteria: - Renal, hepatic disease, immunosuppression, diabetes, current or h/o chronic systemic fungal or viral infections, primary aldosteronism, symptomatic cardiomyopathy, cognitive or behavioral problems	ITT: 1. 30 2. 30 3. 31 4. 30 PP: 1. 27 2. 28 3. 30 4. 28 Attrition: 1. 2 (7%) 2. 2 (7%) 3. 1 (3%) 4. 2 (7%)	Primary Endpoint: Change from baseline to 24 weeks Mean TTSTAND velocity 1. 0.05 (SE 0.07) rises/s 2. 0.04 (SE 0.09) rises/s 3. NR 4. -0.01 (SE 0.06) rises/s 1 vs. 4: 0.06 rises/s (95% CI 0.02 to 0.10); p=0.002 2 vs. 4: 0.05 rises/s (95% CI 0.01 to 0.08); p=0.02 Secondary Endpoints: Mean 6MWT 1. 28.8 (SE 49.7) m 2. 31.0 (SE 51.1) m 3. NR 4. -23.9 (SE 59.6) m 1 vs. 4: 41.6 m (95% CI 14.2 to 68.9); p=0.003 2 vs. 4: 37.1 m (95% CI 9.6 to 64.7); p=0.009 Mean TTRW 10 m (velocity) 1. 0.28 (SE 0.28) m/s 2. 0.16 (SE 0.23) m/s 3. NR 4. 0.02 (SE 0.33) m/s 1 vs. 4: 0.24 m/s (95% CI 0.09 to 0.39); p=0.002 2 vs. 4: 0.13 m/s (95% CI −0.03 to 0.28); p>0.05 Results for prednisone were described only generally.	NA NA NA NA NA NS	Treatment-emergent AE 1. 89.3% 2. 83.3% 3. 83.9% 4. 79.3% Discontinuations due to AE 1. 0 (0%) 2. 0 (0%) 3. 1 (3%) 4. 0 (0%) Serious AE 1. 0 (0%) 2. 1 (3%) 3. 1 (3%) 4. 0 (0%) Change from baseline in height percentile 1. 3.86% (SE 6.16) 2. 0.26% (SE 9.22) 3. −1.88% (SE 8.81) 4. NR 1 vs. 3: 4.98% (95% CI 0.75 to 9.21); p=0.02 2 vs. 3: 1.86% (95% CI −2.27 to 6.00); p>0.05 BMI z score 1. 0.52 (SE 0.62) 2. 0.40 (SE 0.45) 3. 0.41 (SE 0.51) 4. NR p>0.05	NA NS NS NA NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Adequate randomization and allocation concealment methods used via IVWRS. Baseline motor function differed between groups (most tests were better with prednisone and some were better with placebo than vamorolone). Performance Bias: Unclear. Blinded with double dummy design. Method of blinding NR. Detection Bias: Unclear. Method of blinding was NR. Attrition Bias: Low. The number of people who withdrew from the study was small. Primary outcome data was conducted remotely for 10% of assessments, but the COVID pandemic resulted in missing data for other secondary endpoints. Multiple sensitivity analyses evaluating the impact of missing data demonstrated similar results. Reporting Bias: Low. Outcomes reported as pre-specified in the statistical analysis plan. Efficacy outcomes for prednisone were NR in detail. Other Bias: Low. Study was grant funded through partnerships with NIH and multiple patient organizations. Funders had no role in the study design or data analysis. Authors report grant support, honoraria, personal fees and consulting fees from various pharmaceutical companies outside the submitted work. Two authors reported personal fees from the manufacturer of vamorolone. **Applicability**: Patient: 83% of participants were White and 96% were not Hispanic or Latino. Other racial groups were underrepresented. Most applicable for young people (4-7 years old) who retain motor function. The mean 6MWT was over 300m (normal range 400-700m) and members were required to be able to stand from a supine position in < 10 s. Efficacy in people with more severe disease is unknown. Intervention: Dose response observed for motor function outcomes. Recommended FDA-dose of vamorolone is 6 mg/kg/day. Lower doses may be less effective than prednisone for some motor outcomes. Comparator: Placebo appropriate to evaluate efficacy. Efficacy outcomes compared to prednisone, the current standard of care, were only briefly described.

		- Prior oral steroid or immunosuppressant use for > 1 month - Other therapy for DMD within 3 months		Vamorolone 6 mg/kg/day and prednisone were similar for all motor outcomes. Vamorolone 2 mg/kg/day was similar for TTSTAND, 6MWT, & NSAA but less effective than prednisone for TTRW and TTCLIMB.				Outcomes: Relatively short-term study. Outcomes for second period of the study (switching to vamorolone) are not yet reported. Setting: 33 centers in 11 countries in Europe and the US from June 29, 2018, to February 24, 2021. About 44% of enrolled patients were from the US.[3]

Abbreviations: 6MWT = 6 minute walking test; AC = active control; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; DB = double blind; DMD = Duchenne muscular dystrophy; FDA = Food and Drug Administration; h/o = history of; ITT = intention to treat; IVWRS = interactive voice/web response system; m = meters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; NSAA = North Star Ambulatory Assessment; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; s=seconds; SE = standard error; TTCLIMB = time to climb 3 steps; TTSTAND = time to stand from supine; TTRW = time to run/walk 10 meters

NEW DRUG EVALUATION: Delandistrogene moxeparvovec

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

Clinical Efficacy:

Delandistrogene moxeparvovec is an adeno-associated viral vector-based gene therapy that was approved by the FDA in 2023 under the accelerated approval pathway. It is a one-time treatment indicated for patients with Duchenne muscular dystrophy who are ambulatory, 4 to 5 years of age, and have a confirmed mutation in the DMD gene.[7] The viral capsid contains a gene for an engineered, shortened micro-dystrophin protein.[8] Because the gene encoding wild-type dystrophin is the largest known human gene, it cannot be delivered in a viral capsid. Instead, the viral capsid contains a micro-dystrophin protein containing select domains of normal dystrophin. This micro-dystrophin was based on protein identified in a patient with a milder form of the disease called Becker muscular dystrophy.[8] Micro-dystrophin proteins are not normally expressed in any patients, and it is not known if expression correlates with improved symptoms or a reduction in disease progression.[8] There is increasing literature which shows that dystrophin may play an important scaffolding role to recruit additional proteins necessary for normal muscle function such as ion channels, kinases, and neuronal nitric oxide synthase.[8] However, due to size constraints of the viral vector, the dystrophin protein regions responsible to these functions were not included in the micro-dystrophin formed by delandistrogene moxeparvovec.[8] Because the form of micro-dystrophin gene included in delandistrogene moxeparvovec is based on a form of dystrophin present in people with milder symptoms, this gene therapy is not designed to prevent or cure the disease. The goal of this gene therapy is to reduce symptom severity.

Several trials were reviewed by the FDA for approval. Because of the heterogeneous nature of DMD and significant risk of bias with the use of external controls, the FDA primarily focused on information from a phase 2, placebo-controlled, crossover RCT to evaluate efficacy of delandistrogene moxeparvovec.[8] The phase 2 RCT included 41 patients randomized to one-time treatment or placebo.[6] After 48 weeks, patients were crossed over to the alternate treatment group which allowed allowed participants initially randomized to placebo to receive therapy. Even though trial remained blinded, after the crossover at 48 weeks, all patients had received treatment, making the study essentially non-controlled. Data from this RCT was supplemented by information from uncontrolled, single-arm studies. The co-primary endpoints for this trial were change in micro-dystrophin protein expression at 12 weeks and change in NSAA score at 48 weeks.[6] Secondary clinical endpoints included other timed motor function tests such as time to run/walk 10 meters, 100 meter run/walk time, time to climb 4 stairs, and

time to stand from a supine position. Patients included in the trial were 4 to 8 years of age (inclusive) and had a confirmed mutation in the DMD gene resulting in a frameshift between exons 18 and 58.[6] Patients were ambulatory and on a stable dose of corticosteroids for at least 12 weeks. Patients were excluded if they had cardiomyopathy, elevated gamma-glutamyl transferase, or elevated creatinine which may limit applicability to patients with more severe disease.[6]

At 12 weeks, patients administered delandistrogene moxeparvovec had an increase in micro-dystrophin expression compared to placebo (change from baseline of 23.8% vs. 0.14%; p=0.0001).[6] Micro-dystrophin was measured with Western blot and reported as a percentage of normal levels. For patients treated in the first cohort, micro-dystrophin expression was maintained at 60 weeks (19% of normal levels).[6] However, this difference did not correlate with clinical endpoints. There was no statistical difference in NSAA score at 48 weeks with delandistrogene moxeparvovec compared to placebo (change from baseline of 1.7 vs. 0.9 points; LSMD 0.8; 95% CI -1.03 to 2.67; p=0.37).[6,8] Secondary timed motor function tests were also no different between groups.[6]

Data from the first 48 weeks of the phase 2 trial was limited by risk for selection bias due to imbalances in motor function tests at baseline. Patients randomized to treatment with delandistrogene moxeparvovec in the first 48 weeks had lower NSAA scores than patients randomized to placebo (mean score of 19.8 vs. 22.6).[6] The time required to perform other motor function tests was also slightly longer for patients randomized to delandistrogene moxeparvovec. A post-hoc analysis identified that baseline disparities between groups were more apparent for patients 6-7 years of age.[6] Subgroup analyses for patients 4-5 years of age (n=8) identified more balanced motor function at baseline and provided support for FDA approval. In patients 4-5 years of age (n=16), NSAA score improved by 4.3 points (SD 0.7) at 48 weeks with delandistrogene moxeparvovec compared to a 1.9 (SE 0.7) point improvement with placebo.[6] In patients 6-7 year of age (n=25), NSAA score declined with delandistrogene moxeparvovec compared to an improvement for patients receiving placebo (LSMD -0.2 [SE 0.7] vs. 0.5 [SE 0.7]).[8] However, these post-hoc subgroup analyses were conducted without a pre-specified testing plan to control for multiplicity and type 1 error.[8] This increases risk for reporting bias and decreases confidence that the results observed in these subgroup are representative of the true treatment effect.

Current studies show no correlation between change in micro-dystrophin at 12 weeks and functional improvement for patients treated with delandistrogene moxeparvovec. After a change in the analytic process during the clinical trial program, it was retrospectively identified that only 8 patients received the intended study dose in the first 48 weeks of the phase 2 trial.[8] Six patients received about two-thirds of the intended dose and 6 patients received about half the intended dose.[8] At 12 weeks, a dose response was observed for micro-dystrophin expression for members who received low dose, middle dose, and intended dose respectively (mean levels of 3.6% [SD 5.7%], 28.2% [SD 52.2%], and 43.4% [SD 48.6%], respectively).[8] However, there was no commensurate change in functional improvement based on dose received.

Available studies show that there is a persistent immune response to viral capsids after administration of delandistrogene moxeparvovec.[8] This immune response is expected to cross-react with other adeno-associated viral vectors of different serotypes and could result in immunity to any future gene therapies.[8] Because of this immune response, testing for antibody titers is recommended before administration, and it is unlikely that members will be eligible to receive any type of subsequent gene therapy.[8] Re-administration of delandistrogene moxeparvovec is not recommended.

Delandistrogene moxeparvovec was FDA approved through the accelerated approval pathway based on change in micro-dystrophin level.[7] The clinical benefit has not been established, and available data from blinded, placebo-controlled trials show no overall motor function improvement compared to placebo.[6,8] Continued approval is dependent on a subsequent phase 3, placebo-controlled confirmatory trial which was completed in late 2023. Full results from this trial have not yet been published.

Clinical Safety:
The FDA evaluated safety data from 85 people who received an infusion of delandistrogene moxeparvovec enrolled in 3 clinical studies.[8] Of these patients, 73 received the FDA-approved dose.[8] There were changes in the manufacturing process during clinical trials, and only 40 of these patients received delandistrogene moxeparvovec manufactured using the commercialized process.[8] The infusion is administered in conjunction with an increased dose of corticosteroids (1 to 1.5 mg/kg/day prednisone equivalent) for 1 day prior to treatment and for at least 60 days post-treatment to decrease risk of an immune response.[7] If liver function abnormalities occur, then the dose of corticosteroid should be increased (up to 2.5 mg/kg/day).[7] After the 60 day period, the corticosteroid dose is tapered back to the patient's usual maintenance dose over a periods of 2 weeks or longer.[7]

Baseline assessments prior to administration include genetic testing, tests for AAVrh74 binding antibodies, liver function tests, troponin, and platelets.[7] Because of the need for prolonged immunosuppression, delandistrogene moxeparvovec is not recommended if there are signs or symptoms of infection and labeling recommends that patients be up-to-date with relevant immunizations at least 4 weeks prior to therapy.[7]

The most common adverse events observed in clinical trials were vomiting (61%), nausea (40%), acute liver injury (37%), pyrexia (24%), and thrombocytopenia (12%).[8] Thrombocytopenia was generally transient and asymptomatic. Comparisons to placebo are shown in **Table 5**. Acute liver injury was defined as elevated liver function tests 2 to 3 times the upper limit of normal depending on the test. Patients with pre-existing liver impairment, acute or chronic liver disease or elevated GGT were excluded from clinical studies and may have an increased risk for liver injury.[7] Treatment should be postponed until any acute liver injury is resolved. In clinical trials elevations in liver function tests typically occurred within 8 weeks and resolved with administration of systemic corticosteroids.

During clinical studies, 2 cases of immune-mediated myositis were documented after administration. The reaction was thought to be a T-cell based immune response to a specific region on the transgene.[8] It occurred in patients with deletions involving exons 3-43 and exons 8-9 and was thought to be related to a lack of self-tolerance to this region of the transgene.[8] Therefore, this therapy is contraindicated for anyone with deletions in exons 8 or 9 of the DMD gene.[7] Labeling also includes warnings for patients with deletions in exons 1 to 17 and/or exons 59 to 71 who may also be at risk of severe immune-mediated myositis reactions. If symptoms of myositis occur (e.g., increased muscle pain, weakness, tenderness, dysphagia, dyspnea, or hypophonia), additional immunosuppressant therapy should be considered.[7] Additional warnings in the labeling include acute serious myocarditis and elevated levels of troponin-I which have been observed after administration. Baseline and subsequent monitoring for cardiac injury is recommended.[7]

Table 5. Adverse events occurring in ≥10% of patients and more common than placebo during placebo-controlled studies[7]

	Delandistrogene moxeparvovec N=20 (%)	Placebo N=21 (%)
Vomiting	65%	33%
Nausea	35%	10%
Liver function test increases	25%	0%
Pyrexia	20%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Functional ability or symptom improvement (motor, pulmonary, or cardiovascular)
2) Disease progression
3) Quality of life
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change from baseline to 48 weeks in NSAA score (motor function)
2) Change from baseline to 12 weeks in micro-dystrophin protein expression

Table 6. Pharmacology and Pharmacokinetic Properties.[7]

Parameter	
Mechanism of Action	Delandistrogene moxeparvovec is a recombinant gene therapy containing a non-replicating, adeno-associated virus capsid and single strand DNA expression cassette. The DNA expression cassette contains a promotor and transgene which are intended to express a shortened micro-dystrophin protein, replacing the lack of functional wild-type dystrophin protein for patients with DMD. The promoter region is intended to restrict gene expression to skeletal and cardiac muscle cells. The adeno-associated virus capsid transduction has been documented in skeletal muscle cells, cardiac cells and diaphragm muscle cells.
Oral Bioavailability	NA
Distribution and Protein Binding	Biodistribution was evaluated in animal studies. At 12 weeks following administration, vector DNA was detected in all major organs with highest levels in the liver, followed by the heart, adrenal glands, skeletal muscles and aorta. Micro-dystrophin protein expression was highest in cardiac tissue with lower levels in skeletal muscle, diaphragm and liver. With human testing in 2 clinical studies, vector genome exposure increased from baseline by 2.91 and 3.44 copies per nucleus in muscle biopsies at 12 weeks post-dose.
Elimination	Elimination in the urine and feces after systemic circulation and delivery of viral capsids to target tissues. C_{max} was 0.0049 x 10^{13} copies/mL T_{max} = 5.3 hours post-dose in serum, 13.5 days post-dose in the feces
Half-Life	Serum: about 12 hours; the majority of the drug is expected to be cleared from the serum by 1-week post-dose. Elimination half-life for urine: 40 hours Elimination half-life for feces: 55 hours Elimination half-life for saliva: 60 hours
Metabolism	Capsid is broken down through proteasomal degradation within target cells.

Abbreviations: Cmax = maximum concentration; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; NA = not applicable; Tmax = time to maximum concentration

Table 7. Comparative Evidence Table for Delandistrogene Moxeparvovec.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Mendell, et al. 2023.[6] FDA Clinical Review Memo[8] NCT03769116 Phase 2, DB, crossover RCT	1. delandistrogene moxeparvovec 1.33×10^{14} vg/kg IV one time dose 2. placebo Part 1: 48 weeks Corticosteroid were added or increased to 1mg/kg prednisone equivalent 1 day prior to treatment and continued for ≥ 60 days post-infusion. After 48 weeks, patients were crossed over to the other treatment group and followed for another 48 weeks.	Demographics: - Mean age 6.3 years (SD 1.2) - Daily corticosteroid: 49% - Time since corticosteroid was started: mean ~1 year (range 0.2 to 5 years) - Deflazacort: 33-35% - BMI: 17.2-17.9 kg/m^2 Mean (SD) / Tx / PBO NSAA: 19.8 (3.3) / 22.6 (3.3) Time to rise (s): 5.10 (2.17) / 3.56 (0.65) 4-stair climb (s): 3.69 (1.46) / 3.10 (0.98) 100MRW (s): 61.04 (12.71) / 53.86 (8.30) TTRW 10 meters (s): 5.35 (1.14) / 4.83 (0.72) Key Inclusion Criteria: - Age ≥4 to <8 years - Confirmed DMD gene mutation with frameshift (deletion, duplication or premature stop codon mutation) between exons 18 and 58 - Ambulatory and able to cooperate with motor testing - On stable oral corticosteroid ≥12 weeks - Creatine kinase >1,000 U/L - Percent predicted 100m run/walk time <95th percentile Key Exclusion Criteria: - Cardiomyopathy or impaired CV function on echocardiogram - Other genetic disease - Other lab or physical findings that could affect safety, study completion or outcome assessment (such as gamma-glutamyl transferase ≥3x ULN,	mITT: Patients who received treatment 1. 20 2. 21 Attrition: Part 1 1. 0 2. 0 Part 2 1. 0 2. 2	Primary Endpoint: Change in NSAA score at 48 weeks 1. 1.7 (SE 0.6) 2. 0.9 (SE 0.6) LSMD 0.8; (95% CI -1.03 to 2.67); p=0.37 Change in dystrophin expression as 12 weeks (Western blot) - % of normal 1. 23.8% 2. 0.14% P<0.0001 Secondary Endpoints: Change from baseline to week 48 – negative values indicate improvement TTRW 10 m 1. 0.70 s (SD 1.16) 2. 0.01 s (SD 0.69) 100 m run/walk time 1. 8.67 s (SD 27.96) 2. 2.49 s (SD 7.52) 4-stair climb 1. 0.26 s (SD 1.35) 2. 0.03 s (SD 0.87) Mean time to stand from supine 1. -0.21 s (SD 1.13)	NA	Part 1 Treatment-related AE 1. 17 (85%) 2. 9 (43%) Serious AE 1. 3 (15%) 2. 2 (10%) Discontinuation due to AE 1. 0 (0%) 2. 0 (0%) Rhabdomyolysis 1. 2 (10%) 2. 1 (5%) Liver injury 1. 1 (5%) 2. 0 (0%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Adequate methods for randomization and allocation concealment via IVWRS stratified by age. Patients randomized to treatment in part 1 had worse motor function scores than placebo. Disparities between groups were more apparent for patients 6-7 years of age. Performance Bias: Unclear. Double blinded up to 48 weeks, but method of blinding was not reported. Detection Bias: Unclear. Double blinded but method of blinding was not reported. Attrition Bias: Low. Only 1 patient with missing outcome data for the primary endpoint at 48 weeks. Reporting Bias: High. Post-hoc analyses were conducted for subgroups based on age without pre-specified statistical testing to control for multiplicity and type 1 error. Statistical analyses for secondary outcomes were not reported, but did not have apparent differences between groups. Other Bias: Unclear. Part 2 data after cross over treatment were compared using propensity-match to external controls which increases risk of bias. Controls were only matched based on age, NSAA scores, time to rise, time to walk/run 10 meters, and corticosteroid dose. This method does not control for unknown confounding factors. Study was funded by Sarepta, 6 of study authors were employees of Sarepta and all authors were involved in study design, data analysis, interpretation, writing and manuscript preparation. **Applicability**: Patient: Evidence is most applicable to patients with a confirmed DMD frameshift mutation and less than 8 years of age. Patients were ambulatory, but had an abnormal time to run/walk 100 m for their age. Intervention: Only 8 patients received a dose comparable the commercialized product. Patients were required to be on a stable dose of corticosteroids which is a first-line treatment option for DMD.

		bilirubin ≥3 mg/dL; creatinine ≥1.8 mg/dL; hemoglobin <8 or >18 g/dL; WBC >18,500/ mm^3) - Concomitant disease (including HIV, hepatitis B or C, autoimmune disease, cognitive impairment that could confound motor tests) - Severe infection within 4 weeks - rAAVrh74 antibody titers > 1:400 (e.g., not elevated)		2. 0.44 s (SD 0.91)				Comparator: Placebo is appropriate to determine efficacy. Even though trial remained blinded, after the crossover at 48 weeks, all patients had received treatment, making the study essentially non-controlled. The FDA relied primarily on placebo-controlled data in the first 48 weeks to evaluate efficacy. Outcomes: Outcomes were appropriate to evaluate motor function. Performance on motor function tests is highly dependent on motivating factors and method of administration. There was no correlation between micro-dystrophin expression and functional motor outcomes. Setting: 2 sites in the United States (Ohio and California) from 2018 to 2020.

Abbreviations: 100MRW = 100 meter run/walk time; AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = double blind; dL = deciliter; DMD = Duchenne muscular dystrophy; HIV = human immunodeficiency virus; ITT = intention to treat; IVWRS = interactive voice/web response system; LSDM = least square mean difference; m = meters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NSAA = North star ambulatory assessment; PBO = placebo; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TTRW = time to run/walk; Tx = delandistrogene moxeparvovec; ULN = upper limit of normal; WBC = white blood cell

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form
casimersen	AMONDYS-45	VIAL
deflazacort	EMFLAZA	ORAL SUSP
deflazacort	EMFLAZA	TABLET
eteplirsen	EXONDYS-51	VIAL
viltolarsen	VILTEPSO	VIAL
golodirsen	VYONDYS-53	VIAL

Appendix 2: Abstracts of Comparative Clinical Trials

Guglieri M, Bushby K, McDermott MP, et al. Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. *Jama.* 2022;327(15):1456-1468.

Importance: Corticosteroids improve strength and function in boys with Duchenne muscular dystrophy. However, there is uncertainty regarding the optimum regimen and dosage.
Objective: To compare efficacy and adverse effects of the 3 most frequently prescribed corticosteroid regimens in boys with Duchenne muscular dystrophy.
Design, Setting, and Participants: Double-blind, parallel-group randomized clinical trial including 196 boys aged 4 to 7 years with Duchenne muscular dystrophy who had not previously been treated with corticosteroids; enrollment occurred between January 30, 2013, and September 17, 2016, at 32 clinic sites in 5 countries. The boys were assessed for 3 years (last participant visit on October 16, 2019)., Interventions: Participants were randomized to daily prednisone (0.75 mg/kg) (n = 65), daily deflazacort (0.90 mg/kg) (n = 65), or intermittent prednisone (0.75 mg/kg for 10 days on and then 10 days off) (n = 66).
Main Outcomes and Measures: The global primary outcome comprised 3 end points: rise from the floor velocity (in rise/seconds), forced vital capacity (in liters), and participant or parent global satisfaction with treatment measured by the Treatment Satisfaction Questionnaire for Medication (TSQM; score range, 0 to 100), each averaged across all study visits after baseline. Pairwise group comparisons used a Bonferroni-adjusted significance level of .017.
Results: Among the 196 boys randomized (mean age, 5.8 years [SD, 1.0 years]), 164 (84%) completed the trial. Both daily prednisone and daily deflazacort were more effective than intermittent prednisone for the primary outcome (P < .001 for daily prednisone vs intermittent prednisone using a global test; P = .017 for daily deflazacort vs intermittent prednisone using a global test) and the daily regimens did not differ significantly (P = .38 for daily prednisone vs daily deflazacort using a global test). The between-group differences were principally attributable to rise from the floor velocity (0.06 rise/s [98.3% CI, 0.03 to 0.08 rise/s] for daily prednisone vs intermittent prednisone [P = .003]; 0.06 rise/s [98.3% CI, 0.03 to 0.09 rise/s] for daily deflazacort vs intermittent prednisone [P = .017]; and -0.004 rise/s [98.3% CI, -0.03 to 0.02 rise/s] for daily prednisone vs daily deflazacort [P = .75]). The pairwise comparisons for forced vital capacity and TSQM global satisfaction subscale score were not statistically significant. The most common adverse events were abnormal behavior (22 [34%] in the daily prednisone group, 25 [38%] in the daily deflazacort group, and 24 [36%] in the intermittent prednisone group), upper respiratory tract infection (24 [37%], 19 [29%], and 24 [36%], respectively), and vomiting (19 [29%], 17 [26%], and 15 [23%]).
Conclusions and Relevance: Among patients with Duchenne muscular dystrophy, treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement over 3 years in a composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment; there was no significant difference between the 2 daily corticosteroid regimens. The findings support the use of a daily corticosteroid regimen over the intermittent prednisone regimen tested in this study as initial treatment for boys with Duchenne muscular dystrophy. Trial Registration: ClinicalTrials.gov Identifier: NCT01603407.

Appendix 3: Medline Search Strategy
Ovid MEDLINE(R) ALL 1946 to November 20, 2023

1	vamorolone.mp.	30
2	delandistrogene moxeparvovec.mp.	7
3	delandistrogene moxeparvovec-rokl.mp.	1
4	SRP-9001.mp.	4
5	eteplirsen.mp.	171
6	casimersen.mp.	20
7	viltolarsen.mp.	44
8	golodirsen.mp.	49
9	deflazacort.mp.	641
10	exp Muscular Dystrophy, Duchenne/	7226
11	9 and 10	137
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11	363
13	limit 12 to yr="2021"	26
14	limit 12 to yr="2022 -Current"	71
15	limit 14 to (english language and humans)	50
16	limit 15 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	14

Appendix 4: Prescribing Information Highlights

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

AGAMREE (vamorolone) oral suspension
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
AGAMREE is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage is 6 mg/kg taken orally once daily preferably with a meal, up to a maximum daily dosage of 300 mg for patients weighing more than 50 kg. (2.2)
- In patients with mild to moderate hepatic impairment, the recommended dosage is 2 mg/kg taken orally once daily preferably with a meal, up to a maximum daily dosage of 100 mg for patients weighing more than 50 kg. (2.3)
- Decrease dosage gradually when administered for more than one week. (2.7)

----------DOSAGE FORMS AND STRENGTHS----------
Oral Suspension: 40 mg/mL (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to vamorolone or any of the inactive ingredients in AGAMREE (4)

----------WARNINGS AND PRECAUTIONS----------
- *Alterations in Endocrine Function:* Hypothalamic-pituitary-adrenal axis suppression, cushingoid features, and hyperglycemia can occur. Monitor patients for these conditions with chronic use of AGAMREE. (2.7, 5.1)
- *Immunosuppression and Increased Risk of Infection:* Increased risk of new infections, exacerbation, dissemination, or reactivation of latent infections, which can be severe and at times fatal; signs and symptoms of infections may be masked. (5.2)
- *Alterations in Cardiovascular/Renal Function:* Monitor for elevated blood pressure and monitor sodium and potassium levels in patients chronically treated with AGAMREE. (5.3)
- *Gastrointestinal Perforation:* Increased risk in patients with certain GI disorders; signs and symptoms may be masked. (5.4)
- *Behavioral and Mood Disturbances:* May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. (5.5)
- *Effects on Bones:* Monitor for decreases in bone mineral density with chronic use of AGAMREE. (5.6)
- *Ophthalmic Effects:* May include cataracts, infections, and glaucoma; monitor intraocular pressure in patients chronically treated with AGAMREE. (5.7)
- *Vaccination:* Do not administer live or live attenuated vaccines to patients receiving immunosuppressive doses of corticosteroids. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting AGAMREE. (5.8)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>10% for AGAMREE and greater than placebo) are cushingoid features, psychiatric disorders, vomiting, weight increased, and vitamin D deficiency. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Santhera Pharmaceuticals (Switzerland) Ltd. at 1-844-347-3277 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 inhibitors: The maximum recommended daily dose is 4 mg/kg up to a maximum daily dosage of 200 mg for patients weighing more than 50 kg. (2.6, 7.1)

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

Revised: 10/2023

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

ELEVIDYS (delandistrogene moxeparvovec-rokl) suspension, for intravenous infusion
Initial U.S. Approval: YYYY

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

ELEVIDYS is an adeno-associated virus vector-based gene therapy indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. This indication is approved under accelerated approval based on expression of ELEVIDYS micro-dystrophin in skeletal muscle observed in patients treated with ELEVIDYS. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1, 12, 14)

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

ELEVIDYS is for single-dose intravenous infusion only.

- Select patients for treatment with ELEVIDYS with anti-AAVrh74 total binding antibody titers <1:400. (2.1)
- Recommended dosage: 1.33×10^{14} vector genomes (vg) per kg of body weight. (2.2)
- Postpone in patients with concurrent infections until the infection has resolved. (2.2)
- Assess liver function, platelet counts and troponin-I before ELEVIDYS infusion. (2)
- One day prior to infusion, initiate a corticosteroid regimen for a minimum of 60 days. Recommend modifying corticosteroid dose for patients with liver function abnormalities. (2.2)
- Administer as an intravenous infusion over 1-2 hours. Infuse at a rate of less than 10 mL/kg/hour. (2.4)

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

- ELEVIDYS is a suspension for intravenous infusion with a nominal concentration of 1.33×10^{13} vg/mL. (3)
- ELEVIDYS is provided in a customized kit containing ten to seventy 10 mL single-dose vials, with each kit constituting a dosage unit based on the patient's body weight. (3)

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

- ELEVIDYS is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene. (4)

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

- Acute Serious Liver Injury: Acute serious liver injury has been observed. Monitor liver function before ELEVIDYS infusion, and weekly for the first 3 months after ELEVIDYS infusion. Continue monitoring until results are unremarkable. If acute serious liver injury is suspected, a consultation with a specialist is recommended. (5.1)
- Immune-mediated Myositis: Patients with deletions in the *DMD* gene in exons 1 to 17 and /or exons 59 to 71 may be at risk for severe immune-mediated myositis reaction. Consider additional immunomodulatory treatment (immunosuppressants [e.g., calcineurin-inhibitor] in addition to corticosteroids) if symptoms of myositis occur (e.g., unexplained increased muscle pain, tenderness, or weakness). (5.2)
- Myocarditis: Myocarditis and troponin-I elevations have been observed. Monitor troponin-I before ELEVIDYS infusion, and weekly for the first month after ELEVIDYS infusion. (5.3)
- Pre-existing Immunity against AAVrh74: Perform baseline testing for presence of anti-AAVrh74 total binding antibodies prior to ELEVIDYS administration. (5.4)

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

Most common adverse reactions across studies (incidence ≥5%) were vomiting and nausea, liver function test increased, pyrexia, and thrombocytopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc., at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: X/XXXX

Appendix 5: Key Inclusion Criteria

Population	People with Duchenne Muscular Dystrophy
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1, placebo or standard of care
Outcomes	Symptoms, function, quality of life, morbidity, disease progression, mortality
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Duchenne Muscular Dystrophy

Goal(s):

- Encourage use of corticosteroids which have demonstrated long-term efficacy.
- Restrict use of targeted oligonucleotides for exon skipping ~~and deflazacort~~ to patients with Duchenne Muscular Dystrophy.
- Limit use of ~~deflazacort~~ non-preferred corticosteroids to patients with contraindications or serious intolerance to ~~other~~ preferred oral corticosteroids.

Length of Authorization:

- 6-12 months (criteria-specific)

Requires PA:

- Targeted therapies for exon skipping (see Table 1; pharmacy or physician administered claims)
- Non-preferred corticosteroids for Duchenne muscular dystrophy (e.g., ~~D~~deflazacort, etc)

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 Indications for targeted therapies

Drug	Indication	Examples of amenable mutations (list is not all inclusive)
casimersen (Amondys 45®)	Duchenne muscular dystrophy with mutations amenable to exon 45 skipping	Deletion of exons 44, 46, 46 to 47, 46 to 48, 46 to 49, 46 to 51, 46 to 53, 46 to 55, or 46 to 57
eteplirsen (Exondys 51®)	Duchenne muscular dystrophy with mutations amenable to exon 51 skipping	Deletion of exons 43 to 50; 45 to 50; 47 to 50; 48 to 50; 49 to 50; 50; or 52
golodirsen (Vyondys 53®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58

Viltolarsen (Viltepso®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the request for ~~deflazacort~~a corticosteroid?	**Yes:** Go to #4	**No:** Go to #7
4. Is the patient ≥ 2 years of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
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 include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #6 Document physician attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have a documented contraindication or intolerance to a preferred corticosteroid, such as oral prednisone, that is not expected to crossover to ~~deflazacort~~the requested therapy? Note: deflazacort may be an option for patients with clinically significant weight gain associated with prednisone use.	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of prednisone.

Approval Criteria		
7. Is the request for continuation of treatment previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #8
8. Is the request for an FDA-approved indication (Table 1)?	**Yes:** Go to #9 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
9. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #10	**No:** Go to #12
10. Is the request for combination treatment with 2 or more targeted therapies (e.g., golodirsen and viltolarsen)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. Has the provider assessed baseline renal function as recommended in the FDA label? Recommended monitoring includes serum cystatin C, urine dipstick, and urine protein-to-creatinine within the past 3 months	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Has the patient been on a stable dose of corticosteroid for at least 6 months or have documented contraindication to steroids?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has baseline functional assessment been evaluated using a validated tool (e.g., the 6-minute walk test, North Star Ambulatory Assessment, etc)?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #2	**No:** Go to #3

Renewal Criteria		
2. Has the provider assessed renal function? Recommended monitoring includes urine dipstick monthly, serum cystatin C every 3 months, and protein-to-creatine ratio every 3 months.	**Yes:** Go to #3	**No:** Pass to RPh, Deny; medical appropriateness.
3. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	**Yes:** Go to #4 Document functional status and provider attestation.	**No:** Pass to RPh, Deny; medical appropriateness.
4. Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, etc.)?	**Yes:** Go to #5	**No:** Approve for up to 6 months
5. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)?	**Yes:** Approve for up to 6 months Document provider attestation	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *2/24; 8/21 (SS); 2/21; 6/20; 09/19; 11/17; 07/17*
Implementation: *9/1/21; 3/1/21; 7/1/20; 11/1/19; 1/1/18; 9/1/17*

Delandistrogene moxeparvovec

Goal(s):
- Restrict use of this gene therapy to patients with the FDA-labeled indication.

Length of Authorization:
- 1 lifetime dose

Requires PA:
- Delandistrogene moxeparvovec (pharmacy and physician administered claims)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of genetically-confirmed Duchenne Muscular Dystrophy?	**Yes:** Go to #3 Results of genetic testing are required for approval.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the patient 4 or 5 years of age?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the patient ambulatory (e.g., able to complete a 6 minute walk test or equivalent assessment)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Does the patient have deletions of exon 8 or 9?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Does the patient have deletions of exons 1-17 or exons 59-71? Note: these populations were excluded from clinical studies and may have increased risk for severe immune-mediated myositis reactions.	**Yes:** Pass to RPh. Refer to medical director for review	**No:** Go to #7

Approval Criteria		
7. Has baseline testing been completed and is within normal limits? Recommended baseline testing includes testing for anti-AAVrh74 antibodies (by ELISA), troponin-I, platelets, and liver function tests.	**Yes:** Go to #8 For any testing that is not within normal limits, refer to medical director for review. Liver function tests should be <3x the upper limit of normal.	**No:** Pass to RPh. Deny; medical appropriateness.
8. 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 include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, COVID-19, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #9 Document provider attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the patient able to tolerate an elevated dose of prednisone for at least 60 days and complete necessary ongoing monitoring?	**Yes:** Go to #11 Document provider attestation.	**No:** Pass to RPh. Deny; medical appropriateness.
10. Has the patient received a prior dose of an adeno-based gene therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve single infusion (max 1 dose per lifetime)

P&T/DUR Review: *2/24 (SS)*
Implementation: *TBD*

Drug Use Research & Management Program
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Drug Class Review: COVID-19 Antivirals

Date of Review: February 2024 **End Date of Literature Search:** 10/04/2023

Purpose for Class Review:
Evaluate the efficacy, effectiveness and safety of antivirals approved or authorized to treat coronavirus disease 2019 (COVID-19) in non-hospitalized patients.

Plain Language Summary:
- Coronavirus disease 2019 (COVID-19) is caused by a virus called SARS-CoV-2. Most people who get infected with the virus will have mild to moderate symptoms and recover without needing treatment. People over 50 years of age, those that are not vaccinated, and people with certain medical conditions such as cancer, asthma, diabetes, obesity, or heart disease may be at risk for getting severe COVID-19 and may benefit from treatment with medicine.
- Two medicines called PAXLOVID (nirmatrelvir with ritonavir) and LAGEVRIO (molnupiravir) are pills that can be taken by mouth twice a day over 5 days. A third medicine called VEKLURY (remdesivir) must be given through a vein by infusion once a day over 3 days.
- These medicines have shown to lower the risk of getting hospitalized or dying from COVID-19 in people who have mild or moderate symptoms of COVID-19 and are at risk of severe disease. Real world studies continue to show how effective these medicines are as the virus continues to evolve and people's immunity to the virus changes, either from vaccination or past infections.
- PAXLOVID and LAGEVRIO should be started no later than 5 days after symptoms first appear. Remdesivir should be started no later than 7 days after the first symptoms appear. All 3 medicines must be prescribed by a healthcare provider. Pharmacists have Food and Drug Administration approval to prescribe PAXLOVID if the infection is confirmed by testing.
- There are special considerations that the healthcare provider uses to determine which treatment is best for each person. For example, PAXLOVID can interact with several other medicines in ways that can cause dangerous side effects. LAGEVRIO can harm an unborn baby and is not recommended for use during pregnancy. LAGEVRIO may affect bone growth and cannot be used in growing children.
- It is recommended that these medicines be available for people enrolled in the Oregon Health Plan (OHP) fee-for-service program.

Research Questions:
1. What is the evidence for efficacy of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir in treating COVID-19 infections?
2. What are the harms associated with the use of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir when used to treat COVID-19 infections?
3. Are there specific subpopulations that would be more likely to benefit from the use of one antiviral agent over another to treat COVID-19 infections?

Conclusions:
- Two systematic reviews[1,2] and 3 clinical guidelines[3-5] provide high-quality evidence for the efficacy and safety of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir for treatment of COVID-19 infection.

- A 2023 Cochrane systematic review evaluated all published evidence for the effects of remdesivir on improving clinical outcomes in COVID-19.[1] However, only one RCT (n=562) was conducted in non-hospitalized patients. Participants of that RCT had mild or moderate symptoms that had started 4 days or less prior to screening, and were at risk of progression to severe COVID-19.[1] The primary outcome was a composite of hospitalization related to COVID-9 or death from any cause by day 28. This trial showed that remdesivir decreased the risk of hospitalization up to day 28 compared with placebo (RR 0.28, 95% CI, 0.11 to 0.75; moderate-certainty evidence).[1] No deaths were reported in either arm of this study, so it was not possible to determine if remdesivir impacts 28-day mortality.[1] There were less serious adverse events in the remdesivir arm compared with placebo arm (RR 0.27, 95% CI, 0.10 to 0.70; low-certainty evidence), but no differences in AE of any grade were found between arms (RR 0.91, 95% CI 0.76 to 1.10; moderate-certainty evidence).[1]
- A 2022 Cochrane systematic review assessed the efficacy and safety of ritonavir-boosted nirmatrelvir in treating mild or moderate COVID-19 infection.[2] One RCT (n=2,246) conducted in non-hospitalized patients that compared ritonavir-boosted nirmatrelvir with placebo met inclusion criteria.[2] Trial participants were unvaccinated, without previous confirmed SARS-CoV-2 infection, onset of symptoms of no longer than 5 days, and were at high risk for progression to severe disease.[2] The trial found that ritonavir-boosted nirmatrelvir may reduce all-cause mortality at 28 days versus placebo (RR 0.04, 95% CI, 0.00 to 0.68; low-certainty evidence), and reduce admission to hospital or death within 28 days (RR 0.13, 95% CI, 0.07 to 0.27; low-certainty evidence).[2] There were less serious adverse events with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 0.24, 95% CI, 0.15 to 0.41; low-certainty evidence).[2] No difference in overall treatment-emergent adverse events were found between arms (RR 0.95, 95% CI, 0.82 to 1.10; moderate-certainty evidence).[2] However dysgeusia and diarrhea were more likely to occur with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 2.06, 95% CI, 1.44 to 2.95; moderate-certainty evidence).[2]
- The National Institute of Health (NIH) recommendations for treatment of non-hospitalized adults with COVID-19 are as follows:
    - Oral ritonavir-boosted nirmatrelvir is favored in most high-risk, non-hospitalized adults with mild to moderate symptoms of COVID-19 (Strong Recommendation, Moderate-quality Evidence).[3]
    - Intravenous remdesivir is recommended when ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions) (Moderate Recommendation, Moderate-quality Evidence).[3]
    - Oral molnupiravir is an alternative therapy, for use when the preferred therapies are not available, feasible to use, or clinically appropriate (Weak Recommendation, Moderate-quality Evidence).[3] The NIH panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (Strong Recommendation, Expert Opinion).[3]
- The Infectious Diseases Society of America (IDSA) recommendations for treatment of non-hospitalized people with COVID-19 are as follows:
    - Remdesivir if initiated within 7 days of symptom onset rather than no remdesivir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - Ritonavir-boosted nirmatrelvir if initiated within 5 days of symptom onset rather than no ritonavir-boosted nirmatrelvir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - For adults age 18 years or older who have no other treatment option, molnupiravir if initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional Recommendation, Low Certainty of Evidence).[4]
- The National Institute of Health and Care Excellence (NICE) guidance is similar to the NIH and IDSA recommendations. Ritonavir-boosted nirmatrelvir or remdesivir are considered first- and second-line treatments, respectively, in non-hospitalized adults with mild-to-moderate COVID-19 who are at high risk for progression to severe disease.[5] Molnupiravir is considered a third-line treatment in adults who have no other treatment option.[5]
- Guidance for use in special populations is as follows:
    - Remdesivir is Food and Drug Administration (FDA)-approved for treatment of COVID-19 in pediatric patients aged 28 days and older.[6]
    - Ritonavir-boosted nirmatrelvir is FDA-approved for treatment of COVID-19 in adults.[7]
    - Ritonavir-boosted nirmatrelvir is approved via an FDA emergency use authorization (EUA) for use in pediatric patients aged 12 years and older.[8]

- Ritonavir-boosted nirmatrelvir should not be initiated in patients taking concomitant medications highly dependent on CYP3A4 metabolism until the risk for significant drug interactions is assessed and a plan implemented to prevent adverse reactions.[7]
- The dose of ritonavir-boosted nirmatrelvir should be reduced in patients with impaired renal function (i.e., estimated glomerular filtration rate [eGFR] 30 to 60 mL/min).[7] Ritonavir-boosted nirmatrelvir is not recommended for patients with severe renal impairment (i.e., eGFR < 30 mL/min).[7]
- Molnupiravir is available via an FDA EUA for treatment of COVID-19 in adults.[9]
- Molnupiravir is not authorized under the FDA EUA for use in patients younger than 18 years of age because it may affect bone and cartilage growth.[9]
- Molnupiravir is not recommended for pregnant individuals due to the risk of fetal harm observed in animal models.[9]

- People who are members of racial and ethnic minority groups have higher rates of hospitalization and death from COVID-19 than people who are White.[3] Disparities in the use of antiviral treatments in patients who are not White have been reported; therefore, attention to equitable access is critical.[3] In outpatient studies of the 3 COVID-19 antivirals, Black, Asian, Hispanic, and American Indian populations were underrepresented (see **Table 2**).

Recommendations:

- Create a Preferred Drug List (PDL) class for the antivirals FDA-approved to treat COVID-19 infection and designate ritonavir-boosted nirmatrelvir and remdesivir as preferred agents on the PDL. Ritonavir-boosted nirmatrelvir is only FDA-approved in adults, therefore access for pediatric patients aged 12 to 18 years is only available through the FDA EUA.
- Since molnupiravir is only available through EUA, it will not have PDL status until it is FDA-approved. If it receives FDA-approval, recommend making molnupiravir preferred on the PDL with age restrictions in patients aged 17 years and younger due to risk of adverse effects.

Background:

COVID-19 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] According to the Centers for Disease Control and Prevention (CDC), over one million people have died from COVID-19 in the United States.[10] The NIH has stratified the severity of COVID-19 into four levels:

1. Mild disease: Individuals have symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.[3]
2. Moderate disease: Individuals show evidence of lower respiratory tract disease and have oxygen saturation measured by pulse oximetry (SpO_2) ≥ 94% on room air.[3]
3. Severe disease: Individuals have pneumonia and one of the following: SpO2 < 94% on room air, respiratory rate > 30 breaths/minute, or lung infiltrates > 50%.[3]
4. Critical disease: Individuals have respiratory failure, septic shock, and/or multiple organ dysfunction.[3]

Most symptomatic COVID-19 patients have mild or moderate disease and do not require hospitalization.[11] Patients who develop severe or critical disease require hospitalization with respiratory support.[11] Many factors can increase the risk for developing severe or critical COVID-19 disease.[11] Some of the most common risk factors are age over 50 years, obesity, cardiovascular disease, asthma, and chronic obstructive pulmonary disease.[3,11] Communities that have been historically marginalized or made socially vulnerable due to a lack of access to health care or an inability to socially isolate are at increased risk of SARS-CoV-2 acquisition, COVID-19–related hospitalization, and death.[3,11] These communities include racial and ethnic minorities, essential non-health care workers, and some people with disabilities.[3,11] The severity of COVID-19 is changing as the proportion of individuals who are vaccinated increases and the prevalence of different SARS-CoV-2 variants changes.[12]

Three antiviral agents are currently available for treatment of SARS-CoV-2 infection. Ritonavir-boosted nirmatrelvir (PAXLOVID) is a combination oral drug that inhibits 3-chymotrypsin-like cysteine protease, an enzyme necessary to produce other functional SARS-CoV-2 proteins.[12] Ritonavir does not have anti-SARS-COV-2 activity, but is used as a pharmacokinetic booster to slow the metabolism of nirmatrelvir and allow for twice daily dosing.[12] Ritonavir-boosted nirmatrelvir tablets are FDA-approved for treatment of adults with mild-to-moderate COVID-19 infection who are at risk for severe COVID-19 and hospitalization.[7] Ritonavir-boosted nirmatrelvir is available via the FDA EUA for pediatric patients aged 12 to 17 years, and its use must be consistent with the terms and conditions of the EUA.[8]

A second oral antiviral, molnupiravir (LAGEVRIO) is a prodrug of N-hydroxycytidine (NHC), an oral ribonucleoside analog that causes viral genome replication errors.[12] Molnupiravir has FDA EUA for use in adults with mild-to-moderate symptoms of COVID-19 who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.[9]

The third antiviral, remdesivir (VEKLURY) is administered via intravenous (IV) infusion. Remdesivir is a nucleotide prodrug of an adenosine analog, and binds to the viral RNA-dependent RNA polymerase which inhibits viral replication by prematurely terminating RNA transcription.[6] Remdesivir is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are: 1) hospitalized, or 2) not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[6]

A comparison of the 3 antiviral indications and dosing is presented in **Table 1**. Additional details including pharmacology, pharmacokinetics, warnings, precautions and use in special populations for each drug are summarized in **Appendix 1**.

Table 1. Antivirals to Treat Mild-to-Moderate COVID-19 in People at High Risk for Progression to Severe COVID-19 Disease.

Drug Name (Brand Name, Manufacturer)	FDA Approval or FDA EUA	Age Range	Route/Strength	Dose and Frequency
Molnupiravir[9] (LAGEVRIO, Merck)	• EUA effective 12/23/2021.	• Adults	• Oral • 200 mg capsules	• Four x 200 mg capsules orally every 12 hours x 5 days • Start within 5 days of symptom onset.
Nirmatrelvir (Ritonavir-boosted)[7,8] (PAXLOVID, Pfizer)	• FDA approval 5/25/2023 for adults. • EUA effective 12/22/2021 and continues to authorize eligible pediatric patients not covered under the FDA approval.	• FDA-approved: Adults • EUA: Children aged 12 to 18 years weighing at least 40 kg	• Oral • Nirmatrelvir 150 mg with Ritonavir 100 mg tablets co-packaged	• Two nirmatrelvir 150 mg tablets with one ritonavir 100 mg tablet orally twice daily x 5 days. • For patients with moderate renal impairment (eGFR 30 to 59 mL/min): Reduce dose to one nirmatrelvir 150 mg with one ritonavir 100 mg tablet orally twice daily for 5 days. • Not recommended in patients with severe renal impairment (eGFR <30 mL/min).

				• Not recommend in patients with severe hepatic impairment (Child-Pugh Class C). • Start within 5 days of symptom onset.
Remdesivir[6] (VEKLURY, Gilead)	• FDA approval 10/22/2020.	• Adults and children 28 days of age and older and weighing at least 3 kg	• Intravenous infusion • 100 mg vial	• 200 mg IV on day 1 followed by 100 mg IV for 2 consecutive days. • Pediatric dose is 5 mg/kg on day 1 followed by 2.5 mg/kg on days 2 and 3. • Start within 7 days of symptom onset.
Abbreviations: eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; kg = kilograms; mg = milligrams; mL = milliliters; min = minutes.				

Differences in participants studied across the COVID-19 antiviral RCTs do not permit direct comparisons or formal quantitative indirect comparisons of safety and effectiveness between the 3 antivirals currently recommended for COVID-19 treatment.[12] For example, the molnupiravir trial enrolled substantially larger proportions of individuals with obesity compared to the nirmatrelvir/ritonavir trial.[13] In addition, there were variabilities in the timing of trial enrollment which affected the primacy causal variant observed in the trials and impacted the vaccination status of study participants between trials.[12] Factors that must be considered when reviewing these trials include: 1) the rapid evolution of SARS-CoV-2 leading to variants with treatment resistance and with different morbidity and mortality impacts; 2) the enrollment of predominantly unvaccinated patients in early trials; and 3) the uncertain generalizability of data related to hospitalization rates and other health care resource utilization from studies conducted prior to the advent of the Omicron variant and based predominately or exclusively in countries outside of the United States (US).[12] An overview of the pivotal trials that provided safety and efficacy evidence for use of antivirals in treating COVID-19 is provided in **Table 2**. Currently, there are no comparative head-to-head trials for the 3 antivirals approved or authorized to treat COVID-19.

Table 2. Key RCTs in Outpatient Adults with Mild-to-Moderate COVID-19 at High Risk for Severe Disease.

Trial Details	Intervention	Inclusion/Exclusion Criteria	Outcomes	Baseline Characteristics	Results
Bernal A, et al.[13] MOVe-OUT • DB, MC, Phase 2/3 RCT • N=1,433 • 107 sites in 20 countries • Enrollment: 5/6/2021-10/2/2021	1. Molnupiravir 800 mg orally twice daily x 5 days (n=709) Vs. 2. Placebo orally twice daily x 5 days (n=699)	**Inclusion:** • Age ≥18 yrs • Mild or moderate symptom onset within 5 days • Not vaccinated • ≥1 risk factor for severe disease **Exclusion:** • Unwillingness to use contraception during treatment and at least 4 days after treatment completion	**Primary Endpoints:** • Incidence of hospitalization or death from any cause through day 29 • Incidence of adverse events	Age (median): 43 yrs Gender (female): 51% US enrollment: 6% Race/ethnicity: • 57% White • 7% American Indian • 7% Alaska Native • 5% Black • 3% Asian Risk factors: • BMI ≥30: 74% • Age >60 years: 17% • Diabetes: 16%	**Hospitalization or Death from any Cause through Day 29** 1. 6.8% (n=48) 2. 9.7% (n=68) Difference: -3.0% 95% CI, -5.9 to -0.1 **Mortality** 1. 0.1% (n=1) 2. 1.3% (n=9) **Adverse Events** 1. 1.4% (n=10) 2. 2.9% (n=20)

		• Prior COVID-19 vaccination • HBV or HCV infection with complications			**Serious Adverse Events** 1. 0.7% (n=5) 2. 1.9% (n=13)
Hammond J, et al.[14] EPIC-HR • DB, MC, Phase 2/3 RCT • N=2,246 • 343 sites in 21 countries • Enrollment: 7/16/2021-12/9/2021	1. Nirmatrelvir 300 mg with ritonavir 100 mg orally every 12 hours x 5 days (n=1039) Vs. 2. Placebo orally every 12 hours x 5 days (n=1046)	**Inclusion:** • Age ≥18 yrs • Mild or moderate symptom onset within 5 days • Not vaccinated • ≥1 risk factor for severe disease **Exclusion:** • Prior COVID-19 infection or vaccination • HIV infection	**Primary Endpoint:** • COVID-19-related hospitalization or death from any cause through day 28 **Secondary Endpoints:** • Adverse events	Age (median): 46 yrs Gender (female): 49.5% US enrollment: 41% Race/ethnicity: • 72% White • 5% Black • 14% Asian • 9% American Indian or Alaska Native Risk factors: • BMI ≥30: 33% • Age >60 years: 12% • Diabetes: 12% • Hypertension: 33%	**Hospitalization or Death from any Cause through Day 28** 1. 0.77% (n=8) 2. 6.31% (n=65) Difference: 5.62% 95% CI, 7.21 to 4.03 P< 0.001 **Mortality** 1. 0% (n=0) 2. 1.15% (n=12) **Adverse Events** 1. 7.8% (n=86) 2. 3.8% (n=42) **Serious Adverse Events** 1. <0.1% (n=1) 2. 0% (n=0)
Gottlieb RL, et al.[15] PINETREE • DB, MC Phase 3 RCT • N=562 • 64 sites in 4 countries • Enrollment: 9/18/2020-4/8/2021	1. Remdesivir 200 mg IV on Day 1 followed by 100 mg IV on Days 2 and 3 (n=279) Vs. 2. Placebo (n=283) IV on days 1-3	**Inclusion:** • Laboratory-confirmed SARS-CoV-2 infection ≤4 days from screening • Aged ≥12 yrs • ≥1 risk factor for disease progression or 60 yrs and older • Symptom onset ≤7 days from randomization • ≥1 ongoing COVID-19 symptom **Exclusion:** • COVID-19 vaccination • Receipt of supplemental oxygen	**Primary Endpoints:** • COVID-19-related hospitalization or death from any cause by Day 28 • Occurrence of AEs	Age (median): 50 yrs Gender (female): 48% Adolescents: 1.4% (n=8) US enrollment: 94% Race/ethnicity: • 80% White • 8% Black • 6% American Indian • 3% Asian • 42% Hispanic Risk factors: • BMI ≥30: 55% • Age >60 years: 30% • Diabetes: 62% • Hypertension: 48%	**Hospitalization or Death from any Cause through Day 28** 1. 0.7% (n=2) 2. 5.3% (n=15) HR: 0.13 95% CI, 0.03 to 0.59 P=0.0008 **Mortality** 1. 0 2. 0 **Adverse Events** 1. 12.2% (n=34) 2. 8.8% (n=25)

		• Previous hospitalization or treatment for COVID-19			**Serious Adverse Events** 1. 1.8% (n=5) 2. 6.7% (n=19)
Abbreviations: BMI = body mass index; CI = Confidence Interval; COVID-19 = coronavirus disease; DB = double blind; HR = Hazard Ratio; HBV = hepatitis B; HCV = hepatitis C; IV = intravenous; LOS = length of stay; MC = multi-center; n = number; RCTs = randomized controlled trials; US = United States; WHO = World Health Organization; yrs = years					

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, and warnings and precautions.

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

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

Systematic Reviews:
Remdesivir for Treatment Of COVID-19
A 2023 Cochrane systematic review evaluated all evidence from RCTs on the effect of remdesivir on clinical outcomes in COVID-19.[1] Literature was searched through May 21, 2022.[1] Non-hospitalized individuals with asymptomatic or mild COVID-19 infection were differentiated from hospitalized individuals with moderate to severe COVID-19.[1] Nine RCTs (n=11,218) met inclusion criteria, however only one (n=562) of the 9 RCTs was conducted in the outpatient setting in symptomatic people with a risk of progression to severe disease.[1] The population in the outpatient RCT differed significantly from the hospitalized population in terms of baseline disease severity, clinical course, and duration of the treatment (3 days versus 10 days, respectively), so the data were analyzed separately.[1] Risk of bias for the outpatient RCT was considered to be low for risk of hospitalization (clinical worsening) and safety outcomes.[1] Risk of bias for clinical improvement by day 14 was estimated as high as a large number of missing values and analyses were not performed as pre-defined by protocol, with a high risk of selective reporting.[1]

Data from this RCT showed that remdesivir decreased the risk of hospitalization up to day 28 compared with placebo (RR 0.28, 95% CI, 0.11 to 0.75; risk difference [RD] 46 fewer per 1000, 95% CI, 57 fewer to 16 fewer; n=562; moderate-certainty evidence).[1] No deaths were reported in either arm of this study, so it was not possible to determine if remdesivir impacts 28-day mortality.[1] There were less serious adverse events (in the remdesivir arm compared with placebo arm (RR 0.27, 95% CI, 0.10 to 0.70; low-certainty evidence), but no differences in AE of any grade were found between arms (RR 0.91, 95% CI 0.76 to 1.10; moderate-certainty evidence).[1] The applicability of this evidence to current practice may be limited by the recruitment of participants from mostly unvaccinated populations exposed to early variants of the SARS-CoV-2 virus at the time the study was undertaken.[1]

Nirmatrelvir Combined with Ritonavir for Treatment of COVID-19

A 2022 Cochrane systematic review assessed the efficacy and safety of ritonavir-boosted nirmatrelvir in treating COVID 19.[2] Literature was searched through July 11, 2022. Only one trial (n=2,246) met inclusion criteria, an RCT conducted in outpatients with mild to moderate COVID-19 which compared ritonavir-boosted nirmatrelvir with standard of care plus placebo.[2] Trial participants were unvaccinated, without previous confirmed SARS-CoV-2 infection, had a symptom onset of no more than 5 days before randomization, and were at high risk for progression to severe disease.[2] No evidence is currently available on ritonavir-boosted nirmatrelvir to treat hospitalized people with COVID-19 or to prevent a SARS-CoV-2 infection.

Ritonavir-boosted nirmatrelvir compared to standard of care plus placebo may reduce all-cause mortality at 28 days (RR 0.04, 95% CI, 0.00 to 0.68; 1 study, n= 2,224; estimated absolute effect: 11 deaths per 1000 people receiving placebo compared to 0 deaths per 1000 people receiving nirmatrelvir/ritonavir; low-certainty evidence), and may reduce hospitalization or death within 28 days (RR 0.13, 95% CI, 0.07 to 0.27; estimated absolute effect: 61 admissions or deaths per 1000 people receiving placebo compared to 8 admissions or deaths per 1000 people receiving nirmatrelvir/ritonavir; low-certainty evidence).[2]

There were less serious adverse events with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 0.24, 95% CI, 0.15 to 0.41; low-certainty evidence).[2] No difference in overall treatment-emergent adverse events were found between arms (RR 0.95, 95% CI, 0.82 to 1.10; moderate-certainty evidence).[2] However dysgeusia and diarrhea were more likely to occur with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 2.06, 95% CI, 1.44 to 2.95; moderate-certainty evidence).[2]

In summary, there is low-certainty evidence that ritonavir-boosted nirmatrelvir reduces the risk of all-cause mortality and hospital admission or death based on one trial investigating unvaccinated COVID-19 participants with symptom onset of no more than 5 days, without previous infection, who were at high risk for progression to severe disease.[2]

After review, 10 systematic reviews were excluded due to poor quality (e.g., network meta-analyses),[16-22] or wrong study design of included trials (e.g., observational).[23-26]

Guidelines:

National Institute of Health: Therapeutic Management of Nonhospitalized Adults with COVID-19

The most recent NIH update on treatment of outpatients with COVID-19 was issued July 21, 2023.[3] The NIH recommends that several factors be considered before treatment is selected for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications, the potential for significant drug-drug interactions, the patient's pregnancy status, time from symptom onset, and the *in vitro* activity of the available drug against currently circulating SARS-CoV-2 variants and subvariants.[3] Most of the data that support the use of the recommended treatment options come from clinical trials that enrolled individuals who were at high risk of disease progression and who had no pre-existing immunity from COVID-19 vaccination or prior SARS-CoV-2 infection.[3] The proportion of hospitalizations and deaths in the placebo arms of these trials was high compared to what is observed currently in populations where most people are vaccinated or have had prior SARS-CoV-2 infection.[3] Although these trials demonstrated the efficacy of using antiviral drugs in high-risk populations, it is difficult to know their precise effectiveness in the current real-world settings.[3]

Available therapies remain beneficial in people who continue to have an increased risk of disease progression.[3] These risk factors of severe disease include older people (i.e., those aged >50 years, but especially those aged ≥65 years) and people who are unlikely to have an adequate immune response to COVID-19 vaccines due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications.[3] Other risk factors include lack of

vaccination or incomplete vaccination; a prolonged amount of time since the most recent vaccine dose (e.g., >6 months); and conditions such as obesity, diabetes, and chronic respiratory, cardiac, or kidney disease.[1 3] Recommendations for patients who are at high risk for progressing to severe COVID-19 are as follows in order of preference:

- Oral ritonavir-boosted nirmatrelvir is favored in most high-risk, nonhospitalized patients with mild to moderate COVID-19 (Strong Recommendation, Moderate-quality Evidence).[3]
    - Ritonavir-boosted nirmatrelvir has high efficacy and has been shown to reduce hospitalization and death when administered to high-risk, unvaccinated, nonhospitalized patients within 5 days of symptom onset.[3,14]
    - Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions.[3]
    - The use of ritonavir-boosted nirmatrelvir may be challenging in patients with severe renal impairment and in patients receiving certain transplant-related immunosuppressants or chemotherapy.[3]
- Intravenous remdesivir is recommended when ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions) (Moderate Recommendation, Moderate-quality Evidence).[3]
- Oral molnupiravir is recommended to be reserved as alternative therapy when preferred therapies are not available, feasible to use, or clinically appropriate (Weak Recommendation, Moderate-quality Evidence).[3]
    - Molnupiravir appears to have lower efficacy[13] than the other options recommended by the NIH Panel, although no RCTs have directly compared these therapies.[3]
    - The NIH panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (Strong Recommendation, Expert Opinion).[3]

Infectious Diseases Society of America: Treatment of Patients with COVID-19

In March 2020, the IDSA formed a multidisciplinary guideline panel of infectious diseases clinicians, pharmacists, and methodologists with varied areas of expertise to regularly review the evidence and make recommendations about the treatment and management of persons with COVID-19.[4] The process used a living guideline approach and followed a rapid recommendation development checklist.[4] The most recent treatment update was published April 12, 2023. After a review of published evidence, medications that are **not** recommended for outpatient treatment of COVID-19 include: hydroxychloroquine, chloroquine, azithromycin, lopinavir/ritonavir, inhaled corticosteroids, famotidine, ivermectin, and colchicine.[4] The antidepressant, fluvoxamine, is recommended only in the context of a clinical trial (no recommendation; insufficient evidence).[4] In 2 RCTs that studied symptomatic ambulatory patients with COVID, fluvoxamine failed to demonstrate a beneficial effect on mortality at 28 days compared to no fluvoxamine (RR 0.69; 95% CI, 0.38 to 1.27; low-quality evidence).[4]

The overall certainty of evidence for the use of remdesivir in patients with mild-to-moderate COVID-19 was low due to concerns about imprecision, as less than half of the original projected sample size was enrolled leading to few events and fragility of the effect estimate.[4] However, compared to prior trials, giving remdesivir early in the course of infection appears to have a robust effect within the limitation of a small sample size.[4] The panel agreed that benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk for severe disease.[4] The evidence confirms that using remdesivir early in the disease process when viral loads are high confers maximum benefit.[4] The evidence for the use of remdesivir in children is limited.[4] For ambulatory children at risk for severe disease, one RCT included 8 children aged 12 to 18 years, limiting confidence in the available direct evidence for ambulatory care.[4] A report of 77 children who received remdesivir through compassionate use early in the pandemic found good tolerability in this population with a low rate of serious adverse events.[4]

The overall certainty of the evidence for the use of ritonavir-boosted nirmatrelvir in ambulatory patients is low. There are concerns with the inability to exclude potential risks to bias because of limited availability of study details, and there is imprecision due to a low number of events reported.[4] The panel agreed that the benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk of severe disease; however, recognized concerns with drug interactions must be considered.[4] The evidence confirms that using ritonavir-boosted nirmatrelvir early in the disease process when viral loads are high confers maximum benefit.[4] Recurrence of symptoms associated with viral rebound has been estimated to occur in ritonavir-boosted nirmatrelvir- treated patients in 0.8% to 6.6% in various trials, including the EPIC-HR trial.[4,14] More data are needed on the potential adverse effects of this medication.[4] In addition, future studies are important to inform the impact of ritonavir-boosted nirmatrelvir in hospitalized patients, in vaccinated high-risk patients with mild-to-moderate COVID-19 and in symptomatic immunocompromised patients with persistently elevated viral loads.[4]

The overall certainty of evidence for the use of molnupiravir in ambulatory patients is low given concerns with data imprecision, driven by few reported events and a relatively small effect size.[4] The use of molnupiravir presents additional considerations and potential concerns regarding viral mutagenesis in immunocompromised persons and safety in persons of reproductive age, for which more data are needed to quantify such effects.[4] The panel recognized that alternative treatment options exist with the possibility of greater benefit with a smaller known safety profile.[4] The guideline panel suggests the use of molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who are within 5 days of symptom onset and have no other treatment options.[4] More data are needed on the potential adverse effects of molnupiravir.[4]

Conditional recommendations supporting the use of remdesivir, ritonavir-boosted nirmatrelvir, and molnupiravir based on low-quality evidence are summarized below. Patient-specific factors (e.g., patient age, symptom duration, renal function, drug interactions), product availability, and institutional capacity and infrastructure should drive decision-making regarding choice of agent.[4] It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.[4] Data for combination of treatments do not currently exist.[4]

- Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at high risk for progression to severe disease (e.g., patients with $Sp0_2 \leq 94\%$ on room air), the IDSA guideline panel suggests remdesivir initiated within 7 days of symptom onset rather than no remdesivir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - Dosing for remdesivir in mild-to-moderate COVID-19 is 200 mg on day one followed by 100 mg on days two and three. Pediatric dosing is 5 mg/kg on day 1 and 2.5 mg/kg on subsequent days.[4]
- In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests ritonavir-boosted nirmatrelvir initiated within 5 days of symptom onset rather than no ritonavir-boosted nirmatrelvir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - Drug/supplement screening needed for potential drug interactions.[4]
    - Dosing based on renal function per manufacturer's guidance.[4]
- In ambulatory patients (≥18 years of age) with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment option, the IDSA guideline panel suggests molnupiravir initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional Recommendation, Low Certainty of Evidence).[4]
    - Molnupiravir is not authorized under the FDA EUA for use in pediatric patients less than 18 years because it may affect bone and cartilage growth.[4]
    - Molnupiravir is not authorized under the FDA EUA for use during pregnancy.[4]

National Institute for Health and Care Excellence: Managing COVID-19 Rapid Guideline

The NICE guidance was published in March 2021 and most recently updated June 22, 2023.[5] Risk factors for progression to severe COVID-19 in adults were defined by the independent advisory group and include: people with Down's syndrome and other genetic disorders, solid cancer, hematological diseases and recipients of hematological stem cell transplant, renal disease, liver diseases , solid organ transplants, immune-mediated inflammatory disorders, asthma, chronic pulmonary obstructive disease, immune deficiencies, HIV/AIDS, and neurological disorders.[5] Most of the RCTs reviewed for the NICE guidance were in unvaccinated patients prior to the emergence of the Omicron variant (see **Table 2** above).[5]

- Ritonavir-boosted nirmatrelvir is recommended as first-line treatment initiated as soon as possible and within 5 days of symptom onset (benefits outweigh harms for almost everyone) for treating COVID-19 in adults, only if the patient is at increased risk for progression to severe COVID-19, as described earlier, and supplemental oxygen for the infection is not needed.[5]
- Remdesivir is recommended as a second-line treatment option (Conditional recommendation; benefits outweigh harms for most people). A 3-day course of remdesivir may be considered for children and young people who weigh at least 40 kg and adults with COVID-19 who:
    - do not need supplemental oxygen for COVID-19, and
    - are within 7 days of symptom onset, and
    - are thought to be at high risk of progression to severe COVID-19. [5]
- Molnupiravir may be considered as a third-line treatment option (Conditional recommendation) for adults with COVID-19 who:
    - do not need supplemental oxygen for COVID-19, and
    - are within 5 days of symptom onset, and
    - are thought to be at high risk of progression to severe COVID-19.[5]

Randomized Controlled Trials:

A total of 365 citations were manually reviewed from the initial literature search. After further review, 365 citations were excluded because of wrong study design, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Specific Drug Information

Table 1. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption/Distribution	Metabolism/Excretion	Pharmacokinetics (mean)
Molnupiravir (LAGEVRIO)[9]	• Prodrug metabolized to NHC, a nucleoside analog which inhibits RNA replication.	• Median T_{max} = 1.5 hrs • 0% protein bound	• Major route of elimination is hepatic.	• Half-life: 3.3 hrs • Cmax: 2330 ng/mL • AUC: 8260 ng/hr/ml • Vd: 142 L
Nirmatrelvir/Ritonavir (PAXLOVID)[7]	• Nirmatrelvir: protease inhibitor which blocks viral replication. • Ritonavir: inhibits metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. It does not have viral activity against the SARS-CoV-2 virus.	• Median T_{max} = 3 hrs • 69% protein bound	• Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal. • Major route of elimination is renal.	• Half-life: 6.05 hrs • Cmax: 3.43 mcg/mL • AUC: 30.4 mcg/hr/mL • Vd: 104.7 L

Remdesivir (VEKLURY)[6]	• Nucleotide analog RNA polymerase inhibitor which reduces RNA transcription.	• T_{max} = 0.67 to 0.68 hrs
		• 88-93.6% protein bound
			• Major route of elimination is hepatic.
			• Metabolic Pathways
			  ○ CES1 80%
			  ○ Cathepsin A (10%)
			  ○ CYP3A 10%
				• Half-life: 1 hr
				• Cmax: 2229 ng/L
				• AUC: 1585 ng/hr/mL
				• Vd: NR

Abbreviations: AUC = area under the curve; C = concentration; CYP = cytochrome P450; hrs = hours; L = liters; mcg = micrograms; mL = milliliters; ng = nanograms; NHC = N-hydroxycytidine; NR = not reported; T = time; Vd = volume of distribution				

Table 2. Use in Specific Populations.

Drug Name	Pediatric Patients	Patients with Renal Impairment	Patients with Hepatic Impairment	Pregnancy/Lactation
Molnupiravir (LAGEVRIO)[9]	• Not authorized for use in patients < 18 yo as it may	• No dose adjustment is recommended.	• No dose adjustment is recommended.	• Based on animal data, may cause fetal harm.

	affect bone and cartilage growth.			Use is not recommended during pregnancy. • Breast feeding is not recommended during treatment and up until 4 days after last dose.
Nirmatrelvir/Ritonavir (PAXLOVID)[7]	• EUA permits use in pediatric patients > 12 yo and older weighing at least 40 kg • Not FDA approved in patients < 18 yo	• Moderate renal impairment (eGFR 30 to 59 mL/min): reduce dose to 2 tablets (nirmatrelvir 150 mg with 1 tablet of ritonavir 100 mg) orally twice daily for 5 days. • Not recommended in severe renal impairment (eGFR <30 mL/min)	• No dose adjustment is recommended in mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. • Not recommended for use in severe hepatic impairment (Child-Pugh Class C) due to lack of data.	• Insufficient data to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse fetal outcomes. • Insufficient data in breast fed infants. • Consider risk versus benefit.
Remdesivir (VEKLURY)[6]	• Approved in pediatric patients 28 days of age and older and weighing at least 3 kg.	• No dose adjustment is recommended.	• No dose adjustment is recommended. • Discontinue if ALT/AST increase to > 10 times the upper limit of normal	• Insufficient pregnancy data is available during first trimester. • No drug-associated risks have been identified in second and third trimesters. • Consider risk versus benefit in lactation.
Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration; EUA = Emergency Use Authorization; FDA = Food and Drug Administration kg = kilograms; mg = milligram; mL = milliliters; min = minutes; yo = years old				

Table 3. Summary of Warnings and Precautions.

Drug Name	Drug Interactions	Hepatic Disease	Risk of HIV-1 Resistance
Molnupiravir (LAGEVRIO)[9]	N/A	N/A	N/A
Nirmatrelvir/Ritonavir (PAXLOVID)[7]	• Contraindicated for co-administration with drugs	• Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in	• Due to coadministration with ritonavir, there may be a risk of developing

	metabolized by CYP3A hepatic pathway.	patients receiving ritonavir. Caution should be exercised in patients with pre-existing hepatic disease, liver enzyme abnormalities, or hepatitis.	resistance to HIV protease inhibitors in people with uncontrolled or undiagnosed HIV-1 infection.
Remdesivir (VEKLURY)[6]	• Avoid co-administration with chloroquine or hydroxychloroquine due to risk of reduced antiviral activity.	• Increased risk of transaminase elevations.	N/A
Abbreviations: HIV = Human Immunodeficiency Virus; N/A = Not Applicable			

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to September Week 4 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 04, 2023

1	COVID-19/ or SARS-CoV-2/ or COVID-19 Drug Treatment/	247189
2	molnupiravir.mp.	421
3	remdesivir.mp.	2492
4	Ritonavir/ or nirmatrelvir.mp.	5572
5	2 or 3 or 4	8009
6	1 and 5	3306
7	limit 6 to (english language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	365

Appendix 3: Key Inclusion Criteria

Population	Patients with mild-to-moderate COVID-19
Intervention	Molnupiravir, nirmatrelvir/ritonavir, and remdesivir
Comparator	Placebo or standard of care
Outcomes	Hospitalization or mortality
Timing	Within 5 to 7 days of symptom onset, depending on antiviral selection
Setting	Outpatients