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, August 3, 2023 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

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

A. Quarterly Utilization Reports
B. Oncology Prior Authorization Updates
C. DUR OLD BUSINESS: CGRP Inhibitors
   1. Public Comment

1:25 PM III. DUR ACTIVITIES

A. ProDUR Report	L. Starkweather (Gainwell)
B. RetroDUR Report	D. Engen (OSU)
C. Oregon State Drug Review	K. Sentena (OSU)

   1. Psychotropic Use in Youth Enrolled in the Oregon Health Plan and Youth in Foster Care with an Emphasis on Antipsychotic Prescription
   2. COVID-19 Therapeutics Update: Where Are We Now?

IV. DUR NEW BUSINESS

1:40 PM	A. Sublingual Buprenorphine Quantity Limit Policy Evaluation	S. Servid (OSU)

   1. Policy Evaluation/Prior Authorization Criteria
   2. Public Comment
   3. Discussion and Clinical Recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS

2:00 PM	A. Daybue™ (trofinetide) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:15 PM	B. BPH Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:35 PM	C. Vowst™ (oral fecal microbiota spores, live-brpk) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:50 PM	BREAK	
3:05 PM	D. Non-injectable Allergen Immunotherapy Class Review 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:20 PM	E. Gene Therapies for Beta-thalassemia and Hemophilia B DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
3:40 PM	F. Endocrine Therapies Class & Prior Authorization Updates 1. GnRH Agonists Class Update/Prior Authorization Criteria 2. Estrogens Prior Authorization Criteria 3. Testosterone Prior Authorization Criteria 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU) S. Servid (OSU)
4:10 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribal Health	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, All Smiles Community Oral Health	Portland	December 2023
William Origer, MD, FAAFP	Physician	Physician Advisor, Hospital Utilization Review, Good Samaritan Hospital	Corvallis	December 2023
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2024
Russell Huffman, DNP, PMHNP	Public	Psychiatric Nurse Practitioner	Salem	December 2024
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia	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	Pharmacy Director, Community Health Centers of Benton & Linn Counties	Corvallis	December 2025

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, June 1st, 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; Douglas Carr, MD; Russ Huffman, PMHNP; Tim Langford, PharmD Caryn Mickelson, PharmD; Robin Moody, MPH; Eriko Onishi, MD; Bill Origer, MD; Eddie Saito, PharmD

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

Audience: Robert Jaramillo, Reata Pharmaceuticals*; David Gross, Pfizer*; Rochelle Yang, Teva*; Erin Nowak, AbbVie*; Aileen Chin, Umpqua Health Pharmacy Student; Jennifer Davis, Gilead; Valerie Ng, LEO Pharma; Melissa Abbott, Eisai; Michele Sabados, Alkermes; Gary Parenteau, Dexcom; Paul Thompson, Alkermes; Amy Hale, Janssen; Teresa Blair, Ipsen; Matt Worthy, OHSU; Amy Breen, Teva; Laurie Krekemeyer, Reata Pharmaceutical; Tiina Andrews, UHA; Chris Ferrin, IHN; Brandie Feger, Advanced Health CCO; Suzanne Stewart, Supernus Pharmaceuticals; Mark Kantor, AllCare CCO; Mark Wolber, Sunovion; Saghi Maleki; Takeda Pharmaceuticals; Lori McDermott, Viking HCS; Haleh Ouranos, Ipsen Neuroscience; Deron Grothe, Braeburn; Ryan Taketomo; Washington State Health; Michael Foster, BMS; Chris Tanaka, ViiVhealthcare; Sean Staff; Tim Chiu; Kailey Skelton, PacificSource CCO; Ted Raszka; Rob Booth, AbbVie; Mark Germann, LEO Pharma; Chris Johnson; Shelly Egbert; Carol Ricciotti, Aimmune; Danny Martinez, CSL Behring

(*) 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 April 2023 Minutes presented by Roger Citron, RPh
ACTION: Motion to approve, 2nd, all in favor

D. Department Update provided by Andrew Gibler, PharmD

E. Legislative Update provided by Trevor Douglass, DC

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Report

B. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Omisirge® (omidubicel-onlv) and Zynyz™ (retifanlimab-dlwr)to Table 1 in the Oncology Agents prior authorization (PA) criteria

C. Orphan Drug Policy Updates
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Joenja® (leniolisib) and Lamzede® (velmanase alfa-tycv) 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. **Hormone Replacement Therapy – A Focus on the Benefits and Risks of Estrogen**
2. **Pharmacological Prevention and Treatment of Mpox**
3. **Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Benefit for Children and Adolescents**

D. Pharmacy & Therapeutics Operating Procedures: Sara Fletcher, PharmD

E. Evaluation of Evidence Methods
1. **Mental Health Clinical Advisory Group Methods:** Andrew Gibler, PharmD
2. **Pharmacy & Therapeutics Committee Methods:** Sarah Servid, PharmD

IV. DUR NEW BUSINESS

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A. Low Dose Quetiapine Drug Use Evaluation:

1. **Mental Health Clinical Advisory Group Summary:** Andrew Gibler, PharmD
2. **Drug Use Evaluation/Proposed PA Criteria:** Sarah Servid, PharmD

Recommendations:

- Update PA criteria for low dose quetiapine to incorporate GAD
- Automatically approve PA requests for extended-release quetiapine with recent claims for an SSRI or SNRI
- Make quetiapine ER preferred

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

The Committee then recommended removing the auto PA for mental health specialists

ACTION: Motion to approve, 2nd, seven in-favor with two opposed

V. PREFERRED DRUG LIST (PDL) NEW BUSINESS

A. Skyclarys™ (omaveloxolone) New Drug Evaluation: Deanna Moretz, PharmD

Recommendations:

- Maintain omaveloxolone as non-preferred on the PDL
- Implement proposed PA criteria to ensure medically appropriate use

ACTION: The Committee amended the proposed PA approval criteria to add questions to ensure the patient is ambulatory and able to swallow. They also amended the renewal criteria adding language regarding slowing progression.

Motion to approve, 2nd, all in favor

B. CGRP Inhibitors DERP Summary: Dave Engen, PharmD

Recommendations:

- No PDL changes recommended based on review of recently published evidence
- Update PA criteria as proposed
- Evaluate costs in executive session

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

C. Severe Inflammatory Skin Disease PA Update: Deanna Moretz, PharmD

Recommendations:

- Revise "Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis" and "Targeted Immune Modulators for Autoimmune Conditions" PA criteria to require a 4-week trial and failure (or contraindication) of either moderate to high potency topical steroids in combination with a topical calcineurin inhibitor (e.g., tacrolimus) or an oral immunomodulator (e.g., cyclosporine, methotrexate, or oral corticosteroids) before approval of dupilumab or upadacitinib treatment for atopic dermatitis.

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

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D. Botulinum Toxins Class Update: Kathy Sentena, PharmD
Recommendations:
- No PDL changes recommended based on review of recently published evidence
- Update PA criteria to allow coverage under EPSDT
- Evaluate costs in executive session

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

E. Clostridioides difficile Drug Class Update & NDE: Deanna Moretz, PharmD
Recommendations:
- Maintain fidaxomicin as non-preferred on the PDL
- Retire current PA criteria and rely on "Non-Preferred" PA criteria to verify FDA-approved indication for C. difficile
- Designate fecal microbiota non-preferred on the PDL and implement proposed "Prevention of C. difficile Recurrence" PA criteria and include bezlotoxumab infusion and fecal microbiota enema
- Retire current bezlotoxumab PA criteria
- Evaluate costs in executive session

ACTION: The Committee rejected the proposal to retire the "Fidaxomicin" PA criteria
Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Douglas Carr, MD; Russ Huffman, PMHNP; Tim Langford, PharmD Caryn Mickelson, PharmD; Robin Moody, MPH; Eriko Onishi, MD; Bill Origer, MD; Eddie Saito, PharmD

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

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. CGRP Inhibitors DERP Summary
Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

B. Botulinum Toxins Class Update
Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

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C. Clostridioides difficile Drug Class Update & NDE
Make metronidazole capsules non-preferred
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: January 2022 - December 2022

Eligibility	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
Total Members (FFS & Encounter)	1,270,424	1,276,063	1,284,291	1,291,200	1,296,769	1,303,371	1,322,427	1,330,020	1,337,959	1,344,339	1,355,484	1,364,931	1,314,773
FFS Members	117,322	110,548	109,789	112,522	113,945	111,881	115,910	113,720	117,050	118,585	118,506	120,719	115,041
OHP Basic with Medicare	8,488	8,161	8,271	8,510	8,597	8,424	8,606	8,473	8,710	8,899	8,720	8,696	8,546
OHP Basic without Medicare	10,889	10,579	10,500	10,595	10,601	10,503	10,497	10,255	10,368	10,396	10,140	10,077	10,450
ACA	97,945	91,808	91,018	93,417	94,747	92,954	96,807	94,992	97,972	99,290	99,646	101,946	96,045
Encounter Members	1,153,102	1,165,515	1,174,502	1,178,678	1,182,824	1,191,490	1,206,517	1,216,300	1,220,909	1,225,754	1,236,978	1,244,212	1,199,732
OHP Basic with Medicare	87,412	88,084	89,468	90,661	92,068	93,206	94,346	95,446	96,256	97,094	98,309	98,992	93,445
OHP Basic without Medicare	68,310	68,509	68,469	68,580	68,801	68,956	69,022	69,064	68,981	69,116	69,282	69,339	68,869
ACA	997,380	1,008,922	1,016,565	1,019,437	1,021,955	1,029,328	1,043,149	1,051,790	1,055,672	1,059,544	1,069,387	1,075,881	1,037,418

Gross Cost Figures for Drugs	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	YTD Sum
Total Amount Paid (FFS & Encounter)	$102,632,429	$98,867,540	$115,964,283	$106,390,145	$111,630,567	$113,411,153	$104,162,196	$117,254,252	$108,765,872	$109,745,769	$111,374,315	$112,635,926	$1,312,834,447
Mental Health Carve-Out Drugs	$11,261,452	$10,860,831	$12,310,707	$11,632,498	$12,126,081	$11,928,952	$11,103,276	$11,887,487	$11,155,206	$11,196,317	$11,312,292	$11,535,933	$138,311,031
OHP Basic with Medicare	$317	$11,314	$7,893	$11,471	$9,259	$10,001	$7,612	$3,774	$5,976	$4,972	$2,989	$9,065	$84,642
OHP Basic without Medicare	$4,085,716	$3,899,804	$4,428,959	$4,144,754	$4,338,839	$4,413,433	$3,991,935	$4,330,888	$4,140,233	$4,048,510	$4,092,917	$4,213,417	$50,129,406
ACA	$7,083,030	$6,859,649	$7,775,102	$7,388,593	$7,684,437	$7,427,324	$7,023,389	$7,484,022	$6,946,361	$7,075,569	$7,148,785	$7,247,605	$87,143,865
FFS Physical Health Drugs	$4,988,504	$4,506,611	$5,042,715	$5,259,893	$5,495,460	$5,206,008	$4,813,022	$5,618,954	$5,108,181	$5,311,372	$5,273,057	$5,249,070	$61,872,848
OHP Basic with Medicare	$187,735	$177,974	$206,926	$200,383	$210,050	$235,210	$209,829	$229,505	$197,445	$178,532	$186,610	$197,105	$2,417,306
OHP Basic without Medicare	$1,131,981	$989,932	$1,095,307	$1,162,612	$1,223,287	$1,192,699	$976,082	$1,218,034	$1,021,988	$1,224,526	$1,088,560	$1,097,663	$13,422,672
ACA	$3,520,775	$3,227,873	$3,624,920	$3,742,419	$3,910,364	$3,647,875	$3,474,077	$3,998,121	$3,736,085	$3,752,916	$3,796,993	$3,715,416	$44,147,834
FFS Physician Administered Drugs	$1,234,816	$1,641,645	$1,751,771	$1,444,195	$1,401,954	$1,692,406	$1,411,950	$1,180,235	$1,471,118	$1,217,309	$1,109,168	$1,220,797	$16,777,364
OHP Basic with Medicare	$152,121	$149,862	$112,369	$142,284	$103,766	$111,635	$181,427	$140,202	$165,564	$158,290	$135,729	$201,377	$1,754,627
OHP Basic without Medicare	$198,491	$523,122	$497,954	$258,208	$319,443	$565,639	$380,604	$105,395	$517,247	$347,962	$127,089	$160,861	$4,002,015
ACA	$402,708	$540,534	$614,452	$555,939	$532,866	$546,440	$387,861	$484,786	$412,768	$395,581	$373,289	$328,084	$5,575,309
Encounter Physical Health Drugs	$67,359,540	$64,521,649	$73,974,871	$69,191,667	$72,407,717	$72,007,377	$67,159,686	$75,692,771	$70,766,134	$71,170,616	$72,026,457	$73,057,083	$849,335,569
OHP Basic with Medicare	$427,247	$393,401	$443,085	$409,996	$426,551	$397,156	$356,086	$412,914	$378,933	$347,974	$388,421	$363,596	$4,745,359
OHP Basic without Medicare	$16,513,387	$16,147,921	$17,628,296	$17,063,076	$17,075,131	$17,309,940	$16,373,315	$17,926,264	$16,774,833	$17,181,860	$16,860,411	$17,246,806	$204,101,240
ACA	$49,553,658	$47,130,531	$54,870,411	$50,683,946	$53,873,848	$53,229,111	$49,218,612	$55,787,223	$52,003,469	$52,205,616	$53,204,102	$53,749,563	$625,510,091
Encounter Physician Administered Drugs	$17,788,117	$17,336,805	$22,884,218	$18,861,893	$20,199,354	$22,576,410	$19,674,262	$22,874,805	$20,265,234	$20,850,154	$21,653,340	$21,573,044	$246,537,634
OHP Basic with Medicare	$1,085,156	$884,118	$1,105,800	$962,226	$989,066	$1,157,204	$1,093,875	$1,033,908	$914,398	$875,382	$1,155,400	$935,875	$12,192,408
OHP Basic without Medicare	$3,855,742	$4,120,405	$5,597,882	$4,460,931	$5,822,642	$4,895,186	$4,570,688	$5,246,370	$4,435,967	$4,648,460	$4,857,008	$5,126,819	$57,638,101
ACA	$12,593,526	$12,070,441	$15,955,169	$13,269,881	$13,205,832	$16,172,140	$13,743,386	$16,220,798	$14,560,980	$14,757,052	$15,129,187	$14,948,199	$172,626,591

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: July 20, 2023

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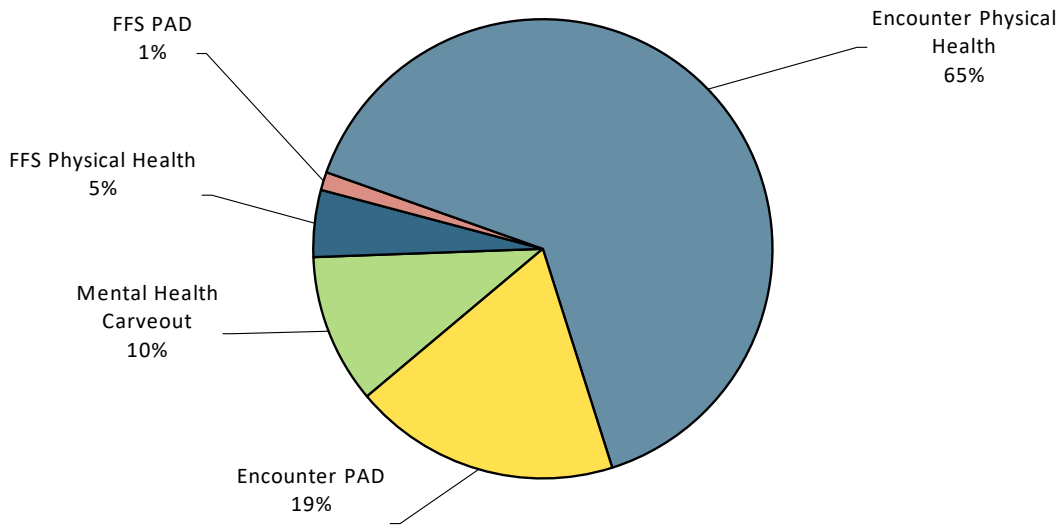
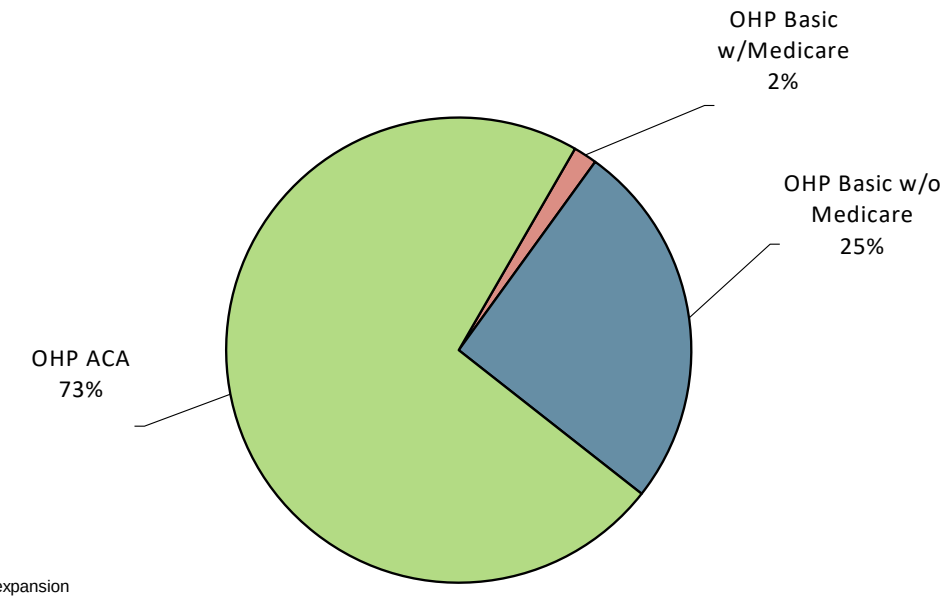
Pharmacy Utilization Summary Report: January 2022 - December 2022

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

Last Updated: July 20, 2023

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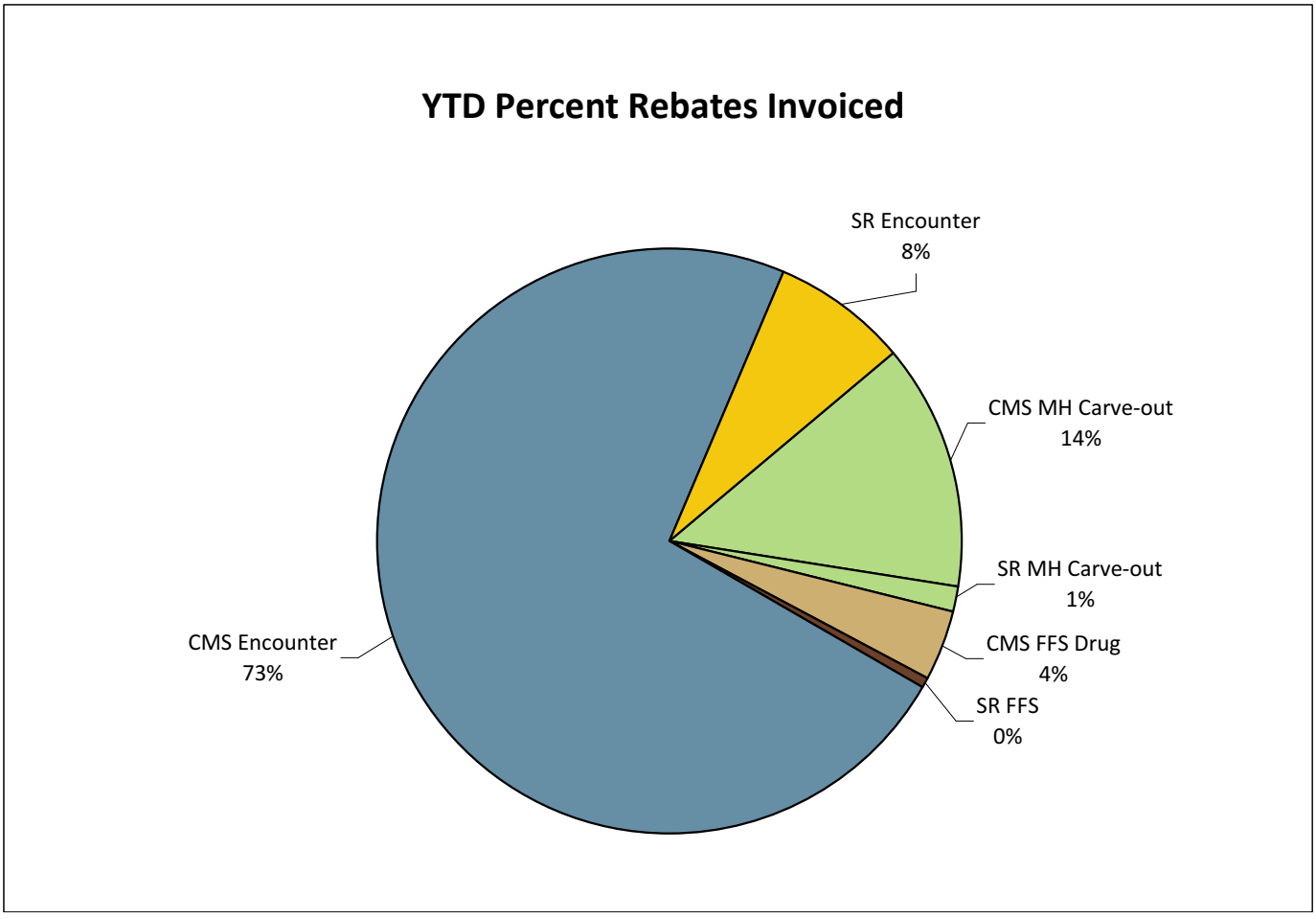
Pharmacy Utilization Summary Report: January 2022 - December 2022

Quarterly Rebates Invoiced	2022-Q1	2022-Q2	2022-Q3	2022-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$118,382,008	$123,107,390	$128,092,412	$124,294,854	$493,876,664
CMS MH Carve-out	$17,107,658	$18,171,503	$16,617,733	$15,330,258	$67,227,153
SR MH Carve-out	$1,341,151	$1,717,023	$2,206,637	$1,975,294	$7,240,105
CMS FFS Drug	$4,798,613	$4,584,749	$5,297,164	$4,709,468	$19,389,995
SR FFS	$506,401	$511,151	$556,094	$421,907	$1,995,553
CMS Encounter	$86,258,076	$89,006,051	$92,536,100	$93,130,051	$360,930,278
SR Encounter	$8,370,109	$9,116,913	$10,878,682	$8,727,876	$37,093,579

Quaterly Net Drug Costs	2022-Q1	2022-Q2	2022-Q3	2022-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$199,082,244	$208,324,475	$202,089,909	$209,461,155	$818,957,783
Mental Health Carve-Out Drugs	$15,984,180	$15,799,005	$15,321,598	$16,738,989	$63,843,772
FFS Phys Health + PAD	$13,861,048	$15,404,016	$13,750,202	$14,249,399	$57,264,665
Encounter Phys Health + PAD	$169,237,015	$177,121,454	$173,018,109	$178,472,768	$697,849,345



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

Last Updated: July 20, 2023

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: January 2022 - December 2022

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$80.79	$77.48	$90.29	$82.40	$86.08	$87.01	$78.77	$88.16	$81.29	$81.64	$82.17	$82.52	$83.22
Mental Health Carve-Out Drugs	$8.86	$8.51	$9.59	$9.01	$9.35	$9.15	$8.40	$8.94	$8.34	$8.33	$8.35	$8.45	$8.77
FFS Physical Health Drugs	$42.52	$40.77	$45.93	$46.75	$48.23	$46.53	$41.52	$49.41	$43.64	$44.79	$44.50	$43.48	$44.84
FFS Physician Administered Drugs	$10.53	$14.85	$15.96	$12.83	$12.30	$15.13	$12.18	$10.38	$12.57	$10.27	$9.36	$10.11	$12.21
Encounter Physical Health Drugs	$58.42	$55.36	$62.98	$58.70	$61.22	$60.43	$55.66	$62.23	$57.96	$58.06	$58.23	$58.72	$59.00
Encounter Physician Administered Drugs	$15.43	$14.87	$19.48	$16.00	$17.08	$18.95	$16.31	$18.81	$16.60	$17.01	$17.51	$17.34	$17.11

Claim Counts	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
Total Claim Count (FFS & Encounter)	1,125,607	1,050,406	1,201,591	1,147,832	1,183,204	1,174,176	1,105,954	1,202,900	1,141,345	1,178,012	1,183,189	1,178,826	1,156,087
Mental Health Carve-Out Drugs	190,963	179,890	204,408	193,127	199,439	197,694	189,742	206,368	194,289	196,539	196,014	197,042	195,460
FFS Physical Health Drugs	38,027	34,927	38,390	36,481	37,555	36,600	34,796	36,892	34,829	35,427	35,588	35,265	36,231
FFS Physician Administered Drugs	10,812	9,810	11,619	10,406	10,511	10,321	9,941	10,175	9,687	9,871	9,820	9,586	10,213
Encounter Physical Health Drugs	773,061	717,778	819,797	787,282	813,499	810,841	757,992	828,568	786,742	818,509	826,529	825,349	797,162
Encounter Physician Administered Drugs	112,744	108,001	127,377	120,536	122,200	118,720	113,483	120,897	115,798	117,666	115,238	111,584	117,020

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$91.18	$94.12	$96.51	$92.69	$94.35	$96.59	$94.18	$97.48	$95.30	$93.16	$94.13	$95.55	$94.60
Mental Health Carve-Out Drugs	$58.97	$60.37	$60.23	$60.23	$60.80	$60.34	$58.52	$57.60	$57.42	$56.97	$57.71	$58.55	$58.98
FFS Physical Health Drugs	$131.18	$129.03	$131.35	$144.18	$146.33	$142.24	$138.32	$152.31	$146.66	$149.92	$148.17	$148.85	$142.38
FFS Physician Administered Drugs	$114.21	$167.34	$150.77	$138.78	$133.38	$163.98	$142.03	$115.99	$151.87	$123.32	$112.95	$127.35	$136.83
Encounter Physical Health Drugs	$87.13	$89.89	$90.24	$87.89	$89.01	$88.81	$88.60	$91.35	$89.95	$86.95	$87.14	$88.52	$88.79
Encounter Physician Administered Drugs	$157.77	$160.52	$179.66	$156.48	$165.30	$190.17	$173.37	$189.21	$175.01	$177.20	$187.90	$193.33	$175.49

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$23.10	$23.25	$23.57	$24.00	$24.03	$24.50	$24.45	$24.99	$25.01	$23.63	$23.23	$23.46	$23.94
Mental Health Carve-Out Drugs	$16.48	$16.41	$16.30	$16.63	$16.81	$17.06	$17.21	$17.56	$17.29	$17.35	$17.32	$17.61	$17.00
FFS Physical Health Drugs	$84.53	$84.23	$87.06	$97.49	$99.77	$99.83	$94.81	$103.37	$106.33	$103.81	$105.44	$106.45	$97.76
Encounter Physical Health Drugs	$22.25	$22.39	$22.75	$22.77	$22.66	$23.29	$23.41	$23.73	$23.74	$22.05	$21.45	$21.66	$22.68

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$538.59	$607.05	$648.16	$641.31	$654.31	$666.14	$670.50	$697.91	$643.95	$616.22	$638.99	$672.70	$641.32
Mental Health Carve-Out Drugs	$946.04	$964.98	$963.32	$962.53	$964.18	$1,020.78	$1,085.38	$1,115.97	$1,146.88	$1,155.28	$1,195.55	$1,234.42	$1,062.94
FFS Physical Health Drugs	$281.53	$314.99	$345.66	$372.20	$375.11	$349.65	$348.48	$400.56	$337.76	$367.77	$355.52	$361.91	$350.93
Encounter Physical Health Drugs	$526.12	$595.19	$637.07	$627.27	$641.73	$653.61	$656.14	$682.17	$625.33	$593.10	$616.88	$650.98	$625.47

Generic Drug Use Percentage	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
Generic Drug Use Percentage	88.3%	89.3%	90.0%	90.2%	90.2%	90.5%	90.7%	90.8%	90.2%	89.9%	90.2%	90.5%	90.1%
Mental Health Carve-Out Drugs	95.4%	95.4%	95.4%	95.4%	95.4%	95.7%	96.1%	96.4%	96.4%	96.5%	96.6%	96.6%	95.9%
FFS Physical Health Drugs	76.3%	80.6%	82.9%	83.0%	83.1%	83.0%	82.8%	83.5%	82.6%	82.5%	82.9%	83.4%	82.2%
Encounter Physical Health Drugs	87.1%	88.2%	89.0%	89.2%	89.3%	89.6%	89.7%	89.7%	89.0%	88.6%	89.0%	89.4%	89.0%

Preferred Drug Use Percentage	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Avg Monthly
Preferred Drug Use Percentage	89.84%	89.81%	89.89%	89.88%	89.89%	89.82%	90.49%	90.42%	90.45%	90.65%	90.48%	90.31%	90.2%
Mental Health Carve-Out Drugs	93.31%	93.29%	93.31%	93.33%	93.31%	93.27%	93.24%	93.13%	93.14%	93.07%	92.87%	92.70%	93.2%
FFS Physical Health Drugs	94.52%	94.43%	94.54%	94.66%	94.80%	94.90%	95.64%	95.77%	95.69%	95.64%	95.79%	95.85%	95.2%
Encounter Physical Health Drugs	88.78%	88.73%	88.84%	88.85%	88.86%	88.79%	89.61%	89.54%	89.59%	89.89%	89.72%	89.54%	89.2%

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: July 20, 2023

Drug Use Research & Management Program
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2023

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	INVEGA SUSTENNA	Antipsychotics, Parenteral	$4,270,335	10.7%	1,736	$2,460	Y
2	VRAYLAR*	Antipsychotics, 2nd Gen	$4,257,156	10.7%	3,486	$1,221	Y
3	REXULTI*	Antipsychotics, 2nd Gen	$2,596,744	6.5%	2,030	$1,279	V
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,535,063	6.4%	1,090	$2,326	Y
5	INVEGA TRINZA	Antipsychotics, Parenteral	$1,128,936	2.8%	152	$7,427	Y
6	TRINTELLIX	Antidepressants	$892,597	2.2%	2,044	$437	V
7	ARISTADA	Antipsychotics, Parenteral	$889,001	2.2%	376	$2,364	Y
8	CAPLYTA*	Antipsychotics, 2nd Gen	$742,834	1.9%	527	$1,410	V
9	BUPROPION XL	Antidepressants	$614,270	1.5%	48,395	$13	Y
10	SERTRALINE HCL	Antidepressants	$603,602	1.5%	62,914	$10	Y
11	DULOXETINE HCL	Antidepressants	$557,286	1.4%	39,015	$14	Y
12	FLUOXETINE HCL	Antidepressants	$531,330	1.3%	46,206	$11	Y
13	TRAZODONE HCL	Antidepressants	$507,823	1.3%	49,752	$10	
14	ESCITALOPRAM OXALATE	Antidepressants	$458,705	1.2%	45,820	$10	Y
15	LYBALVI*	Antipsychotics, 2nd Gen	$445,211	1.1%	343	$1,298	V
16	Epoetin Beta Esrd Use	Physican Administered Drug	$402,826	1.0%	73	$5,518	
17	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$370,716	0.9%	28,942	$13	
18	LAMOTRIGINE	Antiepileptics, Outpatient	$336,028	0.8%	30,842	$11	Y
19	SPRAVATO*	Antidepressants	$334,362	0.8%	284	$1,177	V
20	ATOMOXETINE HCL*	ADHD Drugs	$332,241	0.8%	9,226	$36	Y
21	LATUDA*	Antipsychotics, 2nd Gen	$283,762	0.7%	542	$524	Y
22	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$277,391	0.7%	21,219	$13	Y
23	BIKTARVY	HIV	$270,077	0.7%	108	$2,501	Y
24	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$261,695	0.7%	241	$1,086	Y
25	BUPROPION XL	Antidepressants	$250,190	0.6%	1,405	$178	V
26	LAMOTRIGINE ER	Antiepileptics, Outpatient	$244,106	0.6%	3,757	$65	V
27	VENLAFAXINE HCL ER	Antidepressants	$241,366	0.6%	19,620	$12	Y
28	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$232,504	0.6%	21,125	$11	Y
29	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$227,819	0.6%	1	$227,819	
30	TRIKAFTA*	Cystic Fibrosis	$223,373	0.6%	23	$9,712	N
31	CONCERTA*	ADHD Drugs	$223,279	0.6%	667	$335	Y
32	Elosulfase Alfa, Injection	Physican Administered Drug	$204,898	0.5%	12	$17,075	
33	HUMIRA(CF) PEN*	Targeted Immune Modulators	$191,199	0.5%	55	$3,476	Y
34	INVEGA HAFYERA	Antipsychotics, Parenteral	$190,867	0.5%	12	$15,906	Y
35	CITALOPRAM HBR	Antidepressants	$181,174	0.5%	20,490	$9	Y
36	OLANZAPINE*	Antipsychotics, 2nd Gen	$177,405	0.4%	13,604	$13	Y
37	Iron Sucrose Injection	Physican Administered Drug	$175,038	0.4%	372	$471	
38	PALIPERIDONE ER*	Antipsychotics, 2nd Gen	$172,502	0.4%	1,909	$90	V
39	MIRTAZAPINE	Antidepressants	$172,318	0.4%	12,599	$14	Y
40	VYVANSE*	ADHD Drugs	$167,650	0.4%	990	$169	Y
		Top 40 Aggregate:	**$27,175,680**		**492,004**	**$7,663**	
		All FFS Drugs Totals:	**$39,831,852**		**757,662**	**$677**	

*** 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: July 20, 2023

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Epoetin Beta Esrd Use	Physican Administered Drug	$402,826	3.9%	73	$5,518	
2	BIKTARVY	HIV	$270,077	2.6%	108	$2,501	Y
3	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$227,819	2.2%	1	$227,819	
4	TRIKAFTA*	Cystic Fibrosis	$223,373	2.2%	23	$9,712	N
5	CONCERTA*	ADHD Drugs	$223,279	2.2%	667	$335	Y
6	Elosulfase Alfa, Injection	Physican Administered Drug	$204,898	2.0%	12	$17,075	
7	HUMIRA(CF) PEN*	Targeted Immune Modulators	$191,199	1.9%	55	$3,476	Y
8	Iron Sucrose Injection	Physican Administered Drug	$175,038	1.7%	372	$471	
9	VYVANSE*	ADHD Drugs	$167,650	1.6%	990	$169	Y
10	SABRIL	Antiepileptics, Outpatient	$145,340	1.4%	3	$48,447	N
11	LANTUS SOLOSTAR*	Diabetes, Insulins	$141,055	1.4%	446	$316	Y
12	Ipilimumab Injection	Physican Administered Drug	$136,811	1.3%	10	$13,681	
13	TRULICITY*	Diabetes, GLP-1 Receptor Agonists and GIP The	$136,511	1.3%	243	$562	Y
14	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$135,934	1.3%	77	$1,765	Y
15	STELARA*	Targeted Immune Modulators	$133,925	1.3%	24	$5,580	N
16	Injection, Nivolumab	Physican Administered Drug	$127,100	1.2%	25	$5,084	
17	ELIQUIS	Anticoagulants, Oral and SQ	$122,312	1.2%	321	$381	Y
18	IBRANCE*	Antineoplastics, Newer	$120,718	1.2%	8	$15,090	
19	VERZENIO*	Antineoplastics, Newer	$111,114	1.1%	8	$13,889	
20	Aflibercept Injection	Physican Administered Drug	$106,054	1.0%	181	$586	
21	Inj Pembrolizumab	Physican Administered Drug	$104,119	1.0%	32	$3,254	
22	Etonogestrel Implant System	Physican Administered Drug	$102,295	1.0%	139	$736	
23	COSENTYX PEN (2 PENS)*	Targeted Immune Modulators	$100,054	1.0%	30	$3,335	Y
24	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	$99,423	1.0%	201	$495	N
25	DAYBUE*	STC 99 - Miscellaneous	$94,974	0.9%	2	$47,487	
26	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$93,696	0.9%	9	$10,411	Y
27	EPIDIOLEX*	Antiepileptics, Outpatient	$85,345	0.8%	89	$959	N
28	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$84,083	0.8%	7	$12,012	
29	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$79,798	0.8%	2,636	$30	Y
30	SKYRIZI PEN*	Targeted Immune Modulators	$76,354	0.7%	5	$15,271	N
31	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$75,234	0.7%	1,300	$58	Y
32	Mirena, 52 Mg	Physican Administered Drug	$74,780	0.7%	111	$674	
33	ADVATE	Antihemophilia Factors	$72,499	0.7%	3	$24,166	
34	CREON	Pancreatic Enzymes	$68,757	0.7%	70	$982	Y
35	SPRYCEL	STC 30 - Antineoplastic	$65,721	0.6%	4	$16,430	
36	TASIGNA	STC 30 - Antineoplastic	$65,018	0.6%	7	$9,288	
37	TIBSOVO*	Antineoplastics, Newer	$64,397	0.6%	2	$32,198	
38	CABOMETYX*	Antineoplastics, Newer	$61,425	0.6%	3	$20,475	
39	LENALIDOMIDE	STC 30 - Antineoplastic	$60,511	0.6%	4	$15,128	
40	JYNARQUE	STC 79 - Diuretics	$59,115	0.6%	5	$11,823	
		Top 40 Aggregate:	**$5,090,632**		**8,306**	**$14,942**	
		All FFS Drugs Totals:	**$10,300,215**		**119,470**	**$693**	

*** 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: July 20, 2023

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
epcoritamab-bysp	EPKINLY
glofitamab-gxbm	COLUMVI

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 06/27/2023)
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
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
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA

Generic Name	Brand Name
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
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
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
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI

Generic Name	Brand Name
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
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mobecertinib	EXKIVITY
mosunetuzumab-axgb	LUNSUMIO
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
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
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
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
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA

Generic Name	Brand Name
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

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OHSU Drug Effectiveness Review Project (DERP) Summary Report – CGRP Inhibitors

Date of Review: June 2023

Date of Last Review: October 2021
End Date of DERP Literature Search: November 2022

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

Plain Language Summary:

- This document is a summary of a research report from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). They studied a group of medicines called calcitonin gene-related peptide (CGRP) inhibitors approved in the United States to treat migraine headaches.
- A migraine headache is a moderate to severe throbbing pain that is usually on one side of the head. A migraine headache usually gets worse with light, physical activity, noises, or smells and often causes the affected person to have nausea or vomiting.
- CGRP inhibitor medicines are used to either prevent migraines or to treat a migraine as it happens. There are 8 CGRP inhibitors approved by the Food and Drug Administration (FDA) for migraine treatment in adults: atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, ubrogepant, and zavegepant. CGRP inhibitors come in different forms. Some are made to be long acting and given by injection into the skin or into the veins. Other forms may be shorter acting and taken by mouth. Some are used to treat a migraine headache, while others are used to prevent or decrease how often the headaches happen.
- The DERP found that at 12 weeks, most CGRP inhibitors (eptinezumab, erenumab, Fremanezumab, galcanezumab, and sometimes atogepant or rimegepant) helped reduce the number of migraines per month by about 2 days and improved the quality of life in people with regular migraines compared to no use of this medicine.
- DERP also found that certain CGRP inhibitors (eptinezumab, rimegepant, ubrogepant, and zavegepant) helped stop migraine pain and improved ability to do daily living tasks within 2 hours of taking the medicine.
- This report did not find that people taking CGRP inhibitor medicines had many harmful side-effects, but it is not clear how safe and helpful these medicines are if used often in a short time period or for longer than 12 to 16 weeks.
- The Drug Use Research and Management (DURM) group recommends no changes to our current policy for the use of CGRP inhibitor medicines.

Research Questions:

1. What is the new comparative evidence for efficacy and effectiveness for calcitonin gene-related peptide (CGRP) inhibitors for preventative and acute migraine treatment for the outcomes of headache frequency, reduction in the number of migraines, and freedom from pain?
2. What is the evidence for safety associated with CGRP inhibitors when used for the prevention of migraines and acute migraine treatment (e.g. withdrawals due to adverse events or severe adverse events)?

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3. Are there subpopulations in which CGRP inhibitors would be more effective or cause less harm in the treatment of acute migraines or migraine prevention?

Conclusions:

- The evidence included in this review is based on findings from the 2023 Drug Effectiveness Review Project (DERP) report on CGRP inhibitors.[1] Drugs included in the review are atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, ubrogepant, and zavegepant (**Table 1**).[1] For migraine prevention, the magnitude of treatment effect of CGRP inhibitors was modest among all studies with approximately 0.4 to 3.7 days reduction compared to placebo.[1] Of the studies that evaluated headache severity with the 6-item headache impact test (HIT-6), 15 out of 17 trials reported reductions of 1.9 points or more (higher scores indicate greater impact on quality of life [QoL]; minimum clinically important difference [MCID] 1.5 points).[1]

*Chronic Migraine Prevention (**Table 2**)*

- There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab and galcanezumab reduce the number of migraine days per month (decrease of 1.7 to 2.7 days a month) at 12 weeks compared to placebo. [1]
- QoL was improved, compared to placebo, with the use of eptinezumab, erenumab, and fremanezumab at 12 weeks as measured by the HIT-6 with a difference of 1.1 to 5.6 points, which suggests a variable clinical benefit (4 randomized controlled trials (RCTs); moderate quality of evidence); galcanezumab was more effective than placebo at improvements in QoL based on the Migraine-specific quality of life score (MSQL) measure (moderate quality of evidence). The clinical significance of QoL improvements based on the MSQL are unclear.[1]

*Episodic Migraine Prevention (**Table 3**)*

- The number of migraine days per month were reduced with atogepant, eptinezumab, erenumab, fremanezumab and galcanezumab compared to placebo, with a difference ranging from -0.4 to -3.0 days (18 RCTs; moderate quality of evidence).[1]
- Erenumab, fremanezumab, and galcanezumab were more effective than placebo at improving quality of life based on moderate quality of evidence.[1]

*Chronic or Episodic Migraine [Mixed Populations of Both Types] (**Table 4**)*

- There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab, galcanezumab and rimegepant reduce the number of migraine days per month (range 0.8 to 3.7 fewer days per month) for chronic or episodic migraine at 12 to 24 weeks compared to placebo (5 RCTs).[1]
- There was a statistically significant decrease in migraine days per month for erenumab therapy compared to topiramate (decrease of 1.8 days, 95% confidence interval [CI], -1.3 to -2.4; moderate quality of evidence); erenumab treatment was also associated with larger QoL improvements (moderate quality of evidence).[1]
- There was moderate quality of evidence that eptinezumab and fremanezumab were more effective at improvement of functioning as measured by the HIT-6 (range of effects in mean difference 3.0 points to 5.4 points) compared to placebo which is suggestive of clinical benefit.[1]

*Acute Migraine Treatment **(Table 5**)*

- For the outcome of proportion of patients with freedom from pain at 2 hours, rimegepant and ubrogepant were more effective than placebo (difference range of 7.4% to 16.6%) based on moderate quality of evidence.[1]
- Zavegepant is the newest CGRP inhibitor agent recently FDA approved for acute migraine treatment.[1] One phase 3 RCT reported that at 2 hours post-dose, zavegepant 10 mg and 20 mg were more effective than placebo in proportion of participants achieving freedom from pain (risk difference [RD] 7% and 7.7%, respectively) and freedom from most bothersome symptom (RD 8.3% and 8.9%, respectively) based on low quality evidence.[1] There was no significant difference in these outcomes for zavegepant 5 mg.[1]

Cluster Headache Prevention

- Compared to placebo, there was low quality evidence that galcanezumab was more effective in the short term (1 to 3 weeks) prevention of cluster headache (2.2 to 3.5 fewer attacks) but no difference in cluster headache prevention at weeks 8 to 12.[1]

Acute Cluster Headache Treatment

- No studies were identified with CGRP inhibitors used for acute cluster headache treatment.[1]

Adverse Effects from CGRP Inhibitors

- There was only low quality of evidence available for the comparison of adverse events (AEs) between CGRP inhibitors and placebo for all treatment studied.[1] Adverse events (e.g. constipation, injection site pain, infection), severe adverse events, and discontinuations due to adverse events were rare and similar to placebo for the majority of CGRP inhibitors. [1] Many of the included studies only evaluated treatment of one or few attacks, which may limit the capturing of harms data.

Subgroup Differences in Efficacy and Adverse Events

- There is insufficient evidence for the use of CGRP inhibitors in different subgroups or evidence of benefit beyond 24 weeks. [1]
- There is insufficient evidence of comparative differences between CGRP inhibitors or their use in combination with any other agent.

June Recommendations:

- Update prior authorization criteria (**Appendix 2**).
- After clinical review no changes to the preferred drug list (PDL) are recommended.
- After evaluation of costs in executive session, no changes were made to the PDL.

August Recommendations:

- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- A review in October 2021 updated PA requirements for all therapies in the CGRP inhibitor PDL class. Current PA requires documentation of at least 4 migraines per month, failure of FDA approved migraine prophylactic therapies (beta-blockers, anticonvulsants, and tricyclic antidepressants) and a specialist consult for approval. Erenumab and fremanezumab are currently preferred therapy options in the CGRP inhibitor PDL class.
- There were fewer than 100 claims for CGRP inhibitors during first quarter of 2023 for Oregon Health Plan (OHP) Fee-for-Service (FFS) population.

Methods:

The January 2023 drug class report on Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1] The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

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

Summary Findings:

CGRP inhibitors are migraine therapies used to block CRGP, which is thought to play a role in migraine prevention, acute migraine treatment and cluster headache.[1] There are 8 CGRP inhibitors approved by the Food and Drug Administration (FDA) for migraine treatment in adults (Table 1).[1] CGRP inhibitors come in

various formulations and may be administered subcutaneously [SC], intravenously [IV], or orally.[1] Some agents are monoclonal antibodies that target the CGRP receptor (erenumab) or CGRP ligand (eptinezumab, fremanezumab, and galcanezumab), while others are small molecule agents that inhibit the CGRP receptor (atogepant, rimegepant, ubrogepant, and zavegepant).[1]

Table 1. CGRP Inhibitors Included in DERP Report[1]

Drug	Dose	Approval Date	Approved Indication	Number of RCTs Included
Atogepant QUILIPTA	10 mg, 30 mg, or 60 mg orally once daily	September 2021	Migraine Prevention	2
Eptinezumab VYEPTI	100 mg or 300 mg IV every 3 months	February 2020	Migraine Prevention	6
Erenumab AIMOVIG	70 mg or 140 mg SC every month	May 2018	Migraine Prevention	9
Fremanezumab AJOVY	225 mg SC monthly or 675 mg SC every 3 months	September 2018	Migraine Prevention	7
Galcanezumab EMGALITY	Migraine: 120 mg SC every month Cluster: 300 mg SC every month	September 2018 and June 2019	Migraine Prevention Cluster Headache Prevention	9
Rimegepant NURTEC	75 mg orally as needed for acute migraine attack	February 2020; May 2021 (new indication)	Acute Migraine Treatment Migraine Prevention	3
Ubrogepant UBRELVY	50 mg or 100 mg once orally for acute migraine attack, may repeat dose	December 2019	Acute Migraine Treatment	4
Zavegepant ZAVZPRET	10 mg (one spray) intranasally per 24 hours*	March 2023*	Acute Migraine Treatment	1

*=FDA labeling; product availability anticipated July 2023.

The purpose of this DERP report is to update evidence for the use of CGRP inhibitors since the previous published report in April 2020.[1] Literature was searched through November 8, 2022.[1] Main outcomes of interest were migraine or headache days per month or pain relief for acute migraine, functional outcomes, QoL, SAEs, and discontinuations due to AEs.[1] There is no established clinically important difference for headache day reduction in migraine prevention. Quality of life assessment tools used for the determination of headache severity were the HIT-6, MSQL and Migraine Disability Assessment (MIDAS).[1] The HIT-6 consists of 6 items (pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress) that are ranked from “never”, “rarely”, “sometime”, “very often” or “always”.[1,2] Higher HIT-6 scores are related to a greater impact on quality of life with a range of 36-78 points.[1,2] A score of 60 or more is considered severe impact on QoL.[2] A change of 1.5 units has been suggested as the MCID for the HIT-6 instrument based on clinically relevant changes in primary care populations with migraines.[1,2] The MSQL is a 14-item questionnaire used to determine migraine disability with scores ranging from 0-100, higher

scores indicate a higher quality of life.[1,2] A 6-point scale is used to rate disability from "none of the time" to "all of the time", which are assigned a score of 1-6.[1,2] The MIDAS test is used to quantify headache disability based on a 7-item questionnaire.[1,2] The score is based on activity limitations ranging from little or no disability (0-5) to severe disability (21 or more).[1,2] For the MIDAS, as with many of the migraine quality of life assessments, the scores are not well defined and the MCID has not been determined. A total of 15 new RCTs were identified for a total trial inclusion of 42.[1] All trials were placebo-controlled and there was insufficient evidence for direct comparison of different CGRP inhibitors.[1] One RCT compared rimegepant with sumatriptan for acute migraine treatment and 1 RCT compared erenumab with topiramate for the prevention of chronic or episodic migraine.[1] The quality of studies was considered moderate except for 1 poor quality trial.[1]

Chronic Migraine Prevention

Eptinezumab, erenumab, fremanezumab, and galcanezumab are used for the prevention of chronic migraine. Erenumab and galcanezumab were studied in one randomized controlled trial, eptinezumab in 2 trials, and fremanezumab in 3 trials.[1] Patients in the studies had a mean of 14.1 days to 19.6 days migraine days per month.[1] Outcomes with moderate evidence are presented in Table 2. All therapies were found to be more effective than placebo for the outcomes of number of migraine days per month, for the percent of patients with a 50% reduction in migraine days, and days with acute headache medication use per month.[1] Eptinezumab, erenumab, and fremanezumab were more effective at improving functioning at 12 weeks compared to placebo as measured by the HIT-6 (range 1.1 to 5.6 points).[1] The evidence for serious adverse events and discontinuations due to adverse events were associated with low or very low quality of evidence.[1] Trial summaries for the individual drugs and their outcome measures are presented below.

Table 2. CGRP Inhibitors for Chronic Migraine Prevention[1]

Drug	**Results** (Mean difference from placebo; 95% CI; all reported statistically significant results based on an alpha equal to .05) **Outcome:** Migraine days per month	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Eptinezumab	<u>*Dodick et al*</u> 100 mg: -2.1 (-3.8 to -0.4) 300 mg: -2.7 (-4.4 to -0.9) <u>*Lipton et al*</u> 100 mg: -2.0 (-2.9 to -1.2) 300 mg: -2.6 (-3.4 to -1.7)	2 RCTs; Weeks 1 to 12 Weeks 1 to 12	Moderate
Erenumab	70-mg and 140-mg doses: -2.5 (-3.5 to -1.4)	1 RCT; Weeks 9 to 12	
Fremanezumab	<u>*Bigal et al**</u> 225 mg (monthly): -1.8 (-3.5 to -0.14) 900 mg (quarterly): -2.0 (-3.7 to -0.26) <u>*Sakai et al*</u> 225 mg (monthly): -1.7 (-2.5 to -0.8) 675 mg (quarterly): -1.7 (-2.6 to -0.8)	3 RCTs; Weeks 9 to 12 Monthly Quarterly	

	Silberstein et al 225 mg (monthly): -1.8 (No CI reported) 675 mg (quarterly): -1.7 (No CI reported)	Weeks 9 to 12	
Galcanezumab	Range: -2.1 to -1.9	1 RCT; Weeks 4 to 12	
	Outcome: Percentage of patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	*Dodick et al* 100 mg: 14.6%/NNT 7 (No CI reported) 300 mg: 16.5%/NNT 7 (No CI reported) *Lipton et al* 100 mg: 18.2% (11.1 to 25.4)/ NNT 6 300 mg: 22.1% (14.9 to 29.2)/ NNT 5	2 RCTs Weeks 1 to 12 Weeks 1 to 12	Moderate
Erenumab	70-mg: RR 1.70 (1.29 to 2.23) 140-mg: RR 1.75 (1.34 to 2.30)	1 RCT 12 weeks	
Fremanezumab	*Sakai et al* 225 mg (monthly): 15.9% (7.8 to 24.0)/NNT 7 675 mg (quarterly): 15.9% (7.9 to 24.0)/NNT 7 *Silberstein et al** 225 mg: RD 22.7% (16.4 to 29.1)/NNT 5 675 mg: 19.5% (13.3 to 25.8)/NNT 6	2 RCTs Weeks 4 to 16 Weeks 9 to 12	
Galcanezumab	120 mg: 28%/NNT 4 (No CI reported) 240 mg: 28%/NNT 4 (No CI reported)	1 RCT Weeks 4 to 12	
	Outcome: Days with acute migraine medication use per month		
Erenumab	70 mg: -1.9 (-2.6 to -1.1) 140 mg: -2.6 (95% CI, -3.3 to -1.8)	1 RCT Weeks 9 to 12	Moderate
Fremanezumab	*Bigal et al** 225 mg: -2.2 (-4.0 to 0.3) 900 mg: -2.0 (-3.9 to -0.20) *Silberstein et al** 225 mg: (monthly): -2.3 (No CI reported) 675 mg (quarterly): -1.8 (No CI reported)	3 RCTs Weeks 9 to 12 Weeks 9 to 12	Moderate

	Sakai et al 225 mg (monthly): -1.3 (-2.2 to -0.4) 675 mg (quarterly): -1.4 (-2.3 to -0.6)	Weeks 4 to 16	
Galcanezumab	*Detke et al* 120 mg: -2.5 days (-3.3 to -1.8) 240 mg: -2.0 days (-2.8 to -1.3)	1 RCT Weeks 4 to 12	Moderate
	Outcome: Mean point change in HIT-6		
Eptinezumab	100 mg: -1.7 (No CI reported) 300 mg: -4.2 (-6.3 to -2.1) -2.9 (-3.9 to -1.8)	1 RCT Week 12	Moderate
Erenumab	70 mg: -5.6 (-6.5 to -4.6) 140 mg: -3.1 (-3.9 to -2.3)	1 RCT Week 12	
Fremanezumab	*Sakai et al* 225 mg (monthly): -1.6 (-2.9 to -0.2) 675 mg (quarterly): -1.5 (-2.9 to -0.2) *Silberstein et al** 225 mg: (monthly): -2.4 (No CI reported) 675 mg (quarterly): -1.9 (No CI reported)	2 RCTs Weeks 4 to 16 Week 12	
	Outcome: Mean point change in MSQL		
Galcanezumab	120 mg: -5.1 (-8.0 to -2.1) 240 mg: -6.3 (-9.6 to -3.0)	1 RCT Weeks 4 to 12	Moderate

*=Patients in the 225-mg group received 675-mg of fremanezumab at baseline and 225-mg of fremanezumab at weeks 4 and 8

Abbreviations: CI = confidence interval; HIT-6 = headache impact test; MSQL = Migraine-specific quality of life score; NNT = number needed to treat; RCT = randomized controlled trial

Episodic Migraine Prevention Atogepant, eptinezumab, erenumab, fremanezumab, and galcanezumab were studied for episodic migraine prevention.[1] Patients had a history of 6.6 to 11.3 migraine headache days per month at baseline.[1] All therapies were more effective than placebo for the reduction in mean number of headache days per month by 1 to 2 days (range 0.4 days to 3 days).[1] All 5 drugs improved QoL/functional measures although there were different instruments employed (e.g. HIT-6, MIDAS, MSQL) and variable quality of evidence (moderate quality evidence for erenumab, fremanezumab, and galcanezumab; low quality evidence for atogepant and eptinezumab).[1] The evidence for serious adverse events and discontinuations due to adverse events were similar to placebo (very low quality of evidence).[1] Trial summaries for the individual drugs and their primary outcome measures with at least moderate quality evidence are presented in **Table 3**.

Table 3. CGRP Inhibitors for Episodic Migraine Prevention[1]

Drug	**Results** (Mean difference from placebo; 95% CI; all reported statistically significant results based on an alpha equal to .05) **Outcome:** Migraine days per month	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Atogepant	*Ailani et al* 10-mg: -1.2 (-1.8 to -0.6) 30-mg: -1.4 (-1.9 to -0.8) 60-mg: -1.7 (-2.3 to -1.2) *Goadsby et al* 10-mg: -1.2 (-1.9 to -0.4) 30-mg: -0.9 (-1.6 to -0.3) 60-mg: -0.7 (-1.4 to -0.1)	2 RCTs Week 12 Week 12	Moderate
Eptinezumab	*Ashina et al.* 100-mg: -0.7 (-1.3 to -0.1) 300-mg: -1.1 (-1.7 to -0.5) *Dodick et al.* 1,000-mg: -1.0 (-2.0 to 0.1)	2 RCTs Week 12 Weeks 5 to 8	
Erenumab	*Dodick et al; Kawata et al.* 70-mg: -1.0 (-1.6 to -0.5) *Goadsby et al.; Buse et al.; Kawata et al.* 70-mg: -1.4 (-1.9 to -0.9) 140-mg: -1.9 (-2.3 to -1.4) *Sakai et al.* 70-mg: -2.3 (-3.0 to -1.6) 140-mg: -1.9 (-2.6 to -1.2) *Sun et al.* 70-mg: -1.1 (-2.1 to -0.2) *Wang et al.*	6 RCTs Weeks 9 to 12 Months 4 to 6 Months 4 to 6 Weeks 9 to 12 Week 12	

	70-mg: -1.1 (-1.8 to -0.4) 140-mg: -1.7 (-2.5 to -0.9)		
Fremanezumab	*Bigal et al.* 225-mg: -2.8 (-4.1 to -1.6) 675-mg: -2.6 (-3.9 to -1.4) *Dodick et al.* 225-mg: -1.5 (-2.0 to -0.9) 675-mg: -1.3 (-1.8 to -0.7) *Sakai et al.* 225-mg: -3.0 (-3.7 to -2.2) 675-mg: -3.0 (-3.8 to -2.2)	3 RCTs Weeks 9 to 12 Weeks 9 to 12 Week 12	
Galcanezumab	*Dodick et al.* 1.2 (90% CI, -1.9 to -0.6) *Skljarevski et al.; Oakes et al.; Ayer et al.* 120-mg: -0.9 (No CI reported) 300-mg: -0.9 (No CI reported) *Skljarevski et al* 120 mg: -2.0 (-2.6 to -1.5) 240-mg: -1.9 (-2.4 to -1.4) *Stauffer et al.* 120-mg: -1.9 (-2.5 to -1.4) 240-mg: -1.8 (-2.3 to -1.2)	5 RCTs Weeks 9 to 12 Weeks 9 to 12 6 months 6 months	
	Outcome: Percentage patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	*Ashina et al.* 100 mg: RD = 12.4 (3.2 to 21.5)/NNT 9 300 mg: 18.9 (9.8 to 28.0)/NNT 6	2 RCTs Week 12	Moderate
Erenumab	*Reuter et al.* 140-mg: OR, 2.7 (1.4 to 5.2) *Sakai et al.* 70 mg: OR = 5.6 (2.6 to 12.1) 140 mg: OR = 4.7 (2.2 to 10.0)	6 RCTs Weeks 9 to 12 Weeks 9 to 12	

	Goadsby et al. 70 mg: OR = 2.1 (1.5 to 2.9) 140 mg: OR = 2.8 (2.0 to 3.9) *Sun et al* 70 mg: OR = 2.0 (1.2 to 3.4) *Wang et al.* 70 mg: OR = 1.5 (1.1 to 2.1) 140 mg: OR = 2.2 (1.6 to 3.2) *Dodick et al.* 70 mg: OR = 1.59 (1.12 to 2.27)	Months 4 to 6 Weeks 9 to 12 Week 12 Weeks 9 to 12	
Fremanezumab	*Bigal et al.* 225 mg: RD = 21.2% (7.6 to 34.7)/NNT 5 675 mg: RD = 22.7% (9.2 to 36.1)/NNT 5 *Dodick et al.* 225 mg: RD = 19.8% (12.0 to 27.6)/NNT 6 675 mg: RD = 16.5% (8.9 to 24.1)/NNT 7 *Sakai et al* 225 mg monthly: RD = 30.1% (19.6 to 40.6)/NNT 4 675 mg quarterly: RD = 34.1% (23.4 to 44.7)/NNT 3	Weeks 9 to 12 Weeks 9 to 12 Months 4 to 6	
Galcanezumab	*Dodick et al.* 150 mg (every 2 weeks): RD = 25.2% (12.1 to 38.4)/NNT 4 *Sakai et al.; Shibita et al.* 120 mg: RD = 29.1% (18.6 to 39.7)/NNT 4 240 mg: RD = 27.8% (17.3 to 38.4)/NNT 4	5 RCTs Weeks 9 to 12 Months 1 to 6	

	Skljarevski et al. 120 mg: RD = 23.3% (15.6 to 31.0)/NNT 5 240 mg: RD = 20.5% (12.7 to 28.3)/NNT 5 *Stauffer et al.* 120 mg: RD = 23.8% (15.8 to 31.8)/NNT 5 240 mg: RD = 22.5% (14.4 to 30.6)/NNT 5	Weeks 9 to 12 6 months	
	Outcome: Mean point change in HIT-6 from baseline		
Erenumab	*Dodick et al., Reuter et al., Sakai et al., Goadsby et al., Sun et al, Wang et al.* HIT-6 Improvement: Range = -3.0 to -1	6 RCTs Weeks 9 to 12	Moderate
	Outcome: Mean point change in MIDAS/MSQL from baseline		
Fremanezumab	*Bigal et al.* (MIDAS) 225 mg: -14.5 (-26.8 to -2.2) 675 mg: -15.2 (-27.6 to -2.8) *Dodick et al.* (MIDAS) 225 mg: -7.0 (-10.5 to -3.5) 675 mg: -5.4 (-8.9 to -1.9) *Sakai et al.* (MIDAS) 225 mg: -5.2 (-8.1 to -2.3) 675 mg: -5.1 (-8.1 to -2.2)	3 RCTs Weeks 9 to 12 Weeks 9 to 12 Week 12	Moderate
Galcanezumab	*Dodick et al., Sakai et al., Shibata et al., Tatsuoka et al., Skljarevski et al* MIDAS: Range = -9.2 to -3.0 MSQL: Range = -8.8 to -5.8	5 RCTs Months 4 to 6 Months 4 to 6	Moderate

Abbreviations: CI = confidence interval; HIT-6 = headache impact test; MIDAS = Migraine Disability Assessment; MSQL = Migraine-specific quality of life score; NNT = number needed to treat; RCT = randomized controlled trial

Chronic or Episodic Migraine Prevention

For chronic or episodic migraine prevention (study populations included both types and results were not stratified), there was moderate quality of evidence from 5 RCTs that eptinezumab, erenumab, fremanezumab, galcanezumab, and rimegepant were more effective than placebo in reduction of migraine days per month (range 0.8 to 3.7 fewer days per month).[1] Only eptinezumab, erenumab, and fremanezumab were more effective than placebo in outcomes of percentage of participants with at least 50% reduction in migraine days (moderate quality evidence).[1] There was moderate quality evidence that erenumab resulted in a statistically significant decrease in migraine days per month compared with topiramate (MD -1.8 [95% CI, -1.3 to -2.4]; it also was associated with larger improvements in QoL (moderate CoE). About 39% of the topiramate group had at least 1 adverse event leading to treatment discontinuation compared to 11% of those on erenumab which may have resulted in significant attrition bias. Eptinezumab and fremanezumab were more effective than placebo at improvement in function as measured by the HIT-6 (range 3.0 to 5.4 points; moderate quality of evidence).[1] **Table 4** summarizes these findings.

Table 4. CGRP Inhibitors for Chronic or Episodic Migraine Prevention (Mixed Populations)[1]

Drug	**Results** (Mean difference from placebo unless noted; 95% CI; all reported statistically significant results based on an alpha equal to .05)	**Number of Trials; Assessment Timing**	**Quality of Evidence**
	Outcome: Migraine days per month		
Eptinezumab	100-mg: -2.7 (-3.4 to -2.0) 300-mg: -3.2 (-3.9 to -2.5)	1 RCT Weeks 1 to 12	Moderate
Erenumab	70 mg or 140 mg: -1.6 (-2.5 to -0.7)	1 RCT Weeks 16 to 24	Moderate
Fremanezumab	225 mg (monthly): -3.5 (-4.2 to -2.8) 675 mg (quarterly): -3.1 (-3.8 to -2.4)	1 RCT Weeks 1 to 12	Moderate
Galcanezumab	120 mg: -3.1 (-3.9 to -2.3)	1 RCT Weeks 4 to 16	Moderate
Rimegepant	75 mg: -0.8 (-1.5 to -0.2)	1 RCT Weeks 9 to 12	Moderate
	Outcome: Percentage patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	100 mg: 29.1%/NNT 4 300 mg: 36.4%/NNT 3	1 RCT Weeks 1 to 12	Moderate
Erenumab	*Reuter et al* (vs Topiramate) Erenumab: 55% Topiramate: 31% RD = 22%/NNT 5	1 RCT Weeks 16 to 24	Moderate
Fremanezumab	225 mg (monthly) and 675 mg (quarterly): 34%/NNT	1 RCT Weeks 1 to 12	Moderate
	Outcome: Mean Change HIT-6 Score		
Eptinezumab	100 mg: -3.8 (-5.0 to -2.5) 300 mg: -5.4 (-6.7 to -4.2)	1 RCT Weeks 1 to 12	Moderate
Erenumab	70 mg and 140 mg (vs Topiramate):	1 RCT	Moderate

	-3.2 (-4.3 to -2.1)	Weeks 16 to 24	
Fremanezumab	225 mg: -3.8 (-5.0 to -2.7) 675 mg: -3.0 (-4.1 to -1.8)	1 RCT Week 12	Moderate

Abbreviations: CI = confidence interval; HIT-6 = headache impact test; NNT = number needed to treat; RCT = randomized controlled trial

Acute Migraine Treatment

Rimegepant and ubrogepant are two small molecule CGRP inhibitors used for the acute treatment of migraine. A third and the newest CGRP agent, zavegepant, had not yet been FDA approved at the time of the review.[1] Rimegepant and ubrogepant were studied in 3 randomized controlled trials (**Table 5**).[1] There was moderate quality evidence that rimegepant and ubrogepant were more effective than placebo for the outcomes of freedom from pain at 2 hours and freedom from most bothersome symptom at 2 hours.[1]

Zavegepant (Zavzpret®) was approved by the FDA in March 2023 after completion of the DERP report.[1] The efficacy and safety of zavegepant was studied in one phase 2/3, double blind RCT (N=1,581) at multiple sites in the US. The study included mostly females (86%) with a 1-year history of migraine of at least 2 attacks per month where untreated migraines lasted 4 to 72 hours.[1] Patients with history of hemiplegic migraine, unstable medical conditions, opioid use, or recent use of nasal sprays were excluded.[1] Patients were randomized into 4 groups of roughly equal proportions and given either zavegepant 5-mg, 10-mg, 20-mg or placebo.[1] Primary endpoints were freedom from pain or freedom from most bothersome symptoms at 2 hours post-dose.[1] There was low quality evidence that at two hours post-dose, zavegepant 10 mg and 20 mg were more effective than placebo in proportion of participants achieving freedom from pain (RD 7% and 7.7%, respectively) and freedom from most bothersome symptom (RD 8.3% and 8.9%, respectively).[1] Zavegepant 5 mg comparison to placebo did not reach statistical significance for the pre-defined study outcomes.[1]

The new CGRP inhibitor agent zavegepant and those agents with at least moderate quality evidence for acute migraine treatment outcomes are reported in Table 5.

Table 5. CGRP Inhibitors for Acute Migraine Treatment[1]

Drug	**Results*** (Mean difference from placebo unless noted) **Outcome:** Proportion patients with freedom from pain at 2 hours post-dose	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Rimegepant	vs. Placebo *Croop et al* 75 mg: 10.4% (6.5% to 14.2%) /NNT 10 *Lipton et al* 7.6% (3.3% to 11.9%)/NNT 14 *Marcus et al* 16.2% (5.2% to 27.1%)/NNT 7 vs. Sumatriptan *Marcus et al*	3 RCTs; 2 hours all trials 1 RCT N/A	Moderate

	-3.6% (-17.2% to 9.9%) *No statistically significant difference as calculated by DERP authors*		
Ubrogepant	*Dodick et al* 50-mg: 7.4% (2.6% to 12.1%)/NNT 14 100-mg: 9.4% (4.6% to 14.2%)/NNT 11 *Lipton et al* 50-mg: 7.5% (2.6 % to 12.5%)/NNT 14 *Voss et al* 50-mg: 12.0% (2.6 to 21.4)/NNT 9 100-mg: 16.6% (12.4 to 22.4)/NNT 6	3 RCTs; 2 hours all trials	Moderate
Zavegepant	*Croop et al* 5 mg: 4.2% (not statistically significant) 10 mg: 7% (1.6 to 12.5)/NNT 15 20 mg: 7.7% (2.2 to 13.1)/NNT 13	1 RCT; 2 hours	Low
	Outcome: Proportion of patients with freedom from most bothersome symptom at 2 hours post-dose		
Rimegepant	*Croop et al* 75 mg: 8.3% (3.4% to 13.2%)/NNT 13 *Lipton et al* 12.4% (6.9% to 17.9%)/NNT 9	2 RCTs; 2 hours all trials	Moderate
Ubrogepant	*Dodick et al* 50-mg: 10.8% (4.6% to 17.0%)/NNT 10 100-mg: 10.0% (3.9% to 16.1%)/NNT 10 *Lipton et al* 50-mg: 11.5% (5.4% to 17.5%)/NNT 9	2 RCTs; 2 hours all trials	Moderate
Zavegepant	*Croop et al* 5 mg: 5.4% (not statistically significant) 10 mg: 8.3% (1.5 to 15.0)/NNT 13 20 mg: 8.9% (2.2 to 15.6)/ NNT 12	1 RCT; 2 hours	Low

*=95% CI; all reported statistically significant results based on an alpha equal to .05 unless otherwise noted
Abbreviations: CI = confidence interval; NNT = number needed to treat; RCT = randomized controlled trial

Acute Cluster Headache Treatment

There were no new studies identified that assessed the effectiveness of CGRP inhibitors for acute cluster headache prevention since the previous DERP report.[1]

Cluster Headache Prevention

For cluster headache prevention, there was low-quality evidence that galcanezumab is not effective and very low quality of evidence for harms due to the rarity of events.[1] Although galcanezumab resulted in statistically significant reduction in cluster headache attack frequency per week during weeks 1 through 3 compared to placebo (range 2.2 to 3.5 fewer), there was no difference at weeks 8 to 12 (range 0.8 fewer to 1.3 more attacks per week).[1]

Adverse Events from CGRP Inhibitors

The DERP review was unable to determine a relationship between active CGRP treatment and adverse events (e.g. constipation, injection site pain, infection, etc.) due to the infrequent reporting of severe adverse events and discontinuations due to adverse events.[1] The frequency of AEs, SAEs, and discontinuations due to AEs was similar between active treatment groups and placebo for virtually all indications, drugs, and dosages (very low quality of evidence).[1] Erenumab had fewer discontinuations due to AEs compared to topiramate (moderate quality of evidence).[1] No discontinuations due to AEs were reported in trials that compared rimegepant to sumatriptan (very low quality of evidence).[1] Liver injury due to treatment was uncommon with CGRP treatment in studies that reported that outcome.[1]

Subgroup Differences in Efficacy and Adverse Events

There were few studies that reported subgroup findings.[1] Five fremanezumab studies evaluated efficacy among participants who were not taking preventative medications compared to the full study population and reported similar efficacy.[1] There were no studies found for use of CGRP inhibitors in combination with any other agent.

Evidence Limitations

Studies were industry sponsored and evidence was downgraded due manufacturer sponsorship and extensive involvement in the trials themselves.[1] There were no head-to-head trials that directly compared two or more CGRP inhibitors.[1] Many trials were of short duration (12 weeks) preventing long-term evidence for efficacy and harms in a condition that is typically treated chronically as long-term therapy.[1] Only studies of single, acute migraine attacks were assessed, therefore effectiveness and safety of repeated use is unknown.[1] Most studies employed an electronic headache diary during a run-in phase so generalizability to a less selective population was uncertain.[1] Patients who were pregnant or those with clinically significant psychiatric or medical conditions were excluded so the effects in a less selective study population was unknown.[1] Most studies included a high majority of females and did not report information on race and ethnicity.[1]

References:

1. Drug Effectiveness and Review Project (DERP). Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention. Center for Evidence-based Policy, Oregon Health & Science University; 2023.
2. Institute for Clinical and Economic Review. Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value. Final Evidence Report. July 2018. Accessed March 14, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_Migraine_Final_Evidence_Report_070318.pdf

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
erenumab-aooe	AIMOVIG AUTOINJECTOR	AUTO INJCT	SQ	Y
fremanezumab-vfrm	AJOVY AUTOINJECTOR	AUTO INJCT	SQ	Y
fremanezumab-vfrm	AJOVY SYRINGE	SYRINGE	SQ	Y
atogepant	QULIPTA	TABLET	PO	N
eptinezumab-jjmr	VYEPTI	VIAL	IV	N
galcanezumab-gnlm	EMGALITY PEN	PEN INJCTR	SQ	N
galcanezumab-gnlm	EMGALITY SYRINGE	SYRINGE	SQ	N
galcanezumab-gnlm	EMGALITY SYRINGE	SYRINGE	SQ	N
rimegepant sulfate	NURTEC ODT	TAB RAPDIS	PO	N
ubrogepant	UBRELVY	TABLET	PO	N
zavegepant	ZAVZPRET	SPRAY	NS	N

Appendix 2: Prior Authorization Criteria

Calcitonin Gene-Related Peptide (CGRP) antagonists

Goal(s):

- Promote safe use of CGRP inhibitors in adult patients
- Promote use that is consistent with medical evidence and product labeling for migraine prevention, acute migraine treatment and cluster headache prevention (Table 1).

Length of Authorization:

- Initial: Up to 3 months
- Renewal: Up to 6 months

Requires PA:

- All calcitonin gene-related peptide (CGRP) antagonist pharmacy and practitioner 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. FDA Approved Indications for CGRP antagonists

Drug	FDA Approved Indication
Atogepant	Preventative migraine treatment
Eptinezumab	Preventative migraine treatment
Erenumab	Preventative migraine treatment
Fremanezumab	Preventative migraine treatment
Galcanezumab	Preventative migraine treatment and cluster headache prevention
Rimegepant sulfate	Acute migraine treatment and preventative treatment of episodic migraine
Ubrogepant	Acute migraine treatment
Zavegepant	Acute migraine treatment

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication (Table 1)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 6
6. Is the request for acute (abortive) migraine treatment AND the patient is an adult (18 years or older)?	**Yes:** Go to #12	**No:** Go to #7
7. Is the request for the prevention of cluster headache AND the patient is an adult (18 years or older)?	**Yes:** Go to #15	**No:** Go to #8

Approval Criteria		
8. Is the request for prophylactic therapy and there is documentation that the patient has experienced 4 or more migraine days in the previous month AND the patient is an adult (18 years or older)?	**Yes:** Document migraine days per month _____ Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient had an adequate trial (2-6 months) without response, or has contraindications, to at least 3 of the following OHP preferred drugs (in the same or different classes)? • Propranolol immediate-release, metoprolol, or atenolol • Topiramate, valproic acid, or divalproex sodium • Amitriptyline, nortriptyline, or venlafaxine OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the above migraine prophylaxis agents?	**Yes:** Document agents used and dates _____ _____ Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
10. Is the request for erenumab and the patient has pre-existing hypertension or risk factors for hypertension?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 3 months
12. In a patient with acute migraines, has the patient failed to receive benefit from adequate trials of abortive therapy (2 or more different triptans) or have contraindications to triptans?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.
13. Does the patient have chronic migraines?	**Yes**: Go to #14	**No**: Approve for 3 months

Approval Criteria		
14. Does the patient have a history of at least 4 migraines a month AND is on preventative migraine therapy (excluding other CGRP inhibitors)?	**Yes:** Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness
15. Has the patient failed to receive benefit from at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, prednisone, suboccipital steroid injection, topiramate)?	**Yes**: Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2
2. Is the renewal request for acute migraine treatment?	**Yes:** Go to #5	**No:** Go to #3
3. Is the renewal request for migraine prevention?	**Yes:** Go to #4	**No:** Go to # 6
4. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	**Yes:** Document response. Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
5. Has the patient demonstrated a response to therapy as indicated by a reduction in headache frequency and/or intensity?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
6. Is the renewal request for cluster headache prevention?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical Appropriateness

7. Does the patient have documentation of a positive response, indicated by a reduction in the number of cluster headaches per month?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 6/23 (DE); 10/21 (KS), 8/20 (KS); 5/19; 9/18 (DE)
Implementation: 7/1/23; 1/1/2022; 11/1/2018

ProDUR Report for April through June 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	2	1	0	1	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,060	550	0	1,507	1.1%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	8,774	2,773	0	5,996	5.1%	N/A
ER (Early Refill)	**Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)**	**Set alert/Deny claim**	**107,813**	**22,921**	**142**	**84,747**	**63.5%**	**21.3%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	37,858	11,137	2	26,666	22.2%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	983	215	0	766	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	5	4	0	1	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	832	269	0	563	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	500	208	0	289	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	1	1	0	0	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**40**	**32**	**0**	**8**	**0.0%**	**80.0%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	10,870	3,382	1	7,461	6.4%	N/A
		Totals	**169,738**					

ProDUR Report for April through June 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)	9,152	1,795	7,357	95,762	9.5%	19.6%
ER	Prozac (Fluoxetine)	6,387	1,278	5,109	65,607	9.7%	20.0%
ER	Lexapro (Escitalopram)	6,261	1,170	5,091	66,806	9.3%	18.7%
ER	Celexa (Citalopram)	2,367	437	1,930	28,774	8.2%	18.5%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	8,767	1,685	7,082	92,886	9.4%	19.2%
ER	Trazodone	7,572	1,533	6,039	71,286	10.6%	20.2%
ER	Cymbalta (Duloxetine)	5,542	1,116	4,426	55,966	9.9%	20.1%
ER	Effexor (Venlafaxine)	3,494	665	2,829	35,644	9.7%	19.0%
ER	Remeron (Mirtazapine)	2,104	373	1,731	18,076	11.6%	17.7%
ER	Elavil (Amitriptyline)	1,800	385	1,415	21,216	8.4%	21.4%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	5,243	1,294	3,949	37,411	13.9%	24.7%
ER	Abilify (Aripiprazole)	4,476	892	3,582	35,438	12.6%	19.9%
ER	Zyprexa (Olanzapine)	2,931	654	2,277	23,015	12.7%	22.3%
ER	Risperdal (Risperidone)	2,242	543	1,699	15,348	14.5%	24.2%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	4,183	807	3,376	42,115	9.9%	19.3%
ER	Lorazepam	317	98	219	13,964	2.2%	30.9%
ER	Alprazolam	213	49	164	8,219	2.5%	23.0%
ER	Diazepam	103	27	76	4,608	2.2%	26.2%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	6,948	1,453	5,495	53,121	13.0%	20.9%
ER	Intuniv (Guanfacine ER)	1,942	345	1,597	14,987	12.8%	17.8%
ER	Depakote (Divalproex)	1,842	527	1,315	13,884	13.2%	28.6%
ER	Suboxone (Buprenorphine/Naloxone)	130	47	83	2,182	5.9%	36.2%

ProDUR Report for April through June 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	April	4,194	133	268	701	1	2,871	46	0	174
ER	May	5,242	212	324	745	4	3,721	56	0	180
ER	June	5,669	296	273	796	6	4,011	55	0	232
	Total =	**15,105**	**641**	**865**	**2,242**	**11**	**10,603**	**157**	**0**	**586**
	Percentage of total overrides =		**4.2%**	**5.7%**	**14.8%**	**0.1%**	**70.2%**	**1.0%**	**0.0%**	**3.9%**

ProDUR Report for April through June 2023			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
April	DC	7	$ 1,613.47
	DD	38	$ 8,638.18
	ER	345	$ 70,495.84
	HD	2	$ 2,723.90
	ID	38	$ 8,155.96
	LR	4	$ 564.06
	MX	4	$ 487.48
	TD	24	$ 6,152.01
	April Total	**462**	**$ 98,830.90**
May	DC	1	$ 238.99
	DD	25	$ 7,804.67
	ER	48	$ 7,702.87
	ID	17	$ 2,700.32
	MX	1	$ 20.10
	TD	1	$ 1,332.69
	May Total	**93**	**$ 19,799.64**
June	DC	1	$ 100.41
	DD	10	$ 1,575.12
	ER	41	$ 6,539.49
	ID	13	$ 2,025.47
	TD	2	$ 743.01
	June Total	**67**	**$ 10,983.50**
		Total 2Q2023 Savings =	**$ 129,614.04**

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

Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	18	13	12	
		Unique Patients Identified	18	13	12	
		Total Faxes Successfully Sent	12	8	8	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	3	7		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$2,781	$14,327		
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	119	103	84	7
		Unique Patients Identified	120	103	86	7
		Total Faxes Successfully Sent	76	83	62	4
		Prescriptions Changed to Recommended Within 6 Months of Intervention	67	54	26	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$75,794	$38,619	$9,330	
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	109	56	383	16
		Unique Patients Identified	110	56	414	16
		Total Faxes Successfully Sent	69	35	257	11
		Prescriptions Changed to Recommended Within 6 Months of Intervention	42	24	92	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$8,139	$4,005	$7,544	

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	2	9	3	1
		Total Faxes Successfully Sent	1	5	2	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent		3		
		Prescriptions Unchanged after 3 Months of Fax Sent		4		
		Safety Monitoring Profiles Identified	2	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0	$579		

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	1064	776	818	
		High risk patients identified	6	9	1	
		Prescribers successfully notified	6	9	1	
		Patients with change in antipsychotic drug in following 90 days		2		
		Patients with continued antipsychotic therapy in the following 90 days	5	9	1	
		Patients with discontinuation of antipsychotic therapy in the following 90 days	1			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	55	54	54	6
		Total prescribers identified	55	54	53	6
		Prescribers successfully notified	53	54	52	
		Patients with claims for the same antipsychotic within the next 90 days	31	26	28	
		Patients with claims for a different antipsychotic within the next 90 days	2	2	2	

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	80	57	66	
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	56	20	24	
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	207	169	185	
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	39	28	26	
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	3	17	13	7
		Letters Sent To Providers		1		
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	1	9	13	
		Letters Sent To Providers	1	7	12	
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	8	10	12	4
		Letters Sent To Providers	4	8	4	
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	31	10	10	
		Letters Sent To Providers	5	1		
	Lock-In	RetroDUR Profiles Reviewed		10	5	
		Locked In		0	0	
	Polypharmacy	RetroDUR Profiles Reviewed	18	1	5	
		Letters Sent To Providers	1			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	16	16	13	2
		Total prescribers identified	15	16	13	2
		Prescribers successfully notified	15	12	12	
		Patients with paid claims within next 60 days	12	12	7	
		Patients with denied claim within next 60 days	13	11	4	

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	83	92	106	11
		Total prescribers identified	82	91	106	11
		Prescribers successfully notified	61	91	106	
		Patients with discontinuation of therapy within next 90 days	19	19	42	11
		Patients with new prescription for naloxone within next 90 days	6	9	5	
		Average number of sedative drugs dispensed within next 90 days	21	25	16	0
		Average number of sedative prescribers writing prescriptions in next 90 days	21	25	16	0
	Oncology Denials	Total patients identified	1	2	2	
		Total prescribers identified	1	2	2	
		Prescribers successfully notified	1	2	2	
		Patients with claims for the same drug within the next 90 days		1		
		Patients with claims for any oncology agent within the next 90 days		1		
	TCAs in Children	TCA Denials in Children	26	21	52	4
		Total patients identified	12	10	19	5
		Total prescribers identified	12	10	19	5
		Prescribers successfully notified	8	6	15	
		Patients with claims for a TCA within the next 90 days	3	2	1	

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Psychotropic Use in Youth Enrolled in the Oregon Health Plan and Youth in Foster Care with an Emphasis on Antipsychotic Prescriptions – * Correction to Previous Posting

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An estimated 11-20% of children in the United States have a mental health condition.[1] Given a national pediatric psychiatrist shortage, more non-psychiatrists are prescribing psychotropic medications to children. The implications of this may include increased rates of polypharmacy, more prescriptions without an FDA-approved indication, inadequate treatment, and increased side effect risks. Research has shown that although there has been a decline in the use of antipsychotics in the general pediatric population, the rate of antipsychotic use among youth in foster care has increased in the past decade.[1,2]

The purpose of this newsletter is to (a) describe the prescribing of psychotropic medications to youth in foster care within the Oregon Health Plan (OHP), the programs available to support non-psychiatric providers who prescribe psychotropic drugs, and (b) review the *Antipsychotics in Children* safety edit policy recently implemented in the OHP population.

Background

Few antipsychotics have been studied in young children, and the efficacy and safety has not been established for any antipsychotic in children less than 5 years of age. The FDA has approved the use of some antipsychotics 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 approved indications for irritability associated with autism for patients at least 5 and 6 years of age, respectively.[3,4] Bipolar I disorder and schizophrenia are also approved for use in adolescents, but not in young children (**Table 1**). Clinical practice guidelines recommend non-pharmacological therapy (e.g., cognitive behavioral therapy) as first-line therapy for children before an antipsychotic is prescribed.[5–7]

Table 1. FDA-Approved Indications and Ages for Oral Second-generation Antipsychotics in Children[8]

FDA-Approved Indications and Ages			
Drug	Schizophrenia	Bipolar I disorder	Major depressive disorder (adjunct)
aripiprazole*	≥ 13 yrs	≥ 10 yrs	≥ 18 yrs
asenapine maleate	≥ 18 yrs	≥ 10 yrs	
brexpiprazole	≥ 13 yrs		
lurasidone HCl	≥ 13 yrs	≥ 10 yrs	
olanzapine	≥ 13 yrs	≥ 10 yrs	≥ 18 yrs
paliperidone†	≥ 12 yrs		
quetiapine fumarate∞	≥ 13 yrs	≥ 10 yrs	
risperidone‡	≥ 13 yrs	≥ 10 yrs	

Key: * Aripiprazole is also approved for irritability associated with Autistic Disorder for ages ≥6 yrs and Tourette's Disorder for ages ≥6 yrs; † Paliperidone is also approved for schizoaffective disorder ≥18 yrs; ∞ Quetiapine is also approved for Bipolar depression ≥18 yrs; ‡ Risperidone is also approved for irritability associated with Autistic Disorder for ages ≥ 5 yrs

Use of antipsychotics in children can be associated with significant risk of long-term adverse events (AE).[9]

- Weight gain is common and increases with longer treatment exposure.
- Prolactin levels are often increased from risperidone and paliperidone treatment, which may result in unwanted conditions, such as gynecomastia and galactorrhea.
- Risk of akathisia and extrapyramidal symptoms (EPS) are increased with virtually all SGAs, clozapine having the lowest risk and risperidone have the highest.
- Potential effects on total cholesterol, low-density lipoprotein (LDL), triglycerides, and fasting glucose should be monitored with use of any SGA, but particularly with olanzapine and quetiapine.
- Elevated liver enzymes may necessitate discontinuation for some individuals.

Prescribing Psychotropics to Oregon Youth in Foster Care

In 2022, Oregon had over 5,000 youth in foster care. National data from 2021 estimated 391,000 youth were in foster care nationwide.[10,11] The Children's Bureau reported that nationally 80% of youth in foster care have serious mental health needs.[11] In Oregon, under 13% of youth in foster care statewide used one or more psychotropic medications to assist in managing their mental health conditions.[12]

Youth in Oregon foster care programs are comprised of a diverse population with some requiring complex care. In Oregon, youth in foster care prescribed psychotropics receive comprehensive oversight (Figure 1). In 2010, a law

went into effect that requires Oregon Department of Human Services (ODHS) and coordinated care organizations (CCOs) to provide a mental health assessment before a child in foster care receives more than one psychotropic medication or any antipsychotic, unless there is an urgent medical need.[12] Further expansion of oversight followed with engagement in the Center for Health Care Strategies 6 state collaborative.[13]

In 2010, a registered nurse authorization process for psychotropic medication administration (with physician consultation) was implemented and centralized in 2019. ODHS staff provide oversight in two pathways. They complete annual reviews based on reports generated by *Oregon State University Drug Use Research and Management Group*, which identify diagnosis history, prescribing history and prescribing and metabolic monitoring flags (potential concerns). Moreover, all new prescriptions require completion of an authorization form by the provider, and these requests receive same day reviews by ODHS nursing staff prior to authorization.

When annual reviews raise potential concerns, chart notes are requested and reviewed by ODHS nursing staff. In both pathways of oversight, nurses and providers have access to the expertise of the Oregon Psychiatric Access Line about Kids (OPAL-K) for clinical review. OPAL-K is a state-funded program whose mission is to provide prescribing primary care clinicians in Oregon with child psychiatry phone consultations. OPAL-K evaluates prescriptions and associated chart notes and makes recommendations for ODHS to either approve or not authorize the prescription after consultation with the prescribing provider. If a case is flagged for OPAL-K review, primary care clinicians are scheduled to have a consultation. These consultants will review the case with the provider. Providers may provide more clinical data that will reverse a recommendation for changing the present flagged psychotropic regimen. If changes are needed, the OPAL-K consulting child psychiatrist will review more appropriate treatment options to consider.

Figure 1. Psychotropic Prescribing for Foster Care Youth in Oregon

1. All new prescriptions for psychotropics require authorization by a Psychotropic Oversight nurse at ODHS.
2. Every child receives (at a minimum) an annual psychotropic medication authorization by a Psychotropic Oversight nurse using Medicaid pharmacy claims data reports generated by OSU.
3. OPAL-K child psychiatrists are available for nurse consultation if needed.
4. Consults with OPAL-K psychiatrists are available to support any provider in Oregon who has prescriptive authority.

Oregon Fee-for-Service Policy

The OHP has a long-standing program to review all mental health drugs prescribed to youth in foster care. Moreover, several programs exist to ensure appropriate prescribing for Medicaid members who are not enrolled in foster care. An overview of prescribing patterns and interventions are outlined in Figure 2. These policies were developed with input from experts in mental health and child psychiatry and are intended to support safe and appropriate use of psychotropics in children. In October 2022, policies were expanded to include prior authorization for use of antipsychotics *for all children younger than 5 years of age enrolled in OHP*. These additional safety measures apply to both youth in foster care and members not enrolled in foster care.[8] The policy targets children after their first prescription to accommodate prescribing for urgent or acute symptoms and to avoid interruptions in therapy during transitions of care for patients newly enrolled in OHP. A prior authorization is required for continued therapy with documentation of clinical rationale, metabolic monitoring, use of first-line non-pharmacologic therapy, and consultation with a child psychiatrist.

As part of this new PA policy, OHA performs outreach to the prescribing providers to notify them of the PA requirement, provide education on evidence-based use of non-pharmacological therapy, and facilitate access to services for appropriate patients (as previously described).

Figure 2. Medicaid Programs to Improve Prescribing Practices for Mental Health Drugs in Youth

1. Prior authorization and provider notification for all antipsychotics prescribed for >30 days in members ≤5 years of age.
2. Provider referral for OPAL-K review for patients less than 10 years of age prescribed antipsychotics without FDA indication for more than 90 days. Members are prioritized for referral based on duration of therapy, glucose testing, diagnoses, and specialist involvement.
3. Pharmacy profile reviews and provider notification (by fax) for youth < 5 years of age, with prescriptions for ≥4 or more psychotropics, or with recent psychotropic prescriptions from 3 or more providers.

Retrospective Study of Psychotropic Prescribing in Oregon Foster Care Youth

A descriptive, retrospective study of the psychotropic prescribing patterns in a small subset of Oregon youth in foster care evaluated 110 psychotropic medication authorization forms for *newly* prescribed therapy. Youth included for review were identified through screening and flagged by an ODHS nurse, trained and authorized to approve therapy, for psychiatrist review. These profiles represent some of the most complex cases in the foster care program. Of interest were off-label prescriptions, polypharmacy, and other factors that may influence psychotropic medication authorization by OPAL-K psychiatrists.

Medication reviews were flagged from psychotropic medication authorization (PMA) forms labeled for urgent review by a Psychotropic Oversight nurse at ODHS. The study included PMAs that were approved and denied in the timeframe from 12/02/2020 to 6/10/2022. ODHS labels the forms as "urgent" to expedite the review process and shorten the length of time that children are waiting for their prescriptions. Youth under 18 years of age (*N* = 110) who were in foster care when the PMA form was sent to OPAL-K were included in the analyses. Data on demographics, working diagnoses, medications, off-label prescribing, polypharmacy, prescribing clinician clinical degrees, and prescription approval status were de-identified and evaluated with univariate and bivariate statistics. Logistic regression models were used to examine factors associated with psychotropic medication prescription authorization. This study was approved by the Oregon Health and Science University Institutional Review Board.

The prescribed medications were categorized into eight classes: antipsychotics, antidepressants, stimulants, alpha agonists, benzodiazepines, non-benzodiazepine anxiolytics, mood stabilizers, and other. Primary diagnoses were categorized into nine disorders according to DMS-5 classification: trauma-related, attention deficit hyperactive, depressive, attachment, adjustment, autism spectrum, anxiety, neurodevelopmental, psychotic, and disruptive.[5] Autism spectrum disorder was separated from the other neurodevelopmental disorders because FDA approves certain antipsychotics to treat specific symptoms associated with autism.

The sample included 57 males assigned at birth (51.8%) and 53 females assigned at birth (48.2%). The age range for this sample was 4-18 years (mean: 11 years) (**Table 2**). Psychiatric mental health nurse practitioners prescribed 41.8% of new medications, psychiatrists prescribed 33.6%, and physician assistants prescribed 10.0%. The three most prescribed medications were aripiprazole (20.9%), risperidone (14.5%), and clonidine (7.3%). The three most prescribed medication classes were antipsychotics (46.4%), antidepressants (15.5%), and alpha agonists (11.8%). 80.9% percent of the prescriptions had no FDA-approved indication, although 30.0% of off-label prescribing were supported by evidence in the psychiatric literature. Fifty-three percent of the study participants were prescribed 4 or more psychotropic medications or 2 psychotropic medications in the same drug class (polypharmacy).

Medications were most frequently prescribed for agitation (31.8%), anxiety (15.5%), and sleep disruption (14.5%). The 3 most frequent primary diagnoses were trauma-related disorders (30%), attention-deficit/hyperactivity disorder (ADHD) (27.3%), and depressive disorders (18.2%). Sixty percent of the study participants had either a trauma-related disorder or documented trauma. Eighty-four percent of children had 2 or more psychiatric disorders. Sixty-four percent of the sample were screened for review because the prescribed medication was off-label, 41.8% were screened for review because of polypharmacy, and 10.9% were neither off-label nor had polypharmacy. An OPAL-K psychiatrist authorized 53.6% of the medications, and 46.4% were not approved. Most denials were because the medication was off-label (64.5%) or polypharmacy (41.8%). Denials would result in scheduling an appointment with an OPAL-K psychiatrist.

Table 2. Characteristics of Youth in Oregon Foster Care Prescribed a New Psychotropic Medication between 12/02/2020 and 6/10/2022

	Not Authorized (*n*=51)	Approved (*n*=59)	Total (*N*=110)
Age			
Mean (*SD*)	12.2 (3.69)	10.8 (4.32)	11.4 (4.09)
Median [Min, Max]	13.0 [4.00, 17.0]	11.0 [4.00, 18.0]	13.0 [4.00, 18.0]
Off-label			
No	4 (7.8%)	17 (28.8%)	21 (19.1%)
Yes	47 (92.2%)	42 (71.2%)	89 (80.9%)
Polypharmacy			
No	26 (51.0%)	26 (44.1%)	52 (47.3%)
Yes	25 (49.0%)	33 (55.9%)	58 (52.7%)
Trauma Present			
No	19 (37.3%)	25 (42.4%)	44 (40.0%)
Yes	32 (62.7%)	34 (57.6%)	66 (60.0%)
Prescribing Clinician			
Non-psychiatrist	43 (84.3%)	30 (50.8%)	73 (66.4%)
Psychiatrist	8 (15.7%)	29 (49.2%)	37 (33.6%)
Mental Health Comorbidities			
No	8 (15.7%)	9 (15.3%)	17 (15.5%)
Yes	43 (84.3%)	50 (84.7%)	93 (84.5%)
Prescribed Medication			
Antipsychotic	31 (60.8%)	20 (33.9%)	51 (46.4%)

Non-antipsychotic	20 (39.2%)	39 (66.1%)	59 (53.6%)

SD = standard deviation

Findings from the retrospective review of youth in this sub-group found that Oregon's system identifies youth with potential prescribing flags (polypharmacy, antipsychotic use, and off-label psychotropic medications). Identification led to meaningful oversight and reductions in practices unsupported by evidence or clinical reasoning. OPAL-K's psychotropic medication review system is a valuable asset in mitigating inappropriate prescriptions. Continuing support for educating and assisting non-psychiatrist prescribing clinicians, increasing access to non-pharmacological therapy, and improving oversight of medications is a necessary practice to ensure appropriate use of psychotropic medications for youth in foster care. A collaborative and consultative practice is effective in changing provider prescribing. Non-psychiatric providers are encouraged to use consultation services like OPAL-K, and especially prior to prescribing antipsychotic medications, escalating polypharmacy, or prescribing without an FDA-approved indication.

Conclusion

The prescription of psychotropics for foster care children needs to be carefully balanced between benefit and harms, and substantiated by evidence. Oregon has a robust program to optimize medication use for foster care children. Providers are encouraged to confer with OPAL-K to facilitate appropriate prescribing of medications used to treat mental health disorders in children via a collaborative consultation experience. Moreover, OHP policies can assist providers to optimize treatment for children who are prescribed psychotropics.

Peer reviewed by: Andrew Gibler, PharmD, RPh, Clinical Pharmacy Policy & Programs Manager, Oregon Health Authority, Health Policy & Analytics Division and Amanda Parish, LCSW, Clinical Coordinator, Mental Health Clinical Advisory Group.

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COVID-19 Therapeutics Update: Where Are We Now? *(Evidence updated through 3/31/23)*

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Introduction

As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to mutate since the original strain was identified, options to treat Coronavirus Disease 2019 (COVID-19) have also changed in the past year. All of the medications listed in Table 1 have received, or had received, approval or emergency use authorization (EUA) by the US Food and Drug Administration (FDA) to treat or prevent COVID-19.

Table 1. Medications Authorized or Approved by FDA from 2020-2022 to Prevent or Treat COVID-19.

Antivirals: Molnupiravir Nirmatrelvir – ritonavir Remdesivir Immune Modulators: Anakinra Baricitinib Tocilizumab	Monoclonal Antibodies: Bamlanivimab Bamlanivimab – estesevimab Bebtelovimab Casirivimab – imdevimab Sotrovimab Tixagevimab – cilgavimab COVID-19 Antibodies: Convalescent plasma

With the emergence of the SARS-CoV-2 Omicron variant and its subvariants[1], the FDA has revoked the Emergency Use Authorization (EUA) of all the monoclonal antibodies so they can no longer be prescribed. The immune modulators are restricted to hospitalized patients with COVID-19 who require supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO). This leaves only the antivirals and convalescent plasma to treat COVID-19 in non-hospitalized individuals at high risk for progressing to severe disease. As the COVID-19 landscape continues to change with an evolving virus and increasing population immunity, this article will present updated research for these outpatient treatments.

Nirmatrelvir and Ritonavir (PAXLOVID)

The FDA granted EUA for nirmatrelvir and ritonavir (NM/r) in December 2021 to treat mild or moderate COVID-19 in individuals at high risk for developing severe disease, including hospitalization or death.[2] The drug product was recently endorsed by an FDA advisory committee for full FDA approval.[3]

Table 2. Nirmatrelvir and Ritonavir Treatment.[2]

Mechanism of Action	Viral protease inhibitor that halts viral replication
Authorized Use	Emergency Use Authorization for treatment of mild to moderate COVID-19
Eligible Population	Age ≥12 years, weight ≥40 kg, at high risk for severe disease
Prescribing Window	Initiate within 5 days of symptom onset
Assessment	Renal impairment; hepatic impairment; drug interactions
Administration Route	Oral
Duration of Therapy	5 days

Authorization of NM/r was based on the Phase 3 trial, EPIC-HR (Table 3).[4] The trial included unvaccinated, non-hospitalized patients with mild or moderate COVID-19 who had at least 1 risk factor for developing severe disease. The trial started in July 2021 and was completed in December 2021. Delta was the predominant circulating SARS-CoV-2 variant during the clinical trial.[4]

Table 3. Results from Phase 3 EPIC-HR Trial.[4]

Primary Endpoint	Nirmatrelvir-ritonavir	Placebo
COVID-19-related hospitalization or all-cause death	0.77%	6.31%
	-5.62% (95% CI, -7.21 to -4.03); NNT = 18 over 28 days if treated within 5 days of symptoms onset	
Abbreviations: CI = confidence interval; NNT = number needed to treat		

In the unpublished Phase 3 trial EPIC-SR, vaccinated patients with COVID-19 treated with NM/r who were at low risk for progressing to severe disease did not experience alleviation of symptoms any faster than those given placebo.[5,6] The study also did not find that NM/r reduced risk of hospitalization from COVID-19 or all-cause death.[5,6] In the unpublished Phase 3 trial EPIC-PEP, post-exposure prophylaxis with NM/r did not provide protection from positive COVID-19 test results in asymptomatic adults exposed to household contacts with COVID-19.[6,7] Therefore, NM/r should be reserved for individuals with mild or moderate COVID-19 who are at high risk for severe disease.

Real world effectiveness and safety of NM/r should be routinely monitored as levels of immunity against COVID-19 change and SARS-CoV-2 variants continue to evolve. From January through March 2022, Clalit Health Services, which covers 52% of the Israeli population, found that NM/r continued to reduce COVID-19-related hospitalizations and death from the B.1.1.529 Omicron variant in people 65 years of age and older, but NM/r did not reduce these events in people 40-64 years of age.[8] Likewise, data from a population-based cohort in Ontario, Canada, also found that NM/r continued to reduce COVID-19-related hospitalizations and death in older vaccinated adults (median age of 77 years).[9] The drug remained well tolerated in those eligible for treatment.[8,9] The FDA has concluded that NM/r has likely retained efficacy at reducing hospitalizations and death in high risk vaccinated individuals or individuals with immunity from previous infection, even with the SARS-CoV-2 Omicron variant and its subvariants.[6]

Rebound phenomenon after treatment with NM/r has been reported in the literature, but cases have been mild and all have resolved without further intervention.[10-12] In a cohort of 484 high-risk patients treated with NM/r, only 4 patients (0.8%) experienced rebound of mild symptoms.[12] The FDA could not identify a clear association between NM/r treatment and COVID-19 rebound in a comprehensive analysis, and data show that this phenomenon is observed in both those treated with NM/r and those not treated.[6]

Treatment with NM/r may help prevent "Long COVID", the disease encompassing the post-acute sequelae of SARS-CoV-2 infection, based on a retrospective study from the US Department of Veterans Affairs.[13] There are also case reports that NM/r helped treat "Long COVID"[14] and this may be an area of study where clinical trials are warranted. Study data will begin to emerge that will help clinicians understand how best to treat these individuals.

Pregnancy is a risk factor for severe COVID-19 and has been associated with higher rates of complications in pregnancy or childbirth, so individuals with COVID-19 who are pregnant are eligible for NM/r.[15] No other oral treatment options are available for patients who are pregnant or breast-feeding. A case series of 47 pregnant patients with mild or moderate COVID-19 at high risk for severe disease (64% had an additional morbidity) were treated with NM/r without serious adverse events.[16] The American College of Obstetricians and Gynecologists advise obstetric care clinicians to consider the use of NM/r in non-hospitalized pregnant individuals with mild to moderate COVID-19, particularly if one or more additional risk factors are present (e.g. body mass index >25, chronic kidney disease, diabetes mellitus, cardiovascular disease).[17] Clinicians should weigh the available data against the individual risks of COVID-19 in pregnancy for each case.[17]

It is not yet known whether longer durations of NM/r treatment are beneficial in patients with mild or moderate COVID-19 who are moderately or severely immunocompromised. Pfizer is currently conducting a randomized clinical trial (EPIC-IC, NCT05438602) that evaluates longer durations of NM/r treatment for immunocompromised individuals with mild or moderate COVID-19.[18]

Molnupiravir (LAGEVRIO)

The FDA granted EUA for molnupiravir in December 2021 to treat mild or moderate COVID-19 in adults at high risk for developing severe disease, including hospitalization or death.[19]

Table 4. Molnupiravir Treatment.

Mechanism of Action	Nucleoside analog that inhibits viral replication by viral mutagenesis
Authorized Use	Emergency Use Authorization for treatment of mild to moderate COVID-19
Eligible Population	Age ≥18 years, at high risk for severe disease, and other treatments not accessible or available
Prescribing Window	Initiate within 5 days of symptom onset
Assessment	Pregnancy status, contraceptive status, breastfeeding status
Administration Route	Oral
Duration of Therapy	5 days

Authorization of molnupiravir was based on the Phase 3 trial, MOVe-OUT (Table 5).[20] The trial included unvaccinated, non-hospitalized adults with mild or moderate COVID-19 who had at least 1 risk factor for developing severe disease. Individuals who were pregnant or breastfeeding were excluded. The trial started in May 2021 and was completed in November 2021. Delta was the predominant circulating SARS-CoV-2 variant during the clinical trial.[20]

Table 5. Results from Phase 3 MOVe-OUT Trial.[20]

Primary Endpoint	Molnupiravir	Placebo
All-cause hospitalization or death	6.8%	9.7%
	-3.0% (95% CI, -5.9 to -0.1); NNT = 34 over 29 days if treated within 5 days of symptoms onset	
Abbreviations: CI = confidence interval; NNT = number needed to treat		

Real world effectiveness and safety of molnupiravir should also be routinely monitored as levels of immunity against COVID-19 change and SARS-CoV-2 variants continue to evolve. From April through August 2022, the United Kingdom's National Health Service conducted an open-label randomized clinical trial in vaccinated patients infected with the B.1.1.529 Omicron variant.[21] Individuals who received molnupiravir instead of usual care did not experience a reduction in all-cause hospitalization or death in the first 28 days, but patients reported a faster time to full recovery of COVID-19 symptoms versus usual care (9 days vs. 15 days).[21] Molnupiravir continued to show a strong safety profile in those who received treatment.[21]

Because molnupiravir induces mutagenesis into the viral genome, there is potential that molnupiravir could drive viral mutations that spread. A study, which has not yet been peer-reviewed, investigated global RNA sequencing databases and found a signature in viral RNA that may be associated with molnupiravir mutagenesis.[22] The study makes a case that molnupiravir could yield mutated SARS-CoV-2 with the capacity to spread, but it is not clear whether molnupiravir can contribute to new infectious variants, or whether it is simply creating weakened viruses unable to spread or cause disease. It is already well understood that SARS-CoV-2 has the capacity to generate plenty of mutations on its own, even in the absence of molnupiravir.[1]

Remdesivir (VEKLURY)

A 3-day course of remdesivir was approved by the FDA in January 2022 for non-hospitalized infants, children and adults with mild or moderate COVID-19 in order to prevent progression to severe disease.[23] Previously, use of remdesivir was limited to hospitalized patients after trials found 5 days of remdesivir provided clinical benefit but did not reduce mortality.[23]

Table 6. Remdesivir Treatment.[23]

Mechanism of Action	Nucleotide analog ribonucleic acid (RNA) polymerase inhibitor that halts viral replication
Approved Use	Approved for treatment of mild to moderate COVID-19
Eligible Population	Age ≥28 days, weight ≥3 kg, at high risk for severe disease
Prescribing Window	Initiate within 7 days of symptom onset
Assessment	Renal impairment, hepatic impairment, prothrombin time
Administration Route	Intravenous infusion
Duration of Therapy	3 days

Approval of remdesivir for outpatient use was based on the Phase 3 trial, PINETREE (Table 7).[24] The trial included unvaccinated, non-

hospitalized children and adults with mild or moderate COVID-19 who had at least 1 risk factor for developing severe disease. The trial started in September 2020 and was completed in April 2021. Delta was the predominant circulating SARS-CoV-2 variant during the clinical trial.[24]

Table 7. Results from Phase 3 PINETREE Trial.[24]

Primary Endpoint	Remdesivir	Placebo
COVID-19-related hospitalization or all-cause death	0.7%	5.3%
	HR 0.13 (95% CI, 0.03 to 0.59); NNT = 22 over 28 days if treated within 7 days of symptoms onset	
Abbreviations: CI = confidence interval; HR = hazard ratio; NNT = number needed to treat		

Real world effectiveness and safety of remdesivir should also be routinely monitored as levels of immunity against COVID-19 change and SARS-CoV-2 variants continue to evolve. A 3-day outpatient course of remdesivir in high-risk patients from Italy who had mild or moderate COVID-19 from February through May 2022 was retrospectively compared to matched controls who did not receive antiviral treatment, including oral antivirals.[25] The study showed that remdesivir continues to significantly reduce the risk of disease progression, including hospitalization.[25] A single-center, prospective cohort study in Toronto, Canada, also found that remdesivir continues to provide significant protection against hospitalization in solid organ transplant patients with mild or moderate COVID-19.[26] Remdesivir has also continued to demonstrate that it is safe and well tolerated.[25,26]

Convalescent Plasma

Convalescent plasma is an antibody-rich blood product donated from people who have recently recovered from COVID-19, preferably from one of the predominant circulating variants. The FDA has granted EUA for use of convalescent plasma in non-hospitalized patients with immunosuppression, which is supported by clinical trials and a systematic review with meta-analysis.[27-30]

Table 8. Convalescent Plasma Treatment.[27]

Mechanism of Action	Direct neutralization of the virus
Authorized Use	Emergency Use Authorization for treatment of COVID-19 in people with immunosuppression
Eligible Population	Adult and pediatric patients with immunosuppression at high risk for severe disease
Prescribing Window	Not specified
Assessment	Prior history of severe allergic reactions or anaphylaxis to plasma transfusion
Administration Route	Intravenous infusion
Duration of Therapy	Based on physician's medical judgement

Conclusion

As SARS-CoV-2 continues to evolve, it is important to continue to study authorized or approved treatments. The COVID-19 antivirals currently available continue to demonstrate real world effectiveness and safety in individuals with mild or moderate COVID-19 since they were originally studied in Phase 3 clinical trials. These treatments may not have the same efficacy as when they were originally studied due to increasing immunity, but they continue to provide real benefit, such as faster resolution of symptoms and decreased risk for hospitalization, especially to those who are older. The National Institutes of Health, which regularly updates their COVID-19 treatment guidelines, gives its strongest recommendation for NM/r, but remdesivir is also a preferred therapy.[31] Molnupiravir is limited as an alternative option because of its presumed lower relative efficacy versus the other antivirals.[31]

NIH COVID-19 Treatment Guidelines[31] for Patients at High Risk of Progressing to Severe COVID-19

Preferred therapies:

- Ritonavir-boosted nirmatrelvir
- Remdesivir

Alternative therapy when preferred therapies are not available or clinically appropriate:

- Molnupiravir

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Policy Evaluation: Quantity Limits for Buprenorphine

Plain Language Summary

- Buprenorphine is a medicine that can help people who are dependent on opioids stop taking them. Buprenorphine may help people manage opioid withdrawal and helps people stay in treatment for their opioid dependence.
- The Food and Drug Administration has approved buprenorphine up to 24 mg daily for people who are dependent on opioids. Most people need at least 16 mg daily to stop taking heroin. But in Oregon, more and more people are using fentanyl instead of heroin. Fentanyl is a more potent opioid and may cause more severe withdrawal symptoms compared to heroin. There are no large studies that evaluate the most effective dose of buprenorphine for people who use fentanyl.
- Buprenorphine claims for people enrolled in the Oregon Health Plan fee-for-service program are currently limited to 24 mg daily. However, a review of claims data shows that some people may need higher doses to manage symptoms of opioid dependence. We recommend increasing the dose limit for buprenorphine to 32 mg daily.

Purpose:

The purpose of this policy evaluation is to quantify the daily doses of sublingual buprenorphine or buprenorphine/naloxone products prescribed to Oregon Health Plan (OHP) fee-for-service (FFS) members with opioid use disorder (OUD) and to evaluate the impact of the current FFS 24 mg daily dose limit.

Research Questions:

1. For people with paid claims for sublingual buprenorphine, what proportion of members have a daily dose greater than 24 mg or 32 mg?
2. For members with paid or denied FFS claims for sublingual buprenorphine, what diagnoses are present in medical claims that are potential indications for therapy?

Conclusions:

- Most guidelines recommend that the dose of sublingual buprenorphine be individualized and titrated to control symptoms and cravings associated with OUD. Available evidence shows that higher daily doses (≥16 mg) may increase treatment retention and decrease illicit opioid use, but the evidence was limited to people dependent on heroin and most studies have only evaluated buprenorphine up to 24 mg daily.
- The Food and Drug Administration (FDA) and Substance Abuse and Mental Health Service Administration (SAMHSA) recommend doses up to 24 mg daily.[1] The Veterans Association and Department of Defense (VA/DOD) recommend flexible dosing schedules up to 32 mg daily,[2] and the National Institute for Health and Care Excellence (NICE) does not make any specific recommendations for buprenorphine dose limits.[3]
- Although prevalence of illicit fentanyl continues to increase in Oregon, there is insufficient evidence to identify what dose of buprenorphine is needed to control symptoms in people dependent on fentanyl. Limited data from uncontrolled studies and patient surveys indicates that addition of buprenorphine in fentanyl dependence may be associated with increased rates of precipitated withdrawal and that doses higher than 24 mg daily may

be needed to control symptoms of OUD.[4-6] However, efficacy of specific doses in people who are dependent on fentanyl has yet to be confirmed in controlled trials.

- Despite the 24 mg daily dose limit in place by the FFS program, some FFS members are prescribed doses above this limit. Of members with paid claims for sublingual buprenorphine or buprenorphine/naloxone products from 10/1/21 to 9/30/22, about 13% (n=49) had an average daily dose between 24 and 32 mg in the 90 days following their first claim. About 2% had an average dose greater than 32 mg daily. Under the current policy members can get higher doses by being prescribed more than one formulation of buprenorphine or by consistently refilling prescriptions early. The current early refill threshold is set at 80%.
- Only 31 members had a denied FFS claim due to the 24 mg quantity limit and no paid claim on the same day from 10/1/21 to 9/30/22.
- The proportion of members with presence of an OUD diagnosis in medical claims was consistent across all buprenorphine doses (>87%). The proportion of members that had common comorbid pain diagnoses increased with larger daily doses of buprenorphine. Most members with denied claims had a diagnosis of OUD (76%).
- This evaluation is limited by the small number of members reviewed. However, a post-hoc analysis with less stringent inclusion and exclusion criteria demonstrated similar trends.

Recommendations:

1. Increase dose limit to 32 mg daily for sublingual buprenorphine formulations. Update current prior authorization (PA) criteria to permit use of higher doses for OUD with medical justification (**Appendix 2**).
2. Implement a days' supply limit for all sublingual buprenorphine formulations (in addition to the 32 mg daily quantity limit) to provide better enforcement of quantity limits.

Background

Guidelines for the treatment of OUD recommend buprenorphine as one of the first-line treatment options for symptom management.[1,3,7] Both buprenorphine and methadone help maintain people in treatment and decrease use of illicit opioids.[7,8] Choice between these treatment options is typically dependent on individual patient characteristics and preferences. One primary difference in these treatment options is that buprenorphine can be administered in the clinic or dispensed by a pharmacy and self-administered by the patient at home, whereas methadone for OUD continues to remain available only to be administered in a clinic setting. Historically, use of buprenorphine for OUD has also been regulated under the federal Drug Addiction Treatment Act (DATA)-waiver program. However, recent changes to the program have removed this regulatory requirement.[9] Buprenorphine can be now prescribed by any provider with a Drug Enforcement Administration (DEA) number.

A 2014 Cochrane systematic review evaluated outcomes associated with different doses of buprenorphine.[8] The review included 31 RCTs (n=5430) and evaluated maintenance therapy with methadone or buprenorphine in people dependent on opioids.[8] Heroin was the most common type of opioid use reported. Trial durations ranged from 2 to 52 weeks.[8] Fifteen RCTs were conducted in the United States, 9 were conducted in Europe, 4 in the Middle East, 2 in Australia, and one in Asia. Most trials had small numbers of enrolled patients, but the largest trial enrolled 736 participants.[8] Flexible dosing to manage symptoms (rather than fixed dosing) was used in only 11 RCTs, which limits applicability to clinical practice. Buprenorphine was compared to methadone in 20 RCTs. Trials evaluating fixed doses of buprenorphine typically evaluated 16 mg daily or less.[8] Two RCTs with flexible dosing regimens reported doses up to 32 mg daily, but average dose for the enrolled participants in these trials was less than 24 mg.[8] Only one RCT reported and average dose over 24 mg daily.[8] The authors concluded that there was moderate quality evidence that buprenorphine doses of 16 mg daily or higher were better at suppressing illicit opioid use (by urinalysis) compared to lower doses (3 RCTs; n=729, standardized mean difference -1.17; 95% CI -1.85 to -0.49).[8]

Other systematic reviews have documented similar results with buprenorphine, noting increased treatment retention with daily doses above 16 mg daily compared to lower doses. [10,11] Importantly, they also note a lack of studies which evaluate doses higher than 24 mg daily. [10,11] A 2022 systematic review evaluated how buprenorphine impacts self-reported opioid cravings during maintenance therapy for OUD.[12] One included study documented that doses of 24 or 32 mg daily reduced opioid cravings compared to 8 mg daily after 3 months of treatment.[12] Doses of 8-16 mg daily also demonstrated decreased craving symptoms compared to 1 mg daily.[12]

One significant limitation of the current evidence is that most trials have included people who are dependent on heroin. However, the prevalence of synthetic opioids like fentanyl continues to increase. Fentanyl is an opioid that is over fifty times more potent than heroin and is often combined with other opioids or cocaine to increase its euphoric effects.[13] In Oregon, law enforcement seizures of counterfeit pills containing fentanyl has increased by almost 1200% since 2019 and by 85% since 2020.[14] Presence of fentanyl has also been driving an increase in overdose deaths. Provisional data indicate that overdose deaths of all types has increased by more than 76% from 2011 to 2021, with overdose deaths specifically related to fentanyl and other synthetic opioids increasing by 83% from 2020 to 2021.[15] Fentanyl or fentanyl analogues, including illicitly manufactured derivatives, were the most common type of opioid identified in 2021, present in 48% of all overdose deaths.[15]

There is currently a lack of published data to guide prescribing of buprenorphine dosing necessary to mitigate symptoms in some people dependent on fentanyl. A small case series (n=12) of people who were opioid-dependent and tested positive for fentanyl reported extended clearance of fentanyl and norfentanyl (average clearance of 7 and 13 days, respectively).[16] These longer durations of clearance may contribute to continued symptoms and increased rates of precipitated withdrawal. Small case series and patient surveys have documented increased incidence of precipitated withdrawal reported by patients when using buprenorphine in the presence of fentanyl.[4,5] Additionally, a recent observational study evaluated adherence to buprenorphine therapy based on data from a prescription drug monitoring program in Philadelphia, PA (n=10,669).[6] Study investigators noted that illicit fentanyl was prevalent in the drug supply, and estimated that about 30% of the study population was eligible for Medicaid. The study included members who initiated buprenorphine from January 1, 2017 to December 31, 2018. The primary outcome was adherence to therapy defined as at least 80% of days covered over 6 months.[6] Doses were categorized as low dose (<16 mg daily; n=2024), medium dose (16 to <24mg; n=7918) or high dose (≥24 mg; n=727). Most participants were prescribed medium doses (74%).[6] Overall, adherence at 6 months for the entire study population was 26.6%. [6] Compared to low dose prescriptions, members with medium and high dose prescriptions had increased odds of adherence at 6 months (medium: adjusted OR 1.76, 95% CI 1.55–2.00; high: adjusted OR 5.11, 95% CI 4.30–6.17).[6] Adherence also varied by age, sex, presence of claims for other opioids, zip code poverty level, and buprenorphine formulation (with improved adherence with the film compared to the tablet; OR 1.37 [95 % CI 1.25–1.50]).[6] While these results are consistent with previous randomized controlled trials demonstrating improved treatment retention with higher doses of buprenorphine, they should also be interpreted with caution as this observational study did not control for any potential confounding factors.

Specific organizations have made recommendations on appropriate buprenorphine dosing for OUD. The 2021 guideline from the VA/DOD recommends initial induction doses of 2-8 mg daily with titration by 2-4 mg daily until withdrawal symptoms and cravings are relieved.[2] Maintenance doses are targeted to control cravings and illicit opioid use at daily doses ranging from 12-16 mg (up to 32 mg/day).[2] Regimens should be individualized based on patient factors, including dose reduction for hepatic impairment or divided daily doses (two or three times daily) for patients with comorbid chronic pain.[2] The National Institute for Health and Care Excellence also updated their published guidance for buprenorphine and methadone for management of opioid dependence in 2016.[3] While the evidence evaluated for these recommendations was based primarily on buprenorphine doses of 16 mg or less, they support flexible dosing to manage symptoms of opioid dependence.[3] Specific recommendations for maximum daily dosing were not included.

According to FDA labeling for sublingual buprenorphine products, maintenance doses typically range from 4 to 24 mg per day depending on each individual patient and their clinical response.[17] Current labeling states daily doses greater than 24 mg have not demonstrated a clinical advantage.[17] Clinical information submitted by the manufacturer for approval of Suboxone® (buprenorphine/naloxone) tablets and Subutex® (buprenorphine) tablets included 98 publications. Information from these publications spanned over 15 years and included a variety of study designs for both controlled and uncontrolled trials.[18] The FDA designated 3 studies as pivotal trials evaluated for the efficacy in OUD. These trials for buprenorphine enrolled primarily heroin users and had a high proportion of patients with concomitant cocaine use.[18] The first compared buprenorphine/naloxone or buprenorphine monotherapy tablets 4 to 24 mg daily to placebo over 4 weeks (n=497). [18] Buprenorphine monotherapy and combination therapy demonstrated improvements in negative urine drug screens (17.8% for buprenorphine/naloxone; 20.7% for buprenorphine; and 5.8% for placebo) and opiate craving score.[18] The other pivotal studies compared buprenorphine solution at doses of 4 mg, 8 mg or 16 mg daily to buprenorphine 1 mg solution or methadone 20 and 60 mg daily over 16 weeks (n=1631 participants).[18] The proportion of patients with negative urine drug screens was higher for buprenorphine (34.5%) compared to methadone 20 mg (15.3%) and comparable to methadone 60 mg (27.4%).[18] A larger proportion of members had clean urine drug screens when 8 mg solution daily was compared to 1 mg daily (20.2% vs. 11.6%). There was no statistical difference in negative urine drug screens between 4 mg (20.2%), 8 mg (21.7%), or 16 mg (28.8%) groups.[18] Retention in treatment was also improved with buprenorphine solution 4 mg (52%), 8 mg (53%) or 16 mg (61%) daily compared to 1 mg (40%).[18]

Of note, buprenorphine solution, tablets, and sublingual film are not bioequivalent on a 1:1 mg basis. FDA reviewers noted that sublingual tablets have a relative bioequivalence of about 50-70% compared to sublingual solution in the 4-16 mg range.[18] These differences in absorption between the tablet and solution get larger at higher doses (e.g., 24 mg).[18] FDA reviewers noted similar concerns with bioequivalence between sublingual films and tablets with increased absorption with the films compared to the tablets.[19] When switching between Suboxone® films and tablets, current labeling recommends starting the same dosage of the previously administered product, monitoring for symptoms of over-dosing or under-dosing, and adjusting the dose as needed based on response.[17]

None of the controlled studies used to assess efficacy of sublingual buprenorphine for FDA approval evaluated doses higher than 24 mg daily. However, doses up to 32 mg daily of the buprenorphine solution or 24 mg daily of buprenorphine/naloxone (Suboxone®) tablets were included in open-label safety studies.[18,19] The FDA estimated that at the time of FDA approval, 84 patients (9% of members in pooled studies of buprenorphine solution) received 32 mg daily (7578 person-days, with an average duration of therapy of 90 days per person).[18] Safety concerns observed in clinical trials included risk for abuse and misuse, risk for respiratory depression (especially in conjunction with benzodiazepines), and hepatic adverse events. FDA reviewers also noted concern for diversion of the Suboxone® film. During clinical trials conducted at 3 different study sites, about 12,900 buprenorphine films were provided in excess of the amount that patients were instructed to use. Of these doses, 46% (5,918 films) were missing and not returned.[19] Prescription of higher strength films or tablets may mitigate some of this diversion risk. The maximum dose of buprenorphine/naloxone currently supplied on the market is 12 mg films making it necessary to dispense at least 2 films to achieve a dose of 24 mg daily. With higher quantities, it makes it easier for patients to manage their symptoms of opioid use with a lower dose and still share or sell tablets with others. Because of these concerns, SAMHSA recommends maintenance doses up to 24 mg daily.[1] Because higher doses may unintentionally increase risk of diversion, SAMHSA includes recommendations to document clinical justification for higher doses and have a diversion control plan in place.[1] They also recommend that patients who do not respond 24 mg daily of buprenorphine be considered for methadone treatment.[1]

Beginning 1/1/2020, Oregon legislation was enacted which prohibited use of PA during the first 30 days of medication-assisted treatment for both opioid- and alcohol-related substance use disorders. In accordance, the Pharmacy and Therapeutics Committee updated their policy to remove PA for all products to treat OUD. Because higher doses of sublingual buprenorphine can be used off-label for pain, quanti ty limits of 24 mg daily were maintained for buprenorphine. The goal of this policy evaluation is to evaluate the ongoing utility and impact of the 24 mg quantity limit, in light of increased illicit fentanyl availability.

Methods:

Members were identified for inclusion in the study based on FFS claims for sublingual buprenorphine (First Databank HICL sequence numbers [HSNs] 001762 or 024846; route: sublingual). Members with paid claims and members with denied claims were reported in separate populations. The evaluation window for buprenorphine claims was from 10/1/2021 to 9/30/2022, and the index event (IE) was defined as the first claim in the evaluation window. For each patient, the baseline and follow-up periods were based on the IE.
- The baseline period was defined as the 6 months prior to the IE (exclusive of the IE).
- The follow up period was defined as the 90 days following the IE (inclusive of the IE)

Population 1: Members with Paid Claims for Sublingual Buprenorphine
Inclusion Criteria:

1. Medicaid members with a paid FFS claim sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window

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 FFS eligibility during the follow-up period
4. Members 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 members may be incomplete. Members were identified based on the following benefit packages:

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

Groups were assigned based on the average dose for buprenorphine claims in the 90 days following the IE. The average daily dose was calculated by summing the total dose dispensed with each prescription (quantity dispensed*drug strength*days' supply) divided by the total days covered by buprenorphine (from the first to the last claim in the follow-up period). The days covered by buprenorphine was based on the first date of service and the last date of service plus the days' supply on the last claim and eliminating any days for which there was a gap in care.

Outcomes evaluated in this analysis included:

1. Proportion of members with a diagnosis of OUD in the baseline period (ICD-10 F11x);
2. Proportion of members with a max daily dose of buprenorphine of 24 to 32 mg daily or >32mg daily for the last 7 days covered by buprenorphine during the follow-up period; and
3. Proportion of members who were also included in population #2 (members with denied claims)

Population 2: Members with Denied Claims

Inclusion Criteria:

1. Medicaid members with a denied FFS claim for sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window. Denied claims were included based on error codes for the 24 mg daily quantity limit (error#: 4167) and excluded denials with error codes related to billing (see **Appendix 1**). The first claim in the evaluation window was defined as the IE.

Exclusion criteria

1. Paid claim for sublingual buprenorphine on the same date of service as the denied IE
2. Non-continuous Medicaid eligibility during the baseline period
3. Primary insurance coverage (i.e., TPL) at any time during the baseline period
4. Members with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline period. Claims data for these members may be incomplete. Members were identified based on the following benefit packages:

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

Groups were assigned based on the daily dose for the IE. Buprenorphine doses were categorized into 24-32mg and >32mg daily.

Outcomes evaluated in this analysis included:

1. Proportion of members with a diagnosis of OUD in the baseline period (ICD-10 F11x)
2. Proportion of members with common chronic pain diagnoses in the baseline period (see list of ICD codes)

Results:

<u>Evaluation of Paid Claims for Sublingual Buprenorphine Formulations</u>

Of members with paid FFS claims for sublingual buprenorphine or buprenorphine/naloxone for the 1-year period from 10/1/21 to 9/30/22, about 22% (n=371) were included in this analysis. Most FFS members are automatically enrolled in coordinated care organizations (CCOs) and many were excluded because they were not enrolled in FFS for 90 days following the first claim for buprenorphine (**Table 1**). Baseline demographics for members in the analysis are listed in **Table 2**. The average age of included members was 38 years for members prescribed less than 32 mg daily and 35 for members prescribed over 32 mg daily. All included members were adults. Most members were female and identified as Native American or Alaskan Native. About half of included members had no recent paid claims for sublingual buprenorphine formulations in the 90 days before their first claim in the reporting period. Average Elixhauser Score was slightly higher in members with higher doses potentially indicating increased comorbidities for this group. The Elixhauser index is a weighted measure based on relevant diagnoses submitted on medical claims during the baseline period. The presence or absence of diagnoses are identified in medical claims and categorized into 29

comorbidity variables. Each category is assigned a weighted score from -7 to +12.[20] Lower scores indicate lower disease burden whereas higher scores are indicative of higher disease burden. The index is reported as 2 separate measures which can be used to predict risk of in-hospital mortality (the "M" index) and risk for 30-day readmission (the "R" index).[20]

The current 24 mg quantity limit is enforced per prescription, and members can attain a higher dose if they have multiple concurrent prescriptions for buprenorphine or refill a single prescription early. The average daily dose in the 90 days following the first claim was less than or equal to 24 mg daily for 85% of members. Thirteen percent of members (n=49) had an average daily dose from 24 to 32 mg daily and 2% of members (n=8) had a dose above 32 mg daily.

Presence of OUD diagnosis in the 6 months before the IE was high for all groups (**Table 3**). About 87% of members had a diagnosis of OUD in their medical claims. This analysis also evaluated for presence or absence of common chronic pain conditions. While the list of these conditions in not all inclusive, comorbid OUD and pain conditions were identified for 20% of members with doses of less than or equal to 24 mg daily, 35% of members with 24-32mg daily, and 62% for members with greater than 32 mg daily.

The buprenorphine dose is typically titrated to control symptoms of OUD. To evaluate doses over time, **Table 4** compares average dose over covered days in the entire 90-day follow-up period compared to average dose in the last 7 days covered by buprenorphine. Many members (85%) who had an average dose of 21-32 mg daily over the 90-day period were prescribed 24 mg or less in the last 7 days covered by buprenorphine. This pattern could be a result of:

1) Members with early refills for prescriptions of less than 24 mg daily
2) Dose de-escalation after members are stabilized on buprenorphine
3) Failure to fill a second prescription for members prescribed 2 doses or formulations

Only a small percentage of members with paid claims for buprenorphine also had denied claims for the 24 mg quantity limit (2.5%; n=8).

Table 1. Included population of members with paid claims.

	Total	
Number of included members	#	%
Paid FFS claim for sublingual buprenorphine from 10/1/2021 to 9/30/2022	**1,668**	
After exclusion of Medicare, TPL, and limited drug eligibility groups	1,376	82.5%
After exclusion of non-continuous FFS enrollment in the 90-day follow-up period	449	26.9%
After exclusion of non-continuous Medicaid enrollment in 6-month baseline period	**371**	22.2%

Table 2. Demographics for members with paid claims.

Average Daily Dose	**≤ 24mg daily**		**24.1-32 mg daily**		**>32 mg daily**	
	314	**84.6%**	**49**	**13.2%**	**8**	**2.2%**
Female	168	53.5%	34	69.4%	2	25.0%

Age – mean (range)	38	(18-64)	38	(18-62)	35	(27-41)
<18	0	0.0%	0	0.0%	0	0.0%
18-35	156	49.7%	23	46.9%	4	50.0%
36-64	158	50.3%	26	53.1%	4	50.0%
>=65	0	0.0%	0	0.0%	0	0.0%
Race						
White	28	8.9%	7	14.3%		0.0%
American Indian/Alaskan Native (HNA)	274	87.3%	38	77.6%	8	100.0%
Other	3	1.0%	1	2.0%		0.0%
Unknown	9	2.9%	3	6.1%		0.0%
*Average Elixhauser Score "M"	6		11		-	
*Average Elixhauser Score "R"	20		23		24	
New Start (no paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	163	51.9%	23	46.9%	5	62.5%
Continuation (paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	151	48.1%	26	53.1%	3	37.5%

*Amongst members who had a score

Table 3. Indications for members with paid buprenorphine claims.

Average Daily Dose	**≤24mg daily**		**24.1-32 mg daily**		**>32 mg daily**	
	314	**%**	**49**	**%**	**8**	**%**
OUD Diagnosis in the baseline period						
Present	274	87.3%	43	87.8%	8	100.0%
Absent	40	12.7%	6	12.2%	0	0.0%
Common chronic pain diagnosis in the baseline period	80	25.5%	18	36.7%	5	62.5%
Chronic pain G892x, G894	36	11.5%	9	18.4%	3	37.5%
Dorsalgia M54x	41	13.1%	9	18.4%	3	37.5%
Fibromyalgia M797	7	2.2%	1	2.0%	0	0.0%
Myalgia M791x	10	3.2%	4	8.2%	1	12.5%
Joint Pain M255x	37	11.8%	7	14.3%	1	12.5%
Members in both groups (with pain and OUD)	65	20.7%	17	34.7%	5	62.5%

Members in neither group (no common pain or OUD diagnosis)	25	8.0%	5	10.2%	0	0.0%

Table 4. Doses for members with paid buprenorphine claims.

Average Daily Dose	<= 24mg daily		24.1-32 mg daily		>32 mg daily	
	314	**%**	**49**	**%**	**8**	**%**
Average daily dose over the last 7 days covered by buprenorphine						
≤ 24 mg daily	312	99.4%	42	85.7%	4	50.0%
24.1-32 mg daily	0	0.0%	7	14.3%	1	12.5%
> 32 mg daily	2	0.6%	0	0.0%	3	37.5%
Members who were included in population #2 (with denied claims for higher dose)	3	1.0%	2	4.1%	3	37.5%

Evaluation Denied Claims for Sublingual Buprenorphine Formulations

A second analysis evaluated diagnoses in members with denied claims for sublingual buprenorphine or buprenorphine/naloxone combinations. Over the course of a 1-year period from 10/1/21 to 9/30/22, 64 FFS members had denied claims for greater than 24 mg daily of buprenorphine or buprenorphine naloxone. About one-third of these members (n=21) had complete claims data and were included in this analysis (**Table 5**). The small number of members included in this analysis makes any conclusions from this analysis highly uncertain, and inclusion of a larger group of members may change these results.

Members included in this analysis were adults with an average age of about 35 years. Most identified as white or Native American/Alaskan Native (**Table 6**). Overall, diagnoses present in medical claims were similar to members who had paid claims for sublingual buprenorphine. About 76% of members (n=17) with a denied claim for 24-32 mg daily had a diagnosis of OUD present in their medical claims 6 months before the IE (**Table 7**). Of the 4 members with claims more than 32 mg daily, all had a diagnosis of OUD. Common comorbid pain diagnoses were present for almost half of members who had a denied buprenorphine claim with a dose greater than 24 mg daily.

Table 5. Included population with denied claims for sublingual buprenorphine.

	Total	
Number of included members	#	%
Denied FFS claim for sublingual buprenorphine from 10/1/2021 to 9/30/2022	**64**	
After exclusion of members with paid claim for sublingual buprenorphine on the same day	31	48.4%
After exclusion of Medicare, TPL, and limited drug eligibility groups	27	42.2%
After exclusion of non-continuous Medicaid enrollment in 6-month baseline period	**21**	32.8%

Table 6. Demographics for members with denied claims.

Average Daily Dose	24-32 mg		>32 mg	
	17	%	4	%
Female	8	47.1%	1	25.0%
Age – mean (range)	35	(26-45)	36	(28-45)
<18	0	0.0%	0	0.0%
18-35	10	58.8%	2	50.0%
36-64	7	41.2%	2	50.0%
>=65	0	0.0%	0	0.0%
Race				
White	5	29.4%	1	25.0%
American Indian/Alaskan Native (HNA)	9	52.9%	3	75.0%
Other	0	0.0%	0	0.0%
Unknown	3	17.6%	0	0.0%
*Average Elixhauser Score "M"	12		-	
*Average Elixhauser Score "R"	24		17	
New Start (no paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	9	52.9%	1	25.0%
Continuation (paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	8	47.1%	3	75.0%

*Amongst members who had a score

Table 7. OUD diagnoses in the baseline period for members with denied claims.

Average Daily Dose	24-32 mg		>32 mg	
	17	%	4	%
OUD Diagnosis in the baseline period				
Present	13	76.5%	4	100.0%
Absent	4	23.5%	0	0.0%

Common chronic pain diagnosis in the baseline period	8	47.1%	1	25.0%
Chronic pain G892x, G894	2	11.8%	0	0.0%
Dorsalgia M54x	4	23.5%	1	25.0%
Fibromyalgia M797	0	0.0%	0	0.0%
Myalgia M791x	2	11.8%	0	0.0%
Joint Pain M255x	5	29.4%	0	0.0%
Members in both groups (with pain and OUD)	8	47.1%	1	25.0%
Members in neither group (no common pain or OUD diagnosis)	4	23.5%	0	0.0%

Limitations:

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

- Diagnostic data is based on claims history which may be incomplete or not accurately reflect true patient diagnoses. Social stigma associated with OUD diagnoses (from patients or providers) may result in incomplete or missing diagnoses billed on medical claims. Diagnostic data was evaluated only over a 6-month period, and diagnoses for patients on stable maintenance therapy may be missed if they had infrequent provider visits. Pain diagnoses identified in medical claims only included common diagnoses and do not represent a comprehensive list of pain conditions.
- This analysis does not evaluate use of buprenorphine when administered in a clinical setting. Buprenorphine may be billed using a variety of mechanisms (both pharmacy and medical), but only pharmacy claims were included in this analysis.
- A significant proportion of members identified with paid FFS claims for sublingual buprenorphine were ineligible for inclusion in the study due to the inclusion and exclusion criteria (78%). Most members identified with a sublingual buprenorphine claim were ineligible because they did not remain in FFS for the 90 days following their first prescription for buprenorphine (many members transition into a CCO). This study assumes that included members are still representative of the entire Medicaid population. A post-hoc analysis was conducted which eliminated the 90-day follow-up requirement. Dose for members following their first claim for buprenorphine was calculated based on the average daily dose until CCO enrollment, lost eligibility, or 90 days, whichever was less. This resulted in inclusion of a larger number of members in this study, but shorter follow-up period for many of them. This post-hoc analysis demonstrated similar trends in doses prescribed for included members.
- Because doses for buprenorphine can be titrated based on symptoms and because members can get multiple prescriptions for the similar medications, this analysis used the average daily dose over a 90-day period as a method to determine total daily dose for included members. However, for members whose dose changes over time, this may not be an accurate marker of how many members would be impacted by the 24 mg daily quantity limit.
- Additionally, this analysis relies on claims paid by Medicaid to evaluate doses which may not be an accurate indicator of what dose the member actually takes. This analysis does not include claims for which the member paid cash, and we are unable to quantify actual adherence or any potential diversion.
- Public health data indicates that prevalence of fentanyl use is increasing in Oregon. Fentanyl is a more potent opioid heroin and may lead to more severe withdrawal symptoms upon discontinuation. Some providers may prescribe higher doses of buprenorphine to manage cravings in opioid use disorder for members who are dependent on fentanyl and when symptoms are inadequately controlled with lower doses. For members included in this analysis, we are unable to quantify the type of opioid dependence or the proportion of Medicaid members who are dependent on fentanyl. If illicit fentanyl continues to become more prevalent, then Medicaid members may need higher doses of buprenorphine to adequately manage symptoms of opioid use disorder.

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Appendix 1: Drug Coding

Table A1. Error codes for denied claims

Error Status Code	Error Status Description	Inclusion or exclusion in analysis
4167	DRUG QUANTITY PER DAY LIMIT EXCEEDED	**Include**
2017	RECIPIENT SERVICES COVERED BY HMO PLAN	Exclude
4999	THIS DRUG IS COVERED BY MEDICARE PART D	Exclude
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE	Exclude
4002	Non-Covered Drug	Exclude
513	RECIPIENT NAME AND NUMBER DISAGREE	Exclude
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)	Exclude
238	RECIPIENT NAME IS MISSING	Exclude
2809	DOB IS INVALID	Exclude
628	Other Coverage Reject Code Required for OCC 3	Exclude
643	INVALID OTHER COVERAGE CODE	Exclude
503	DATE DISPENSED AFTER BILLING DATE	Exclude
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER	Exclude
221	DAYS SUPPLY MISSING	Exclude
576	CLAIM HAS THIRD-PARTY PAYMENT	Exclude
205	PRESCRIBING PROVIDER ID MISSING	Exclude
268	BILLED AMOUNT MISSING	Exclude
270	HEADER TOTAL BILLED AMOUNT INVALID	Exclude

Table A2. Buprenorphine doses

Generic Name	GSN	Form	Dose	Buprenorphine Strength
buprenorphine HCl	029312	TAB SUBL	2 mg	2
buprenorphine HCl	029313	TAB SUBL	8 mg	8
buprenorphine HCl/naloxone HCl	051640	TAB SUBL	2 mg-0.5 mg	2
buprenorphine HCl/naloxone HCl	051641	TAB SUBL	8 mg-2 mg	8
buprenorphine HCl/naloxone HCl	066635	FILM	2 mg-0.5 mg	2
buprenorphine HCl/naloxone HCl	066636	FILM	8 mg-2 mg	8
buprenorphine HCl/naloxone HCl	070259	FILM	4 mg-1 mg	4
buprenorphine HCl/naloxone HCl	070262	FILM	12 mg-3 mg	12
buprenorphine HCl/naloxone HCl	071189	TAB SUBL	1.4 mg-0.36 mg	1.4
buprenorphine HCl/naloxone HCl	071190	TAB SUBL	5.7 mg-1.4 mg	5.7
buprenorphine HCl/naloxone HCl	073424	TAB SUBL	8.6 mg-2.1 mg	8.6
buprenorphine HCl/naloxone HCl	073425	TAB SUBL	11.4 mg-2.9 mg	11.4
buprenorphine HCl/naloxone HCl	074685	TAB SUBL	2.9 mg-0.71 mg	2.9

buprenorphine HCl/naloxone HCl	076981	TAB SUBL	0.7 mg-0.18 mg	0.7

Table A3. PICOS for analysis of Paid claims

Population	Medicaid members with a paid FFS claim sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window. AND continuous FFS eligibility in the follow-up period AND continuous Medicaid enrollment in the baseline period
Intervention	Group 1: Members with an average daily dose =<24mg for the days covered by their prescription in the follow-up period
Comparators	Group 2: Members with an average daily dose of 25-32 mg for the days covered by their prescriptions in the follow-up period Group 3: Members with an average daily dose >32mg daily for the days covered by their prescriptions in the follow-up period
Outcomes	1. Proportion of Members with a diagnosis of OUD in the baseline period (ICD-10 F11x) 2. Proportion of Members with a max daily dose of buprenorphine >=24 mg for the last 7 days covered by buprenorphine 3. Proportion of Members who were also included in population #2 (Members with denied claims)
Timing	Evaluation window for sublingual buprenorphine claims: 10/1/21 to 09/30/22. The first claim in the evaluation window is the index event (IE). Baseline period: 6 months before the IE Follow-up period: 90 days after the IE

Table A4. PICOS for analysis of Denied claims

Population 2	Medicaid members with a denied FFS claim for sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window. Denied claims were included based on error codes for the 24 mg QL (error#: 4167) and excluded claims with error codes related to billing errors (see **Appendix 1; Table A1**). The first claim in the evaluation window is the index event (IE). AND continuous Medicaid enrollment in the baseline period AND no paid claim for sublingual buprenorphine on the same date of service
Intervention	Group 1: Daily dose 24-32 mg for the IE
Comparators	Group 2: Daily dose >32mg for the IE
Outcomes	OUD diagnosis in the baseline period (ICD-10 F11x) Common chronic pain diagnoses in the baseline period (see list of ICD codes)
Timing	Evaluation window for sublingual buprenorphine claims: 10/1/21 to 09/30/22 Baseline period: 6 months before the IE

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Prevent use of high-dose transmucosal buprenorphine products for off-label indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Transmucosal buprenorphine products that exceed an average daily dose of ~~24~~ 32 mg per day

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. Is the diagnosis funded by the OHP?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than ~~24~~ 32 mg (e.g., >~~24~~ 32 mg/day or >~~48~~ 64 mg every other day)?	**Yes:** ~~Pass to RPh. Deny; medical appropriateness~~Go to #4	**No:** Go to #~~4~~8
4. Is there documentation of inadequate symptom improvement with 32 mg daily?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there recent documentation (within past month) from a urine drug screen indicating that buprenorphine is being taken?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Has the prescriber evaluated the PDMP in the past 3 months?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Does the member have access to naloxone?	**Yes:** Approve for 30 days. Subsequent requests for continuation of therapy will require documentation of objective clinical benefit with higher doses (e.g. improved management of OUD), documentation of a comprehensive treatment plan for OUD, and ongoing monitoring plan for safety risks.	**No:** Pass to RPh. Deny; medical appropriateness
~~4.~~8. Is the requested medication a preferred agent?	**Yes:** Approve for ~~anticipated length of treatment or~~ 6 months~~, whichever is less~~. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #9
~~5.~~9. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for ~~anticipated length of treatment or~~ 6 months~~, whichever is less~~. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: *8/23 (SS); 2/23 (DM); 12/22; 12/20;11/19; 1/19; 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *TBD; 1/1/2020; 3/1/2019; 4/1/2017; 9/1/13; 1/1/10*

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

New Drug Evaluation: Trofinetide 200 mg/mL, oral solution

Date of Review: August 2023
Generic Name: Trofinetide

End Date of Literature Search: 05/05/2023
Brand Name (Manufacturer): DAYBUE (Acadia Pharmaceuticals, Inc.)
Dossier Received: yes

Plain Language Summary:

- Trofinetide is the first medicine that the United States Food and Drug Administration has approved to treat Rett syndrome in patients aged 2 years and older.
- Rett syndrome is a rare, inherited disorder that affects the way the brain develops. It is most common in females and rarely affects males.
- Most babies with Rett syndrome lose skills, such as the ability to crawl, walk, communicate, or use their hands between 6 and 30 months of age. Rett syndrome affects nearly every aspect of life including the ability to speak, walk and eat. Most people with Rett syndrome:
    - are dependent on a caregiver to complete activities of daily living,
    - have limited mobility resulting in the use of a wheelchair, and
    - have a reduced life expectancy of around 40 to 50 years of age.
- A 12-week study showed trofinetide improved Rett syndrome symptoms by a modest amount compared with placebo. More data is needed to understand the long-term safety and effectiveness of trofinetide.
- The most common side effect of trofinetide is mild to moderate diarrhea, which was reported in 81% of people treated with trofenitide compared with 19% of patients who received placebo in the largest clinical trial.
- For people enrolled in the Oregon Health Plan, providers must explain to the Oregon Health Authority why someone needs trofinetide before Medicaid will pay for it. This process is called prior authorization. We recommend continuing this policy.

Research Questions:

1. What is the evidence for the efficacy of trofinetide for treatment of Rett syndrome?
2. What are the harms associated with the use of trofinetide?
3. Are there specific populations or communities, based on demographic characteristics, who would be more likely to benefit or be harmed from the use of trofinetide?

Conclusions:

- Trofinetide (DAYBUE) is indicated for the treatment of Rett syndrome in adults and pediatric patients aged 2 years and older.[1] The mechanism of trofinetide in treating Rett syndrome is not clear.[2]

Author: Deanna Moretz, PharmD, BCPS

- The efficacy and safety of trofinetide were evaluated in the LAVENDER trial, a double-blind, placebo-controlled, phase 3, randomized clinical trial (RCT) of 187 female patients aged 5 to 20 years with genetically confirmed Rett syndrome.[3] Patients were randomized 1:1 to receive trofinetide 200 mg/kg or matching placebo twice daily for 12 weeks.[3] The co-primary efficacy measures were changes from baseline in the caregiver-reported 90-point Rett Syndrome Behavior Questionnaire (RSBQ) score and the clinician-administered 7-point Clinical Global Impression-Improvement (CGI-I) score at week 12.[3] For the RSBQ score, the least squares mean (LSM) change from baseline to week 12 was −4.9 for trofinetide versus −1.7 for placebo (difference: −3.2; 95% confidence interval [CI] −5.7 to −0.6; P=0.018; low-quality evidence).[2,3] The mean CGI-I score at Week 12 was 3.5 for trofinetide versus 3.8 for placebo (difference: −0.3; 95% CI −0.5 to −0.1; P=0.003; low-quality evidence).[2,3] Efficacy results from a dose-finding phase 2 RCT were considered confirmatory evidence by the FDA to support results from the phase 3 RCT.[4] There is insufficient efficacy data of trofinetide beyond 12 weeks.
- To assess safety in patients 2 to 4 years of age, an open-label pharmacokinetic (PK) bridging study was conducted in 13 children with Rett syndrome.[2] The effectiveness of trofinetide in patients in this age group was hypothesized through extrapolation of the results observed in the LAVENDER study population, based on the similarity of the disease pathophysiology as well as the assumption of similar exposure response relationship between patients aged 2 to 4 years and patients 5 years of age and older.[2]
- The most common adverse effect leading to discontinuation of trofinetide treatment in clinical trials was diarrhea.[1] In the LAVENDER trial, 81% of trofinetide-treated patients reported mild to moderate diarrhea compared with 19% of placebo treated patients.[3] In an open-label, extension trial, diarrhea occurred in 84% of subjects on long-term (greater than 1 year) treatment with trofinetide.[2] Approximately 40% of patients withdrew from both the placebo and active compartor arms due to this adverse event.[2] Of those who did not withdraw from treatment, 50% required concomitant therapy with loperamide to treat the diarrhea.[2] In addition, weight loss greater than 7% from baseline was observed in 12% of patients treated with trofinetide compared with 4% of patients treated with placebo.[1] There is insufficient data for the long-term safety of trofinetide in people with Rett syndrome beyond 1 year.
- According to the FDA reviewers, limitations of the trofinetide evidence include:
    - reliance on one single adequate and controlled study with confirmatory evidence,
    - the limitations of the RSBQ as a tool to measure functional improvement in Rett syndrome,
    - the disproportionate study withdrawal rate (23 trofinetide-treated patients versus 9 placebo-treated patients), and
    - the disproportionate and rapid onset of diarrhea in the trofinetide arm along with the disproportionate use of loperamide in the trofinetide arm, with a risk for functional unblinding (**Table 4**).[4]
- The wholesale acquisition cost of trofinetide is $9,495 for a 450 ml bottle. A patient weighing 50 kg or more would require 60 ml twice daily; or 8 bottles per month which would cost approximately $76,000.
- No specific populations were identified that would be more likely to benefit or be harmed from the use trofinetide. All patients enrolled in the phase 3 RCT had genetically confirmed Rett syndrome and were 5 to 20 years of age.[2] The efficacy of trofinetide in patients that do not have genetically confirmed Rett syndrome and are older than 20 years of age is unknown. The effects of trofinetide in pregnancy and lactation were not evaluated in clinical trials, as pregnant individuals were excluded from study enrollment.[1] Although trofinetide is primarily renally eliminated, no clinical study was conducted to evaluated pharmacokinetic (PK) parameters in renal impairment. Administration of trofinetide to patients with moderate or severe renal impairment is not recommended.[1]

Recommendations:

- Maintain trofinetide as non-preferred on the PMPDP.
- Implement clinical prior authorization (PA) criteria for trofinetide to ensure medically appropriate use.

Background:
Rett syndrome is a rare, progressive, neurodevelopmental disorder which affects approximately 1 in 15,000 live female births worldwide and is even rarer in boys.[2,5] Rett syndrome occurs in all ethnic and racial groups, and at similar rates.[6] This condition is often caused by spontaneous mutations in the methyl-CPG-binding protein 2 (MECP2) gene on the X chromosome.[5,7] Although MECP2 is expressed in all tissues, it is most abundant in the brain, which may be more sensitive to abnormal MECP2 protein than other tissues.[8] Methyl-CPG-binding protein 2 is known to play a role in chromatin organization and transcriptional regulation and is essential for normal brain function.[9] These mutations are almost exclusively inherited from the paternally derived X chromosome, which may explain the high female to male ratio.[10] Most individuals with Rett syndrome have random X-inactivation so that the normal MECP2 allele is expressed in some cells.[8] The normal allele appears to enable affected females to survive but does not protect them from neurodevelopmental abnormalities.[8] Similar pathogenic variants in brothers of affected females most often result in severe neonatal encephalopathy and are lethal to the boys, because all their cells express mutated MECP2 protein.[8] Random inactivation also contributes to the spectrum of phenotypes in Rett syndrome.[8] There are more than 250 known pathogenic variants in MECP2 associated with Rett syndrome.[11] The severity of the Rett syndrome depends on the location and type of mutation on the MECP2 gene.[2] Eight of the most frequently identified mutations account for more than 60% of typical Rett syndrome cases.[12] There is a broad range of clinical and genotypic heterogeneity in Rett syndrome, which has posed a challenge to the study of the condition.[13]

The onset of Rett syndrome occurs most commonly between 6 and 18 months of age, first with a plateau in development and then regression of motor and communication skills.[11] Patients with Rett syndrome develop progressive loss of purposeful hand skills, speech and language regression, gait abnormalities, and development of stereotypical hand movements. (i.e., hand wringing, clapping, tapping, washing, rubbing).[13] Abnormal head growth deceleration, markedly altered height and weight, and epilepsy occur in most patients.[11] Between one and 4 years of age, patients lose the ability to perform skills they previously had mastered.[2] The average age of diagnosis is 2.5 years, but has been trending downwards due to increasing availability of genetic testing.[14] After initial regression, the condition stabilizes and patients usually survive into adulthood.[8] Life expectancy is reduced to approximately 40 to 50 years of age.[2] In the Oregon Health Plan, claims data from 2022 indicated that approximately 114 people have Rett syndrome; 76 people are enrolled in a Coordinated Care Organization, and 31 are enrolled in Fee-for-Service.

The diagnosis of Rett syndrome is based upon clinical and genetic characteristics. Rett syndrome is suspected in individuals who have apparently normal development in the first 6 to 18 months of life followed by regression of purposeful hand skills and spoken language along with the onset of gait abnormalities and stereotypic hand movements.[5] **Table 1** summarizes diagnostic criteria for the 2 types of Rett syndrome: typical (classic) and atypical (variant) Rett syndrome. Postnatal deceleration of head growth also raises suspicion for Rett syndrome, although it does not occur in all individuals with typical Rett syndrome.[5] Rett syndrome accounts for 10% of cases of profound intellectual disability of genetic origin in females.[4] In typical Rett syndrome, 90% of reported cases have the MECP2 mutation, which is a spontaneous mutation in almost all cases.[5] Atypical Rett syndrome may be suspected in individuals who have many but not all of the clinical features of typical Rett syndrome.[4] Atypical Rett syndrome cases generally have a limited phenotype, and only about 75% of patients with Rett syndrome are found to have MECP2 genetic mutations.[4]

Table 1. Required Criteria for Diagnosis of Rett Syndrome[5]

Required Criteria for Typical Rett Syndrome	Required Criteria for Atypical Rett Syndrome
1. A period of regression followed by recovery or stabilization. 2. All main criteria and all exclusion criteria.	1. A period of regression followed by recovery or stabilization. 2. At least 2 out of the 4 main criteria and 5 out of 11 supportive criteria.

3. Supportive criteria are not required, although often present in typical Rett syndrome.	
Main Criteria	
• Partial or complete loss of acquired purposeful hand skills • Partial or complete loss of acquired spoken language • Gait abnormalities: impaired or absence of ability • Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms	
Supportive Criteria	
• Breathing disturbances when awake • Bruxism when awake • Impaired sleep pattern • Abnormal muscle tone • Peripheral vasomotor disturbances • Scoliosis/kyphosis • Growth retardation • Small cold hands and feet • Inappropriate laughing/screaming spells • Diminished response to pain • Intense eye communication	
Exclusion Criteria	
• Brain injury secondary to trauma (peri- or post-natal), neurometabolic disease, or severe infection that causes neurological problems. • Grossly abnormal psychomotor development in first 6 months of life.	

Rett syndrome is divided into 4 progressive stages.[15] Patients initially display seemingly normal early development. Between 6 and 18 months of age, patients experience a period of developmental stagnation (Stage I) and no longer meet their mental, cognitive or motor milestones.[15] Head circumference growth slows and this period lasts for weeks to months.[15] Stage II is defined by rapid developmental regression around the age of 1 to 4 years, in which acquired purposeful hand movements and verbal skills are lost.[15] Microcephaly worsens and breathing irregularities and seizures may arise.[15] Stage III is a pseudo-stationary plateau period in which patients may show mild recovery in cognitive interests, but purposeful hand and body movements remain severely diminished.[15] Stage IV is defined by motor deterioration, dystonia, bradykinesia, and scoliosis, and may last for decades.[15] Many patients are wheelchair and/or gastrostomy-tube dependent.[15] However, not all patients progress to this severe stage.[15]

Treatment options for Rett syndrome are currently limited to supportive care, symptom relief, and managing complications such as epilepsy, dysphagia, scoliosis, spasticity, and constipation.[15] Managing the various symptoms over the lifetime of an individual with Rett syndrome is challenging and often requires the collaboration of numerous providers.[15] Trofinetide is the first FDA-approved treatment for Rett syndrome. As of January 2021, there are 18 Rett syndrome clinics across the United States that are available to consult and/or manage the individual with Rett syndrome.[15] None of the clinics are based in Oregon, the 2

clinics closest to Oregon are located in Oakland, California and Aurora, Colorado.[16] The medical teams that are part of a Rett Syndrome Consortium have prepared a guideline, to help with the evolving management of a person with Rett syndrome across their lifespan.[14]

Three instruments were used to assess trofinetide efficacy in clinical trials. The RSBQ was developed as a diagnostic tool to clinically differentiate people with Rett syndrome from those with other severe intellectual disabilities.[17] The RSBQ is a 45-item rating scale completed by the caregiver and assesses a range of 8 individually assessed symptoms of Rett syndrome (general mood, breathing problems, hand behavior, face movements, body rocking/expressionless face, night-time behaviors, fear/anxiety, and walking/standing).[18] As the questions in the RSBQ include questions regarding the signs of Rett syndrome and not just the symptoms, the RSBQ may detect changes in some of its components that may not clearly be clinically meaningful.[2] Each item is scored as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true), with a maximum possible score of 90 points.[2] Lower RSBQ scores reflect less severity in signs and symptoms of Rett syndrome.[2] A decrease in total score over time may indicate improvement in neurobehavioral features assessed by the questionnaire.[2] A minimal clinically important difference (MCID) has not been determined nor validated for this tool. Although it was not designed to measure symptom improvement in a clinical trial and has not been validated for this purpose, in the absence of any other Rett syndrome-specific instruments, the RSBQ has been used as an outcome measure in clinical trials.[17]

Three ordinal Clinical Global Impression (CGI) scales (Severity, Improvement, and Efficacy) have been used as an outcome measures in psychopharmacology (depression, social anxiety disorder, panic disorder, schizophrenia, and bi-polar disorder) clinical trials.[17,19,20] The CGI scales were designed to provide a basis, independent of ratings on a questionnaire, for the study clinician to make a global assessment of a study patient's condition before and after the initiation of a study medication.[19] This provides a means of determining whether in the view of an experienced clinician the condition under study had improved, worsened, or stayed the same.[19] The CGI-Improvement (CGI-I) score is rated by clinicians to assess whether a patient has improved or worsened relative to baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) in which a 1 point decrease in score from baseline indicates improvement.[20] A CGI-I score of 2 (much improved) is appropriate for definite, unequivocal improvement of a magnitude that makes the clinician confident that the treatment is helping.[19] A score of 3 or 5 (minimally improved or minimally worse) is appropriate if variations in ratings and other criteria appear to represent more than random chance or rating error, but are not definite and unequivocal.[19] A score of 4 (no change) is appropriate for slight variation in either direction of a magnitude that is likely due to chance, natural history, external events, or rating error.[19] Higher scores signify greater severity and/or worse outcomes.[20] The CGI-I scale was recently adapted to assess changes in patients with Rett syndrome.[21] The use of the CGI-I scale in Rett syndrome requires familiarity with the condition that limits its use to major clinical centers and may be difficult to translate into wider use.[17]

The Communication and Symbolic Behavior Scales Developmental Profile-Infant-Toddler Social Composite Score (CSBS-DP-IT-SCS) was used as a secondary outcome in the trofinetide phase 3 RCT. The CSBS-DP-IT-SCS is a 24-item caregiver screening assessment of pre-verbal healthy infants and toddlers aged 6 through 24 months.[22] The instrument was designed to screen healthy children for potential communication deficits.[2] The scale asks parent impressions regarding infant development in 7 domains: emotion and eye gaze, communication, gestures, sounds, words, understanding, and object use.[4] Each item is scored using a three-level rating of frequency: “not yet”, “sometimes”, and “often.”[4] The tool is intended to be a screener in healthy children and was not designed to detect improvement or worsening in communication in the setting of a clinical trial.[4] There is concern that parents may not always be able to objectively assess a neurologically impaired child’s non-verbal cues.[4]

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

Clinical Efficacy:
Trofinetide is indicated for the treatment of Rett syndrome in adults and pediatric patients aged 2 years and older.[1] Trofinetide is supplied as a 200 mg/mL oral solution administered twice daily as a weight-based dose either orally or via gastrostomy tube.[2] The wholesale acquisition cost (WAC) of trofinetide is $9,495 for a 450 ml bottle. A patient weighing 50 kg or more would require 60 ml twice daily, or 8 bottles per month which would cost approximately $76,000. Trofinetide oral solution received FDA approval in March 2023 with fast tracked, priority review under orphan drug and rare pediatric disease designations.[4] Trofinetide is a synthetic analog of the N-terminal tripeptide of insulin like growth factor 1, glycine-proline-glutamate.[4] Based on data from mouse models, it is hypothesized that trofinetide may decrease neuroinflammation potentially leading to normalized synaptic function.[2]

An exploratory dose-ranging phase 2 study was conducted in females aged 5 to 15 years diagnosed with genetically confirmed typical Rett syndrome (**Table 4**).[23] The study had a two-week placebo run-in after which time baseline assessments for the randomized phase were assessed.[23] Patients were given the following trofinetide doses (50mg/kg, 100 mg/kg, and 200 mg/kg) twice daily for 40 days after being up-titrated to their respective dose.[23] The primary outcome was an assessment of adverse effects and serious adverse effects (n=62).[23] Only one participant (200 mg/kg group) was withdrawn from the study because of increased gastroesophageal reflux, moderate diarrhea, and mild vomiting, which resolved uneventfully after discontinuation.[23] Four serious adverse effects occurred in 3 participants: 1 participant receiving placebo, 1 participant receiving 100 mg/kg, and 1 participant receiving 200 mg/kg.[23] Following a review of safety data, an additional 20 patients were randomized 1:1 to placebo or the 200 mg/kg dosing regimen for a total enrollment of 82 patients in the modified intention to treat (mITT) population.[23] The purpose of enriching these groups was to maximize detection of clinical benefit.[23] Secondary outcomes include evidence of efficacy as measured by the RSBQ and CGI-I. Only the 200 mg/kg twice daily dosing regimen showed improvement compared placebo.[23] For change from baseline on day 14 to day 54 in RSBQ total score, trofinetide 200 mg/kg showed evidence of efficacy with 4.4-point difference ($p = 0.042$) compared to placebo.[23] The CGI-I score at day 54 showed a -0.5 unit difference from placebo ($p = 0.029$) favoring 200 mg/kg of trofinetide.[23] These results were considered confirmatory evidence by the FDA to support results from the phase 3 RCT.[4]

The efficacy and safety of trofinetide were evaluated in single double-blind, placebo-controlled, phase 3, RCT (LAVENDER) of 187 female patients aged 5 to 20 years with genetically confirmed typical Rett syndrome.[3] Patients were randomized 1:1 to receive trofinetide 200 mg/kg oral solution (n=93) or matching placebo oral solution (n=94) twice daily for 12 weeks.[3] In the respective trofinetide and placebo groups, 41% and 42% of patients recived the study medication via gastrostomy tube.[3] The dose of trofinetide was based on patient weight to achieve similar exposure in all patients.[3] Patients were stratified into 3 age groups (5 to 10 years, 11 to 15 years, 16 to 20 years) and by baseline RSBQ score (<35 or ≥ 35).[4] The results of this RCT were not published until May 2023, therefore, the trofinetide FDA summary and review were the primary sources for study details prior to publication.[2,4] The mean age of enrolled participants in this trial was 11 years.[2] Most of the patients were White (92%), 6% were Asian, and 2% were Black.[2] Patients with celiac disease, irritable bowel syndrome, and diabetes were excluded from trial enrollment.

The co-primary efficacy measures were changes from baseline in the caregiver administered RSBQ total score and the CGI-I score at week 12.[3] Scores on the RSBQ can range from 0 to 90 with higher scores indicating higher severity of the signs and symptoms of Rett syndrome.[2] The manufacturer proposed the RSBQ as the primary endpoint for the LAVENDER trial, but the FDA did not agree, as it is not clear that small changes on this scale are clinically meaningful.[2] The FDA also noted that many of the items in the scale reflected signs of the disease and not necessarily directly reflect how patients feel or function.[2] Based on FDA recommendations, the CGI-I score was added as a co-primary endpoint to support a statistically significant change in the RSBQ as clinically meaningful.[2] The CGI-I is a 7-point scale rated by clinicians to assess how much a patient's illness has improved or worsened.[21] In general, a one-point change will signify improvement or worsening of the symptoms. For the RSBQ score, the LSM change from baseline to week 12 was −4.9 for trofinetide versus −1.7 for placebo (difference: −3.1; 95% CI −5.7 to −0.6; P=0.0175; low-quality evidence).[2] Although the study was not designed or powered to show a statistically significant difference from

placebo on each RSBQ subscale, change from baseline was directionally in favor of trofinetide.[4] The mean CGI-I score at Week 12 was 3.5 for trofinetide versus 3.8 for placebo (difference: −0.3; 95% CI −0.5 to −0.1; P=0.003; low-quality evidence).[2] According to the FDA, the modest finding of a benefit on these endpoints supports the effectiveness of trofinetide in symptom improvement over 12 weeks in people with Rett syndrome.[4]

A secondary endpoint was the effect of trofinetide on the individual's ability to communicate as assessed by the caregiver using the Communication and Symbolic Behavior Scales Developmental Profile-Infant-Toddler Social Composite Score (CSBS-DP-IT-SCS).[2] On the CSBS-DP-IT score the LSM change was −0.1 for trofinetide and −1.1 for placebo from baseline to Week 12 (difference: 1.0; 95% CI 0.3 to 1.7; p=0.0064).[2] This data seems to indicate that placebo-treated patients worsened in their ability to communicate while trofinetide-treated patients maintained their ability to communicate as assessed by the CSBS-DP-IT-SCS.[4] According to the FDA reviewers, insufficient evidence was provided to justify the administration, scoring, and interpretation of the CSBS-DP-IT-SCS for people with Rett syndrome, as this tool has not been validated for use in this population.[2]

Of the randomized patients, 23 (25%) in the trofinetide arm discontinued the study early compared with 9 patients (10%) in the placebo arm who prematurely withdrew from the study.[3] The majority of trofinetide patients (70%) discontinued the study due to an adverse event (diarrhea or vomiting); while the majority fo placebo-treated patients (56%) withdrew due to COVID-19 quarantine measures.[3] Thirty-eight patients (41%) in the trofinetide arm used loperamide during the study compared with 1 patient (1%) in the placebo arm.[4] Twelve percent of trofinetide-treated subjects (compared to 4% of placebo-treated subjects) experienced a loss of greater than 7% of body weight.[2] This is clinically significant as this is a primarily pediatric population who would be expected to gain weight over time rather than lose a significant amount of weight in a short period of time.[2]

The effectiveness of trofinetide in patients 2 to 4 years of age was hypothesized through extrapolation of the results observed in the LAVENDER study population, based on the similarity of the disease pathophysiology as well as the assumption of similar exposure response relationship between patients aged 2 to 4 and patients 5 years of age and older.[2] An open-label PK study was conducted in 2 treatment periods; 12 weeks to evaluate the drug PK characteristics and 21 months to evaluate long-term safety. Thirteen patients with Rett syndrome between 2 and 4 years of age completed 12 weeks of treatment.[2] The PK analysis demonstrated similar PK exposure of trofinetide and similar safety profiles in the younger pediatric population compared with pediatric patients 5 years of age and older.[2]

Specific details for the Phase 2 and Phase 3 clinical trial (LAVENDER), which contribute to the safety and efficacy data for the use of trofinetide in people with Rett syndrome are described and evaluated below in **Table 4.**

Study Limitations:
According to the FDA reviewers, limitations of the trofinetide evidence are the: 1) reliance on one single adequate and well controlled study with confirmatory evidence, 2) the limitations of the RSBQ as a tool to measure functional improvement, 3) the disproportionate study withdrawal rate (23 trofinetide-treated patients versus 9 placebo-treated patients), and 4) the disproportionate and rapid onset of diarrhea in the trofinetide arm along with the disproportionate use of loperamide in the trofinetide arm, with a risk for functional unblinding (see **Table 4**).[4] There was little racial or ethnic diversity among the enrolled subjects (92% of patients were White and 91% were not Hispanic or Latino).[4] Patients younger than 5 years of age were not enrolled, despite the mean age of symptom onset between 6 and 30 months and diagnosis around 3 years of age. There is insufficient evidence to support the use of the CSBS-DP-IT as an assessment tool in patients with Rett syndrome.[2] This tool is intended to be a screener for healthy children and was not designed to detect improvement or worsening in communication in the setting of a clinical trial.[2] In addition, 12 weeks is relatively short time period to assess functional improvement in a life-long, progressive disease.

A 40-week, open-label extension of LAVENDER (LILAC-1) was conducted to evaluate long term safety and tolerability of trofinetide in 154 patients.[4] Results are not yet published. Information about this trial was obtained from the FDA review of trofinetide.[2] Another open-label extension of LILAC-1 (LILAC-2) is currently ongoing to evaluate long-term safety in 47 patients.[4] Finally, a phase 2/3 RCT (DAFFODIL) is being conducted in 13 patients aged 2 to 4 years of age with Rett syndrome to evaluate safety, tolerability, and PK of trofinetide in this population.[4]

Clinical Safety:
Diarrhea was reported in 81% of trofinetide-treated patients compared with 19% of placebo-treated patients in the phase 3 LAVENDER trial.[3] In this trial vomiting was also reported more frequently in the trofinetide-treated patients compared with placebo-treated patients (27% vs. 10%, respectively).[3] Approximately 17% of trofinetide-treated patients withdrew from therapy due diarrhea or vomiting.[3] In the open-label extension trial, diarrhea occurred in 84% of subjects on long-term (greater than 1 year) treatment with trofinetide.[2] Of those who did not withdraw from treatment, 40% required concomitant therapy with loperamide to treat the diarrhea and prevent dehydration.[2] The manufacturer recommends if patients are taking a laxative prior to starting trofinetide, it should be discontinued before starting therapy.[1]

Weight loss is possible during trofinetide treatment.[1] Weight loss greater than 7% from baseline was observed in 12% of trofinetide-treated patients compared with 4% of placebo-treated patients.[1] This is clinically significant as this is a primarily pediatric population who would be expected to gain weight over time rather than lose a significant amount of weight in a short period of time.[2] Patient weight should be monitored and if significant weight loss occurs, the manufacturer recommends interrupting therapy, reducing trofinetide dose or discontinuing the drug.[1]

Rates of adverse effects observed with trofinetide compared with placebo are presented in **Table 2**.[4] Serious adverse events included 2 events of seizure that were possibly be related to trofinetide; one case of urosepsis from urinary tract infection that occurred in the setting of diarrhea was deemed possibly related by the investigator; and a number of infections and respiratory conditions that occur frequently in the Rett syndrome and cannot be clearly attributed to trofinetide.[4]

Table 2. Adverse Reactions in at least 5% of Patients Treated with Trofinetide Compared with Placebo in the Phase 3 RCT[1]

Adverse Reaction	Trofinetide (n=93)	Placebo (n=94)
Diarrhea	82%	20%
Vomiting	29%	12%
Fever	9%	4%
Seizure	9%	6%
Anxiety	8%	1%
Decreased Appetite	8%	2%
Fatigue	8%	1%
Nasopharyngitis	5%	1%

The effects of trofinetide in pregnancy and lactation were not evaluated in clinical trials, as pregnant individuals were excluded from study enrollment.[1] Although trofinetide is primarily renally eliminated, no clinical study was conducted to evaluated pharmacokinetic (PK) parameters in renal impairment. Administration of

trofinetide to patients with moderate or severe renal impairment is not recommended.[1] The FDA has stipulated to the manufacturer that trofinetide post-marketing trials are required to evaluate the effect of moderate renal impairment on trofinetide elimination and to evaluate potential drug interactions.[4]

Look-alike / Sound-alike Error Risk Potential: No results available

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved symptom scores
2) Improved ability to complete activities of daily living
3) Prolonged survival
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Co-Endpoints:
1) Improved symptom scores as assessed by the caregiver-administered RSBQ and provider-administered CGI-I scoring tools from baseline to 12 weeks.

Table 3. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Unknown
Oral Bioavailability	84% of dose was absorbed following oral administration of a 12-gram dose
Distribution and Protein Binding	Volume of distribution: 80 Liters in adults. Protein binding is low (< 6%).
Elimination	Primarily excreted unchanged (approximately 80% of dose) in the urine.
Half-Life	Half-life is 1.5 hours
Metabolism	Hepatic metabolism is not a not a significant route of trofinetide elimination.

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Glaze, DG, et al[23] DB, MC, PC Phase 2 RCT	1.Trofenetide 50 mg/kg orally twice daily 2.Trofenetide 100 mg/kg orally twice daily 3.Trofenetide 200 mg/kg orally twice daily 4.Volume matched placebo orally twice daily	Demographics: 1. Median age: 9.7 yo 2. Female: 100% 3. Mean weight: 26 kg 4. Mean baseline RSBQ score: 44 points 5. Race -White: 94% -Asian: 4% -Black: 1% -Other: 1% Key Inclusion Criteria: -Aged 5 to 15 yo -Female with genetically confirmed typical RS	ITT (safety): 1. 15 2. 16 3. 17 4. 14 mITT (efficacy): 1. 15 2. 16 3. 27 4. 24 Attrition (ITT): 1. 0	Primary Endpoint: Number of patients with SAEs at 11 weeks (ITT population) 1. 0 2. 1 3. 1 4. 1 Secondary Endpoints: Change from baseline on the RSBQ and CGI-I scores over 40 days (day 14 - baseline to day 54) in mITT population	NA	Diarrhea 1. 4 (27%) 2. 2 (13%) 3. 15 (56%) 4. 1 (4%) Vomiting 1. 1 (7%) 2. 2 (13%) 3. 6 (22%) 4. 3 (13%) (p value and 95% CI NR)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1:1 to trofinetide or placebo via IRTS for 54 days. After safety review, additional 20 patients randomized 1:1 to 200 mg/kg trofinetide or placebo. Stratified by age (≤ 10 yo and > 10 yo). Baseline characteristics were balanced between treatment groups. Performance Bias: Unclear. Placebo and trofinetide supplied in identical packaging and flavoring. Lack of consistency with titration/tapering dosing schedules may have led to variance in volumes of study drug being administered and may have led to unblinding. Adherence to treatment regimen was not assessed. Detection Bias: Unclear. Sponsor, participants, caregivers and clinicians all blinded to treatment assignment. Method of maintain blinding not described.

	*Two-week placebo run in for all patients, baseline assessments recorded on day 14	-Baseline weight 15 to 100 kg -Documented mutation in MeCP2 gene -Able to swallow medication or have it administered via gastrostomy tube <u>Key Exclusion Criteria</u>: -History of long QT syndrome -Unstable seizure profile -Significant gastrointestinal disease -Treatment with insulin or anticonvulsants with liver enzyme inducing effects	2. 0 3. 1 4. 0	a. LSM change in RSBQ Score at 40 days from baseline 1. -3.0 2. -1.5 3. -6.7 4. -2.3 1 vs. 4: NS 2 vs. 4: NS 3 vs 4: p= 0.042 (95% CI NR) b. LSM change in CGI-I score at 40 days from baseline in mITT population. 1. 3.3 2. 3.4 3. 3.0 4. 3.5 1 vs. 4: NS 2 vs. 4: NS 3 vs. 4: p=0.029 (95% CI NR)	NA NA			<u>Attrition Bias</u>: Low. One patient in the 200mg/kg ITT group withdrew due to GI effects. <u>Reporting Bias</u>: Low. Protocol available on line. <u>Other Bias:</u> High. Manufacturer funded the study and contributed to study design and report writing. **Applicability**: <u>Patient</u>: There was little racial or ethnic diversity among the enrolled subjects (94% of patients were White). Patients younger than 5 yo not enrolled, despite mean age of diagnosis at 2.5 yo. All patients had genetically confirmed RS. Cannot extrapolate results to patients with atypical RS. <u>Intervention</u>: Phase 2 dose finding trial to assess safety. <u>Comparator</u>: As no other FDA-approved treatments are available, placebo was an appropriate comparator. <u>Outcomes</u>: Primary outcome was safety assessment. Secondary outcomes: change in symptoms assessed from baseline to 12 weeks in RSBQ and CGI-I scales. MCID not determined for either scale. CGI-I was not designed for RS assessment. <u>Setting</u>: 12 clinical sites in the United States
2. Neul JL, et al.[3] FDA review[2,4] LAVENDER trial DB, PC, PG Phase 3 RCT	1. Trofinetide 200 mg/kg orally or via gastrostomy tube twice daily 2. Placebo 25 ml to 60 mL orally or via tube twice daily	<u>Demographics</u>: 1. Median age: 10.9 yo 2. Female: 100% 3. Mean weight: 30 kg 4. Mean baseline RSBQ score: 44 points 5. Race -White: 92% -Asian: 6% -Black: 2% <u>Key Inclusion Criteria</u>: -Aged 5 to 20 yo -Female with genetically confirmed typical RS -Baseline weight ≥ 12 kg -Documented mutation in MeCP2 gene -CGI-S score ≥ 4 points -Able to swallow medication or have it	<u>ITT:</u> 1. 93 2. 94 <u>Attrition</u>: 1. 23 (25%) 2. 9 (10%)	<u>Co-Primary Endpoints</u>: Change from baseline on the RSBQ and CGI-I scores at week 12. a. LSM change in RSBQ Score at 12 weeks from baseline 1. -4.9 2. -1.7 LSM Difference: -3.1 95% CI: -5.7 to -0.6 P=0.0175 b. LSM change in CGI-I score at 12 weeks from baseline 1. 3.5 2. 3.8 Difference: -0.3 95% CI: -0.5 to -0.1 P=0.003	 NA NA	<u>Any TEAEs</u> 1. 86 (93%) 2. 51 (54%) P<0.0001 <u>Serious TEAE</u> 1. 3 (3%) 2. 3 (3%) P=0.9894 <u>Drug Withdrawal due to AE</u> 1. 16 (17%) 2. 2 (2%) P=0.0005 <u>Diarrhea</u> 1. 75 (81%) 2. 18 (19%) P<0.001	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Randomized 1:1 to trofinetide or placebo via IRTS. Stratified by age and baseline RSBQ severity score. Baseline characteristics were balanced between treatment groups. <u>Performance Bias</u>: High. Placebo and trofinetide supplied in identical packaging and flavoring. Side effects such as severe diarrhea requiring treatment could have led to unblinding of caregiver or investigators, who provided the co-primary endpoint scoring. <u>Detection Bias</u>: High. Sponsor, participants, caregivers and clinicians all blinded to treatment assignment. Method of maintain blinding was not described. Unblinding may have occurred due to adverse effects (diarrhea, vomiting) observed with trofinetide. <u>Attrition Bias</u>: High. Overall high attrition for short term study and with unbalanced overall attrition in the active treatment group compared with placebo (25% vs. 10%). Most withdrawals in the trofinetide group (70%) were due to AEs (diarrhea/vomiting). Most withdrawals in the

		administered via gastrostomy tube -Either no seizures or a stable pattern of seizures and medication within 8 weeks of study enrollment -Caregiver is English-speaking <u>Key Exclusion Criteria</u>: -History of long QT syndrome -Significant cardiovascular, gastrointestinal, or endocrine disease (e.g., thyroid disease or diabetes) -Treatment with insulin, insulin-like growth factor 1, or growth hormone within 12 weeks of study enrollment		<u>Secondary Endpoint</u>: LSM change from baseline on the CSBS-DP-IT-social composite score at 12 weeks 1. -0.1 2. -1.1 Difference: 1.0 95% CI: 0.3 to 1.7 P=0.006	NA	<u>Vomiting</u> 1. 25 (27%) 2. 9 (10%) P=0.0022		placebo group (56%) were due to COVID-19 quarantine measures. <u>Reporting Bias</u>: High. Protocol available on-line. For missing data, last observation carried forward was imputed by the last expected dosing date. Protocol amended during the study to add a plan for managing diarrhea, which may have compromised the blinding of the study. <u>Other Bias:</u> High. Manufacturer funded the study and contributed to study design and report writing. Several authors received personal compensation and research support from the manufacturer, which may resulted in a conflict of interest that could influenced the conduct or outcomes of the study. Four authors are employed by manufacturer. **Applicability**: <u>Patient</u>: There was little racial or ethnic diversity among the enrolled subjects (92% of patients were White and 91% were not Hispanic or Latino). Caregiver had to be English speaking, which excluded non-English speakers. Patients younger than 5 yo not enrolled, despite mean age of diagnos around 3 yo. All patients had genetically confirmed RS. Patients older than 20 yo also excluded, which limited applicability of results to older patients with RS. <u>Intervention</u>: Safe weight-based dosing determined in dose-finding phase 2 trials. Duration of trial was short for a life time condition. <u>Comparator</u>: As no other FDA-approved treatments are available, placebo was an appropriate comparator. <u>Outcomes</u>: Change in symptoms assessed from baseline to 12 weeks in RSBQ and CGI-I scales. MCID not determined for either scale. CGI-I was not designed for RS assessment. <u>Setting</u>: 21 clinical sites in the United States
<u>Abbreviations</u>: AE = adverse effect; ARR = absolute risk reduction; CGI-I = Clinician's Global Impression of Improvement; CSBS-DP-IT = Communication and Symbolic Behavior Scales Developmental Profile-Infant Toddler; CI = confidence interval; FDA = United States Food and Drug Administration; IRTS = interactive response technology system; ITT = intention to treat; kg = kilograms; LSM = least squares mean; MCID = minimal clinically important difference; MECP2 = methyl-CpG-binding protein 2; 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; PG = parallel group; PP = per protocol; RS = Rett syndrome; RSBQ = Rett Syndrome Behavioral Questionnaire; SAEs = serious adverse events; TEAEs = treatment-emergent adverse effects; yo = years old								

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Appendix 1: Prescribing Information Highlights

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

DAYBUE™ (trofinetide) oral solution
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage is twice daily, morning and evening, according to patient weight. DAYBUE can be given with or without food. (2.1)

Patient Weight	DAYBUE Dosage	DAYBUE Volume
9 kg to less than 12 kg	5,000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6,000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or more	12,000 mg twice daily	60 mL twice daily

- Can be given orally or via gastrostomy (G) tube; doses administered via gastrojejunal (GJ) tubes must be administered through the G-port. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Oral solution: 200 mg/mL (3)

----------WARNINGS AND PRECUATIONS----------
- Diarrhea: Most patients experience diarrhea during treatment with DAYBUE. Advise patients to stop laxatives before starting DAYBUE. If diarrhea occurs, patients should start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected. (2.4, 5.1)
- Weight Loss: Weight loss may occur in patients treated with DAYBUE. Monitor weight and interrupt, reduce dose, or discontinue DAYBUE if significant weight loss occurs. (5.2)

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

----------ADVERSE REACTIONS----------
The most common adverse reactions (that occurred in at least 10% of DAYBUE-treated patients and at least 2% greater than in placebo) were diarrhea and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Acadia Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Orally administered CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities: closely monitor for adverse reactions with concomitant use. (7.1)
- OATP1B1 and OATP1B3 substrates for which a small change in substrate plasma concentration may lead to serious toxicities: avoid concomitant use. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Moderate to severe renal impairment: DAYBUE is not recommended. (8.6)

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

Revised: 3/2023

Trofinetide Oral Solution (DAYBUE)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling in patients with Rett syndrome.

Length of Authorization:

- Up to 12 months

Requires PA:

- Trofinetide oral solution

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. Recommended Weight-Based Trofinetide Oral Solution 200 mg/mL Dosing

Patient Weight	Trofinetide Dosage	Trofinetide Volume
9 kg to less than 12kg	5,000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or more	12,000 mg twice daily	60 mL twice daily
Abbreviations: kg = kilograms; mg = milligrams; mL = millilters		

Table 2. Criteria for Diagnosis of Rett Syndrome[1]

Criteria for Typical Rett Syndrome	Criteria for Atypical Rett Syndrome
1. A period of regression followed by recovery or stabilization. 2. All 4 of the main criteria are present. 3. Supportive criteria are not required, although often present in typical Rett syndrome.	1. A period of regression followed by recovery or stabilization. 2. At least 2 out of the 4 main criteria and 5 out of 11 supportive criteria.
Main Criteria	
1. Partial or complete loss of acquired purposeful hand skills 2. Partial or complete loss of acquired spoken language 3. Gait abnormalities: impaired or absence of ability 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms	
Supportive Criteria	

1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis	7. Growth retardation 8. Small cold hands and feet 9. Inappropriate laughing/screaming spells 10. Diminished response to pain 11. Intense eye communication

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of genetically confirmed Rett syndrome?	**Yes:** Go to #5	**No:** Go to #4
4. Does the patient exhibit symptoms indicative of typical or atypical Rett Syndrome (see **Table 2**)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the requested medication prescribed by a neurologist or a provider with experience in treating Rett syndrome?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for an FDA approved age (e.g., 2 years of age and older)?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for an approved weight-based dosing regimen (see **Table 1**)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Has the provider documented specific and measurable goals of therapy? Note: Documentation should include what will be assessed, how progress will be measured, and timeline for assessment. Goals should be attainable within 6 months and relevant to the condition or health of the patient. Documentation of progress toward or achievement of therapeutic goals will be required for renewal.	**Yes:** Document Assessment and Date:_____ 1.Approve Initial Request for enough units up to 14 days to assess tolerance to therapy. 2. Approve enough units to cover subsequent 14-28 days. 3. Approve enough units for up to 6 months (5 to 24 weeks).	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and/or provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness.
2. Has the patient met the goals of therapy described in the initial authorization by the prescribing provider and provider attests to patient's stabilization on therapy?	**Yes:** Approve for 12 months. Document assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 8/23 (DM)
Implementation: TBD

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Drug Class Update: BPH Drugs

Date of Review: August 2023

Date of Last Review: July 2016
Dates of Literature Search: 04/01/2016 - 04/10/2023

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

Purpose for Class Update:
The purpose of this review is to evaluate the literature for new high-quality evidence for the use of medications to treat benign prostatic hyperplasia (BPH) and provide an approval route for unfunded conditions that will be covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program. The Early and Periodic Screening, Diagnostic and Treatment program may allow for treatment of some conditions not normally covered under the Oregon Health Plan (OHP) fee-for-service (FFS) program, for people under 21 years old who are enrolled in Medicaid.

Plain Language Summary:
- This review was done to identify and evaluate new research for the classes of drugs used to treat benign prostatic hyperplasia. Benign prostatic hyperplasia is a condition in men that results in an increase in size of their prostate, which may cause bothersome symptoms. These medications may sometimes be used to treat other conditions of the urinary tract.
- A high-quality review done by Cochrane Database for Systematic Reviews found that one of these classes, called phosphodiesterase inhibitors, was more helpful than a sugar pill (placebo) at improving urinary symptoms, such as having to urinate at night and urinate often. Combination therapy with phosphodiesterase inhibitors and other drugs used to treat benign prostatic hyperplasia was not much better than a phosphodiesterase inhibitor alone at improving symptoms and combination therapy was associated with more side effects.
- A second review done by Cochrane Database for Systematic Reviews found that the drug silodosin was more effective than placebo at improving symptoms related to benign prostatic hyperplasia. Silodosin was found to have similar efficacy to other medications called tamsulosin and alfuzosin. Silodosin was found to have more side effects than the other medications.
- There is a small amount of data, from a research done by Cochrane Database for Systematic Reviews, that a class of drugs called alpha-blockers may help to increase the number of children that pass their kidney stones (small blockages in the kidney). Alpha-blockers were effective at helping to break up kidney stones in adults, who were also receiving a treatment called shock wave lithotripsy (a type of ultrasound treatment).
- A review of treatments used for chronic prostatitis and chronic pelvic pain syndrome in men found that the drug finasteride did help to reduce symptoms in this population. The Oregon Health Plan does not pay for medications to treat chronic prostatitis and chronic pain syndrome.
- A recent guideline by the American Urological Association supports the medications that we are recommending to help patients with benign prostatic hyperplasia.

Author: Kathy Sentena, PharmD

- The Drug Use Research and Management Group recommends no changes be made to the current medication policy that is in place for the treatment of benign prostatic hyperplasia for patients that have fee-for-service medical coverage.

Research Questions:

1. Is there new comparative evidence evaluating treatments for BPH?
2. Is there new comparative harms data for BPH treatments (e.g., hypotension, sexual side effects, withdrawals due to adverse events, severe adverse events)?
3. Are there certain sub-populations (based on age, gender, ethnicity, or comorbidities) in which certain treatments for BPH are more effective or cause less harm?

Conclusions:

- There are five new systematic reviews, one new guideline, one new formulation, and six new safety warnings included in this review.
- A review for the use of phosphodiesterase inhibitors (PDEIs) for the treatment of lower urinary tract symptoms (LUTS) related to BPH was done by Cochrane in 2018.[1] There is low-quality evidence that PDEIs may improve urinary symptoms slightly better than placebo based on the International Prostate Symptom Score (IPSS) (mean difference [MD] -1.89; 95% confidence interval [CI], -2.27 to -1.5).[1] The minimal clinically significant difference (MCID) for IPSS is a change of more than 3 points. There was not a substantial clinical benefit to combination therapy of PDEIs plus alpha-blockers (AB) or PDEIs plus 5-alpha reductase inhibitors (5-ARIs).
- A 2017 Cochrane review evaluated the use of silodosin in men with LUTS due to BPH.[2] Silodosin was more effective at reducing symptoms than placebo based on IPSS scores (MD -2.65; 95% CI, -3.23 to -2.08) (low-quality evidence). In active treatment comparisons, silodosin was not clinically or statistically more effective than tamsulosin or alfuzosin; however, the incidence of sexual adverse effects was higher.
- The off-label use of AB has been studied for removal of renal and urinary tract stones in children and adults. Evidence is limited and of low quality (detailed below), preventing strong conclusions of efficacy.
- There is low-quality evidence from a Cochrane review that AB may be helpful in increasing the stone-free rate in children with small urinary tract stones (RR 1.34; 95% CI, 1.16 to 1.54) when compared to placebo.[3]
- A Cochrane review evaluated the use of AB in adult patients undergoing shock wave lithotripsy for renal or ureteral stones, which demonstrated increased stone clearance more than usual care (RR 1.16; 95% CI, 1.09 to 1.23) (low-quality evidence).[4]
- A Cochrane review found the use of 5-ARIs (e.g., finasteride) to reduce symptoms of chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) more than placebo based on moderate quality of evidence (MD -4.6; 95% CI, -5.43 to -3.77).[5] Alpha-blockers may decrease symptoms but evidence was graded as very low quality.
- An updated 2021 guideline from the American Urological Association (AUA) supports current policy.[6]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of current evidence.
- Update the prior authorization (PA) criteria to clarify the recommendations and to remove the renewal criteria.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- A literature scan in July 2016 resulted in no changes to the PDL.

- There is evidence that therapies for BPH all significantly improve the International Prostate Symptom Score (IPSS) compared to placebo by -3.69 to -7.06 points.
- Preferred therapies are listed in **Appendix 1** and all non-preferred products are subject to PA criteria, which are presented in **Appendix 4**.

Background:
Benign prostatic hyperplasia (BPH), also called benign prostatic obstruction (BPO), is a common condition with an incidence that increases as men age. Prostate size usually begins to increase in men around 40-45 years of age with an incidence of approximately 80% at the age of 80.[6] Benign prostatic hyperplasia is a result of increases in glandular epithelial tissue, smooth muscle, and connective tissue in the prostatic transition zone.[7] Increased frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream are LUTS associated with BPH.[8] Treatment includes lifestyle modifications (e.g., limiting fluid intake, weight control), medical and surgical options. In some men, if BPH is untreated it may result in rising post-void residuals, bladder stones, and recurrent urinary tract infections.

Drug classes used for the treatment of BPH are AB, 5-ARI and PDEIs. Alpha-blockers (e.g., alfuzosin, doxazosin, silodosin, tamsulosin, tamsulosin extended release [ER] and terazosin) are considered first line therapy for most male patients and help to relieve symptoms within days. They have been used off-label in women for kidney stones and lower urinary tract infections. Trial data suggest that the AB class help to reduce IPSS, a measure of prostate symptoms, by 30-40% as well as increase urinary flow rate.[9] Non-selective AB, such as alfuzosin, are less likely to cause erectile dysfunction (ED) compared to selective AB. Alpha-blockers are associated with orthostatic hypotension and some formulations need titration. There is also the potential for AB to cause intraoperative floppy iris syndrome (IFIS), iris trauma and posterior capsule rupture during cataract surgery, and patients should be informed of this risk. Alpha-blockers have demonstrated similar efficacy and if a patient does not receive benefit from one AB, given at an appropriate dose, then it is unlikely that subsequent AB will provide benefit.[6] Phosphodiesterase inhibitors (e.g., tadalafil – only PDEI approved for BPH) are recommended for men with BPH symptoms and concomitant erectile dysfunction (ED).[8] There is no evidence that PDEIs are superior to AB and there is no data to support combination therapy with AB and PDEIs. Anticholinergics are recommended for men with predominately bladder storage LUTS due to BPH. Patients that don't respond to AB or anticholinergic monotherapy may be offered combination therapy with both medications. Beta-3 agonists (e.g. mirabegron), as monotherapy or in combination with AB, may also be considered in patients with storage symptoms despite AB treatment.[8]

Five-alpha reductase inhibitors (e.g., finasteride, dutasteride), are used to prevent progression of BPH symptoms but do not have a role in the acute symptom management of BPH. Five-alpha reductase inhibitors are recommended for prostates larger than 35 g and a treatment duration of 6 to 12 months is needed to reduce prostate size. Improvement in IPSS ranges from 15 to 30% and decreases in prostate volume range from 18 to 28% with the use of 5-ARIs.[9] Treatment with 5-ARIs are used on an ongoing basis to prevent symptom relapse and reduce the need for surgical intervention. Combination therapy with AB and 5-ARIs are used to decrease urinary symptoms and reduce prostate size. Common adverse reactions are reduced libido, ED and ejaculation disorders.

The IPSS is a validated tool used to determine disease severity and LUTS, as well as response to treatments. It is comprised of up to 35 points based on 7 questions, with higher scores indicative of greater symptoms. Symptom severity can be classified by the scores: 0-7 mild; 8-19 moderate; 20-35 severe.[8] Clinically important differences include the percentage achieving a MCID, such as a 30-50% reduction in score from baseline, or achieving a change in IPSS score of 3 points or more following treatment.[6] The IPSS also has a quality of life assessment in which the MCID is defined as >1 point.[6] Another validated tool is the degree of urinary bother and is measured by the Benign Prostatic Hyperplasia Impact Index (BPHII) assessed by scores ranging from 0-13 with higher scores related to a higher degree of bother.[6] A MCID for BPHII has not been determined.

There were less than 200 patients in the Oregon Medicaid fee-for-service (FFS) population who took a medication for BPH in the last quarter of 2022.

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:
Cochrane – Phosphodiesterase Inhibitors for Lower Tract Symptoms Consistent with Benign Prostatic Hyperplasia
A 2018 Cochrane review evaluated the literature to compare the use of PDEIs versus placebo or active therapy (e.g., ABs and 5-ARIs) in men with LUTS due to BPH.[1] Sixteen trials were included lasting 4 to 12 weeks. Drug classes studied were the following: PDEI versus 5-ARI; PDEI + 5-ARI versus PDEI alone; PDEI + AB + 5-ARI versus AB + 5-ARI; PDEI versus 5-ARI; PDEI + 5-ARI vs. PDEI alone; PDEI + AB + 5-ARI versus AB + 5-ARI.[1] Drugs included in the analysis are tadalafil, sildenafil and vardenafil. The primary outcome of interest was urinary symptoms (measured by the IPSS-total score and BPHI score).

Results for the comparisons of PDEIs to placebo and active controls are displayed in **Table 2**.[1] There is low-quality evidence that PDEIs are more effective than placebo based on small reduction in symptoms; however, changes in IPSS scores were not considered clinically meaningful. There is no evidence of superior efficacy of PDEIs compared to alpha-blockers.[1] There is no evidence of a benefit of combination therapy on reduction of symptoms.

Table 2. Summary of Results for the Use of PDEIs compared to Placebo and Active Controls[1]

Outcome	Results	Quality of Evidence	Comments
PDEI vs. Placebo			
IPSS-total score	MD -1.89 (95% CI, -2.27 to -1.5)	Low	There is low quality evidence that PDEIs are more effective than placebo
BPHII	MD -0.52 (95% CI, -0.71 to -0.33)	Low	
Adverse Events	RR 1.42 (95% CI, 1.21 to 1.67)	Low	
PDEI vs. alpha-blockers			
IPSS-total score	MD 0.22 (95% CI, -0.49 to 0.93)	Moderate	No clinical difference in symptoms between PDEIs and alpha-blockers was demonstrated
BPHII score	MD 0.03 (95% CI, -1.1 to 1.16)	Low	
Adverse events	RR 1.35 (95% CI, 0.80 to 2.30)	Low	
PDEI plus alpha-blockers compared to alpha-blockers alone			
IPSS-total score	MD -2.56 (95% CI, -3.92 to -1.19)	Low	

Adverse Events	RR 2.81 (95% CI, 1.53 to 5.17)	Moderate	A small improvement in symptoms was demonstrated with combination therapy; however there were an increased risk of adverse events
PDEI plus alpha-blockers compared to PDEI alone			
IPSS-total score	MD -2.4 (95% CI, -6.47 to 1.67)	Low	A small improvement in symptoms was demonstrated with combination therapy; however, it was not statistically or clinically different from PDEI use alone
PDEI plus 5-ARI compared to 5-ARI alone (short-term: up to 12 weeks)			
IPSS-total score	MD -1.4 (95% CI, -2.24 to -0.56)	Moderate	A small improvement in symptoms was demonstrated with combination therapy but difference was not clinically significant
PDEI plus 5-ARI compared to 5-ARI alone (long-term: 26 weeks)			
IPSS-total score	MD -1.0 (95% CI, -1.83 to -0.17)	Moderate	A small improvement in symptoms was demonstrated with combination therapy but difference was not clinically significant
Adverse Events	RR 1.07 (95% CI, 0.84 to 1.36)	Low	
Abbreviations: 5-ARI = 5-alpha reductase inhibitors; BPH = benign prostatic hyperplasia; BPHII = Benign Prostatic Hyperplasia Impact Index; CI = confidence intervals; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; MD = mean difference; PDEI = phosphodiesterase inhibitors; RR = relative risk			

There is a lack of data beyond 12 weeks for the use of PDEIs in BPH, despite it being a chronic condition. Additionally, there was a lack of high-quality comparative evidence for PDEIs versus active therapy.

Cochrane – Silodosin for the Treatment of Lower Urinary Tract Symptoms in Men with Benign Prostatic Hyperplasia

Cochrane evaluated the use of silodosin for treating LUTS in men with BPH.[2] Silodosin was compared to placebo and active treatments (e.g., tamsulosin and alfuzosin). Nineteen studies, ranging from 4 weeks to 3 months, were identified enrolling 4295 participants. Men enrolled in the trials were a mean age of 66.5 years with an IPSS of 19.1 (indicative of moderate symptoms).[2] Due to lack of allocation concealment, problems with blinding and high amounts of imprecision the quality of the evidence was considered moderate to low. The primary outcome was symptom control, assessed by the IPPS score.

Silodosin was compared to placebo in four studies. There was low quality evidence that silodosin was more effective at reducing symptoms than placebo based on IPSS scores (MD -2.65; 95% CI, -3.23 to -2.08).[2] Quality of life was not clinically improved with the use of silodosin compared to placebo with IPSS-QoL scores of a mean difference of -0.42 lower (-0.71 to -0.13) (moderate quality of evidence) (scores ranged from 0-6 with 0 being best: no symptoms and 6 being worst: terrible). Silodosin use on the incidence of cardiovascular (CV) events is not clear due to very low quality of evidence and non-significant findings (RR 1.28; 95% CI, 0.67 to 2.45).[2] There is moderate quality of evidence that the use of silodosin was associated with a higher number of sexual adverse events (RR 26.07; 95% CI 12.36 to 54.97).[2]

In people that have LUTS due to BPH, silodosin was compared to tamsulosin and there was no statistical or clinical differences between groups based on IPSS scores (MD -0.04; 95% CI, -1.31 to 1.24).[2] For the outcomes of quality of life, treatment withdrawal due to any reason and CV events were not different between groups. There is moderate strength of evidence that sexual adverse events were higher with silodosin compared to tamsulosin (RR 6.05; 95% CI 3.55 to 10.31).[2]

There is low quality evidence that silodosin increases IPSS scores more than alfuzosin in men with LUTS due to BPH (MD 3.83; 95% CI, 0.12 to 7.54; 1 study).[2] Quality of life scores were similar with silodosin and alfuzosin based on the IPSS-QoL (MD 0.14; 95% CI, -0.46 to 0.74) (moderate quality of evidence). Cardiovascular adverse events were not significantly different compared to alfuzosin (RR 0.67; 95% CI, 0.36 to 1.24). Sexual adverse events were higher with silodosin compared to alfuzosin based on moderate strength of evidence (770 more per 1000).

Cochrane – Medical and Surgical Interventions for the Treatment of Urinary Stones in Children

A Cochrane review evaluated management techniques for urinary tract stones of the kidney or ureter in children.[3] Surgical and medical therapies were evaluated. Six RCTs (n=335) examined the efficacy of AB, compared to placebo, in the management of urinary stones with or without analgesics. Studies included the use of doxazosin, tamsulosin, or silodosin. The mean ages of the participants ranged from 20.3 months to 11.1 years and stone size in those treated medically was 2-12 mm.[3]

There was low quality evidence that AB increased the stone-free rate (e.g. passage of stones in children presenting with urinary stones), in study follow-up at up to 4 weeks when compared to placebo (RR 1.34; 95% CI, 1.16 to 1.54).[3] Secondary procedures for residual fragments were less with AB compared to placebo, 141 fewer per 1000 children treated. (very low quality evidence; 1 RCT).

Conclusions are limited by evidence only a few trials enrolling a small number of patients. Evidence was also downgraded due to indirectness and imprecision of study findings.

Cochrane – Alpha-blockers after Shock Wave Lithotripsy for Renal or Ureteral Stones in Adults

A 2020 Cochrane review evaluated the evidence for the use of AB as adjuvant medical expulsive therapy to usual care (e.g., oral or intravenous hydration, NSAIDs, pain medication, and antibiotics if needed) and placebo or usual care alone in adult patients with renal and ureteral stones.[4] There were 40 trials that met inclusion criteria which involved 4793 patients; four of which were placebo controlled. Stone size ranged from 7.1 mm to 13.2 mm.[4] Four ABs were studied: tamsulosin, silodosin, terazosin and alfuzosin. The primary outcome of interest was stone clearance.

Evidence from 36 RCTs found adjuvant AB, in patients undergoing shock wave lithotripsy, increased stone clearance more than usual care (RR 1.16; 95% CI, 1.09 to 1.23) (low quality evidence).[4] Alpha-blockers are often given after lithotripsy to promote stone passage. This finding equates to a stone clearance rate of 69.3% in the control group and 80.4% in the AB group. There is low quality evidence that auxiliary treatment was less or the same in those treated with AB compared to usual care (RR 0.67; 95% CI, 0.45 to 1.00).[4] Major adverse events were lower with AB compared to standard of care with 103 fewer events per 1000 adults treated (low quality evidence). Most adverse events were related to rehospitalizations or emergency room visits. Stone clearance time was shorter with AB compared to standard of care (3.74 fewer days; low quality of evidence).[4]

Quality of evidence is limited as 31 of the 40 trials were open-label, which may increase the risk of bias. Less than half of the studies provided allocation details; therefore, randomization details were deemed unclear. Due to the open-label design of many of the trials, the risk of detection bias was high since the outcome of stone clearance was a subjective finding determined by the investigator.

Cochrane – Pharmacological Interventions for Treating chronic Prostatitis/Chronic Pelvic Pain Syndrome

A 2019 review from Cochrane evaluated the efficacy and safety of using medications, specifically AB and 5-ARIs as it pertains to this review, in men with CP/CPPS.[5] Twenty-six studies were identified for these two classes of drugs (n=2238). Terazosin, doxazocin, phenoxybenzamine, tamsulosin, alfuzosin, and silodosin were the AB studied and 5-ARIs included finasteride. Follow-up ranged from 6 weeks to 6 months.[5] All studies were placebo-controlled.

Alpha-blockers compared to placebo were studied in 24 RCTs. Prostatitis symptoms, based on the NIH-CPSI score, were lower with the use of AB compared to placebo or no intervention in studies lasting up to 6 months; however, the decrease in symptoms was not considered clinically significant (MD -5.01; 95% CI, -7.41 to -2.61) (very low quality of evidence).[5] The NIH-CPSI scores range from 0 to 43, with lower scores indicating more benefit. A clinically significant decrease is 6 points or 25% reduction.[5] The number of patients considered responders (e.g., those with 25% or 6-point reduction) was not different between groups (RR 1.23; 95% CI, 0.94 to 1.61) (very low-quality of evidence).[5] There was low quality evidence that there were more adverse reactions (e.g., postural hypotension, and dizziness) in those treated with AB compared to placebo. Sexual dysfunction was higher with AB but not statistically significant based on moderate evidence (MD 0.26; 95% CI, -1.13 to 1.65).[5]

Finasteride was compared to placebo in two, outpatient studies in men with CP/CPPS. Moderate quality evidence demonstrated a reduction in prostatitis symptoms, based on the NIH-CPSI, with finasteride more than placebo (MD -4.6; 95% CI, -5.43 to -3.77).[5] The difference is not considered clinically meaningful. There was low quality evidence that the number of responders was not different between groups (RR 0.87; 95% CI, 0.33 to 2.30).[5] Adverse events occurred in 21 fewer per 1000 patients taking finasteride compared to placebo.[5]

The main limitations to the evidence in this review were the small number of studies and short duration of follow-up. Issues with study methodology contributed to downgrading of the evidence.

After review, 12 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10–21]

New Guidelines:

American Urological Association – Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia

In 2021 the AUA updated guidance on the management of LUTS in men with BPH.[6] Guideline methods were clearly defined and the evidence was evaluated and graded. Recommendation ranged from expert opinion to strong recommendation, based on the quality of the evidence. Some of the guideline authors did have conflicts of interest that were clearly outlined. Recommendations pertaining to medical treatment of BPH will be discussed.

- Alpha-blockers are recommended for patients with bothersome moderate to severe LUTS/BPH that is bothersome (Moderate recommendation based on Grade A evidence).[6]
- Choice of AB should be determined based on comorbidities (e.g., ejaculatory dysfunction, changes in blood pressure) (Moderate recommendation based on Grade A evidence).[6]
- Alpha-blockers may also be used in patients with acute urinary retention (AUR) related to BPH prior to a voiding trial (Moderate recommendation based on Grade B evidence). Patients should be warned of the risk of IFIS with the use of AB.

- The use of 5-ARIs are recommended in patients with LUTS/BPH with prostatic enlargement (prostate volume > 30 cc on imaging, a prostate specific antigen [PSA] of > 1.5 ng/dL or palpable prostate enlargement in digital rectal exam).[6] (Moderate recommendation based on Grade B evidence).
- The use of 5-ARIs, alone or with AB, are recommended to prevent the progression of LUTS/BPH (Strong recommendation based on Grade A evidence).[6]
- Patients should be advised of the risk of sexual side effects and low risk of prostate cancer associated with 5-ARI therapy. (Moderate recommendation based on Grade C evidence).
- Tadalafil could be considered a treatment option in patients with LUTS/BPH, irrespective of ED (Moderate recommendation based on Grade B evidence).[6]
- Combination therapy with an AB and 5-ARI should only be considered in patients with LUTS due to prostatic enlargement (Strong recommendation based on Grade A evidence).[6]
- Tadalafil in combination with AB should not be offered in patients with LUTS/BPH because there is no advantages in symptoms improvement over monotherapy with either agent alone (Moderate recommendation based on Grade C evidence).

Guidelines for Clinical Context:

<u>EAU – Non-neurogenic Male Lower Urinary Tract Symptoms (LUTS), including Benign Prostatic Obstruction (BPO)</u>

An updated 2023 guideline by the European Association of Urology (EAU) was recently published and included recommendations for the treatment of LUTS in men.[9] A systematic review of the literature was completed and conflicts of interest were disclosed; however, links to this information were disabled so this information could not be critically evaluated. Therefore, recommendations from the EAU will be considered for clinical context. The evidence was graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence. Evidence ranges from 1a to 5, with 1a being systematic reviews of RCTs with low heterogeneity and 5 being expert opinion.[9]

The use of AB are recommended to for men with moderate-to-severe LUTS to reduce urinary symptoms and increase peak urinary flow rate when compared to placebo (Strong recommendation, 1a level of evidence).[9] Five-alpha reductase inhibitors improve symptoms and decrease prostate volume and are recommended for men with moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume >40 mL) (Strong recommendation, 1b level of evidence).[9]

After review, one guideline was excluded due to poor quality.[22]

New Formulations or Indications:

<u>Finasteride and Tadalafil (ENTADFI)</u> – In December of 2021 a new combination product was approved for the treatment of BPH up to 26 weeks in men with an enlarged prostate.[23] The combination contains previously approved medications, finasteride 5 mg, a 5-ARI and tadalafil 5 mg, a PDE5 inhibitor. Finasteride/tadalafil should be taken once daily for up to 26 weeks. Finasteride/tadalafil was compared to placebo/finasteride in one double-blind, parallel-design study lasting 26 weeks. Changes in the primary endpoint, symptoms based on the IPSS, at 12 weeks were a -3.8 for placebo/finasteride compared to -5.5 for finasteride/tadalafil (MD -1.4; p=0.001).[23]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Silodosin[24]	RAPAFLO	December 2020	Use in specific populations	Silodosin is not indicated for females.
Dutasteride[25]	AVODART	January 2020	Warnings and Precautions	Potential risk to male fetus if drug is handled by female who is pregnant. If there is contact with a leaky capsule, hands should be washed immediately.
Tadalafil[26]	CIALIS	February 2018	Use in specific populations	Tadalafil is not indicated for use in females or pediatric patients.
Tadalafil[26]	CIALIS	May 2017	Warnings and Precautions	Reports of sudden loss of vision in one or both eyes have been reported with tadalafil. This could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). Tadalafil should be discontinued and seek care if vision loss occurs.
Dutasteride/tamsulosin[27]	JALYN	December 2020	Contraindications	The combination product is contraindicated in females who are pregnant. Capsules should not be handled by females who are pregnant.
Tamsulosin[28]	FLOMAX	January 2019	Use in specific populations	Tamsulosin is not indicated for use in women.

Randomized Controlled Trials:

A total of 130 citations were manually reviewed from the initial literature search. After further review, all randomized controlled trials were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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24. Rapaflo (Silodosin) [prescribing information]. Madison, NJ. Allergan. December 2020.

25. Advodart (dutasteride) [prescribing information]. Research Triangle Park, NC. GlaxoSmithKline. January 2020.

26. Cialis (tadalafil) [prescribing information]. Indianapolis, IN. Lilly USA, LLC. February 2018.

27. Jalyn (dutasteride/tamsulosin) [prescribing information]. Research Triangle Park, NC. GlaxoSmithKline. December 2020.

28. Flomax (tamsulosin) [prescribing information]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. December 2018.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
terazosin HCl	TERAZOSIN HCL	CAPSULE	Y
doxazosin mesylate	CARDURA	TABLET	Y
doxazosin mesylate	DOXAZOSIN MESYLATE	TABLET	Y
finasteride	FINASTERIDE	TABLET	Y
finasteride	PROSCAR	TABLET	Y
tamsulosin HCl	FLOMAX	CAPSULE	Y
tamsulosin HCl	TAMSULOSIN HCL	CAPSULE	Y
tadalafil	CIALIS	TABLET	N
tadalafil	TADALAFIL	TABLET	N
doxazosin mesylate	CARDURA XL	TAB ER 24	N
alfuzosin HCl	ALFUZOSIN HCL ER	TAB ER 24H	N
dutasteride	AVODART	CAPSULE	N
dutasteride	DUTASTERIDE	CAPSULE	N
silodosin	RAPAFLO	CAPSULE	N
silodosin	SILODOSIN	CAPSULE	N
dutasteride/tamsulosin HCl	DUTASTERIDE-TAMSULOSIN	CPMP 24HR	N
dutasteride/tamsulosin HCl	JALYN	CPMP 24HR	N

Appendix 2: Medline Search Strategy
Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 07, 2023
Search Strategy:

#	Searches	Results
1	tamulosin.mp.	4

2	terazocin.mp.	4
3	doxazocin.mp.	14
4	finasteride.mp. or Finasteride/	3579
5	tadalafil.mp. or Tadalafil/	2658
6	alfuzosin.mp.	634
7	dutasteride.mp. or Dutasteride/	1164
8	silodosin.mp.	483
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	7813
10	limit 9 to (english language and humans and yr="2016 -Current")	1432
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	130

Appendix 3: Key Inclusion Criteria

Population	Men with benign prostatic hyperplasia (BPH)
Intervention	Phosphodiesterase inhibitors, alpha-blockers, 5-alpha reductase inhibitors
Comparator	Placebo or other active therapy
Outcomes	Reduction in urinary symptoms
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Benign Prostatic Hypertrophy (BPH) Medications

Goal(s):

- BPH with urinary obstruction is an OHP-funded treatment. BPH without obstruction is not a funded diagnosis.
- Restrict use for male pattern baldness and erectile dysfunction, which are not OHP-covered conditions.
- Allow case-by-case review for members covered under the EPSDT program for unfunded diagnoses.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at 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 switching to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.		**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
~~3. Is the request for continuation of therapy previously approved by the FFS program?~~	~~**Yes:** Go to **Renewal Criteria**~~	~~**No:** Go to #4~~	
~~4.~~3. Is the request for an alpha-1 blocker?~~, and~~		**Yes:** Go to #~~4~~5	**No:** Go to #6
~~5.~~4. Does the patient have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction?		**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
~~6.~~5. Has the patient tried and not tolerated or not obtained the desired treatment effect on~~failed~~ a 2-month trial of a preferred alpha-1 blocker?	**Yes:** Approve an alpha-1 blocker for up to 12 months	**No:** Pass to RPh. Deny until patient has tried and failed a covered alternative
~~7.~~6. Does the patient have a diagnosis of benign prostatic hyperplasia~~trophy~~ (BPH) or enlarged prostate with obstruction?	**Yes:** Approve for up to 12 months	**No:** Go to #7
~~8.~~7. Does the patient have a diagnosis of unspecified urinary obstruction or BPH without obstruction?	**Yes:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #8 "Not Funded" section.	**No:** Pass to RPh. Go to #8

~~9.~~8. RPh Only: All other conditions need to be evaluated to see if diagnosis is funded:

Funded: covered diagnoses related to prostate may be approved for 1 year.
Not Funded:

- Unfunded diagnoses for patients <21 years of age should be reviewed for medical appropriateness/necessity for members of EPSDT program
  - 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.)?
  - Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products?
  - If patient qualifies for EPSDT benefit and clinic provides supporting literature, approve for up to 12 months.
- Unfunded diagnoses for ≥21 years of age should be denied (not funded by the OHP).

Not Covered: Cosmetic and uncovered diagnoses (e.g., hair growth, erectile dysfunction) should be denied (not covered by the OHP).

- Alpha-1 blockers and 5-alpha reductase inhibitors may be used concurrently for BPH up to 1 year. Alpha-1 blockers may be discontinued once prostate is reduced to normal size.
- If urine retention (obstructive), ask for more specific diagnosis.

Renewal Criteria

1. Is the request for an alpha-1 blocker and does the patient have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient also been taking a 5-alpha reductase inhibitor for the last year?	**Yes:** Recommend against combination therapy exceeding 1 year.	**No:** Approve for the shorter of 12 months or length of the prescription
3. Does the patient have a diagnosis of BPH or enlarged prostate with obstruction?	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does the patient have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction?	**Yes:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #5	**No:** Pass to RPh. Go to #5
5. RPh only: All other indications need to be evaluated as to whether they are a funded condition: • Alpha Blockers and 5-alpha reductase inhibitors may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size. • If urine retention, obstructive, ask for more specific diagnosis. • Unfunded diagnoses for patients <21 years of age should be reviewed for medical appropriateness/necessity for members of EPSDT program ○ Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth,	If funded or qualifies for EPSDT benefit and clinic provides supporting literature, approve for up to 12 months.	If non-funded, deny (not funded by the OHP).

development, ability to participate in school, perform activities of daily living, etc.)? ○ Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products?		

P&T Review: *8/23 (KS),7/16 (KS); 11/12; 9/10; 3/10; 5/08; 2/06*
Implementation: *8/16, 2/21/13; 1/1/11; 4/20/10; 5/22/08; 7/1/06; 9/30/05*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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New Drug Evaluation: oral fecal microbiota spores, live-brpk

Date of Review: August 2023
Generic Name: fecal microbiota spores, live-brpk

End Date of Literature Search: 05/15/2023
Brand Name (Manufacturer): Vowst™ (Seres Therapeutics, Inc.)
Dossier Received: Not available as of May 2023

Plain Language Summary:

- Infections in the large intestine can be caused by bacteria called *Clostridioides difficile* (also called *C. difficile*). The Food and Drug Administration recently approved a medicine named Vowst™ which can be used to prevent infections caused by *C. difficile* in people who have had these infections more than once. This review looks at evidence for the effectiveness and safety of this new medicine.
- Vowst™ is produced by collecting fecal matter from healthy people. The material is then processed to remove any harmful bacteria, but still allows spores from healthy bacteria to be introduced into the large intestine by the Vowst™ capsule. These spores will then attack toxins from the *C. difficile* bacteria to help prevent another infection.
- In a clinical study of 182 people who had more than one *C. difficile* infection, Vowst™ capsules taken by mouth were better than placebo (sham treatment) at preventing another *C. difficile* infection in the first 8 weeks after treatment.
- The most common adverse events reported with the medicine was stomach pain, gas, constipation, and diarrhea.
- The Oregon Health Plan (OHP) covers Vowst™ if needed. Providers must explain to the OHP why someone needs Vowst™ before it is covered by a process called prior authorization.

Research Questions:

1. What is the evidence for the efficacy of oral fecal microbiota spores, live-brpk in preventing recurrent *C. difficile* infections (CDI)?
2. What are the harms associated with the use of oral fecal microbiota spores, live-brpk in recurrent CDI?
3. Are there specific subpopulations of patients (specifically by race, antibiotic use, history of CDI, age, socio-economic status, or comorbidities) for which oral fecal microbiota capsules are more effective or associated with more harm than other therapies used to prevent CDI recurrence?

Conclusions:

- Fecal microbiota spores, live-brpk (VOWST™) oral capsules received FDA approval April 2023.[1] This biologic product was granted Food and Drug Administration (FDA) Priority Review, Breakthrough Therapy, and Orphan Therapy designations.[2] Oral fecal microbiota capsules are indicated to prevent the recurrence of CDI in adults aged 18 years and older following completion of standard-of-care (SOC) antibacterial treatment for recurrent CDI.[1]
- The safety and efficacy of oral fecal microbiota, live-brpk product was evaluated in the ECOSPOR III randomized controlled trial (RCT).[3] This was a phase 3, double-blind, multi-center, placebo-controlled study conducted at 56 sites in the United States and Canada.[3] In this trial, 182 people with 3 or more

recurrent CDIs within 12 months were randomized to receive either 4 capsules of oral fecal microbiota or matched placebo once daily for 3 days following CDI antibiotic treatment (oral vancomycin or fidaxomicin).[3]

- The primary efficacy endpoint of the RCT was CDI recurrence up to 8 weeks after initiation of treatment.[3] Low-quality evidence showed CDI recurrence was lower in patients who received oral fecal microbiota compared to placebo-treated patients (12% vs. 40%; difference: 28%; relative risk [RR], 0.32; 95% confidence interval [CI] 0.18 to 0.58; p<0.001; number needed to treat [NNT] = 4).[3] Similar results were observed regardless of age or initial antibiotic used to treat CDI.[3]
- Adverse events related to, or possibly related to, oral fecal microbiota or placebo occurred in slightly more than half of the patients in each group in the RCT (51% vs. 52%, respectively).[3] The most common adverse events were gastrointestinal (GI) disorders (i.e., flatulence, abdominal pain, abdominal distension, constipation, and diarrhea), most of which were mild to moderate in nature.[3]
- Most of the patients enrolled in the RCT were White. The safety and efficacy of oral fecal microbiota capsules has not been sufficiently studied in Black, Asian, or Pacific Islander populations, or in pediatric patients. Age greater than 65 years did not appear to be a factor in safety or efficacy. Other factors are unknown.

Recommendations:

- Maintain oral fecal microbiota capsules as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP) subject to prior authorization (PA).
- Add oral fecal microbiota capsules to the "Prevention of *C. difficile* Recurrence" clinical PA criteria.

Background:

Medications FDA-approved to treat and prevent CDI were reviewed by the Pharmacy and Therapeutics (P & T) Committee at the June 2023 meeting. Evidence for the efficacy and safety of the recently FDA-approved fecal microbiota enema (REBYOTA) was presented. After reviewing the evidence, the committee made the following recommendations:

- Maintain fidaxomicin as a non-preferred drug on the PMPDP with PA criteria to ensure appropriate utilization.
- Maintain fecal microbiota enema as a non-preferred drug on the PMPDP subject to PA. Create a new set of PA criteria titled "Prevention of *C. difficile* Recurrence" and include bezlotoxumab infusion and fecal microbiota enema in the new PA.

C.difficile infection is one of the most common healthcare-associated infections in the United States and is associated with 15,000 to 30,000 deaths annually due to consequences of severe diarrhea and colitis.[2,4] The pathogenesis of CDI typically occurs as a two-step process: (1) the disruption of the microbiome, a diverse ecosystem that provides essential functions for the host; and (2) exposure to C. difficile spores.[5] The primary risk factor for disease development is antibiotic use, which contributes to the pathophysiology of CDI by creating ecologic gaps within the microbiome.[5] The loss of microbial diversity reduces colonization resistance and negatively impacts microbe-associated functions that are key to host defense.[5] When the balance of microorganisms in the gut is changed, *C. difficile* is allowed to multiply and release toxins causing diarrhea, abdominal pain and fever, and in some cases, organ failure and death.[2] In a disrupted microbiome, there is an increase in the abundance of proinflammatory Gram-negative *Proteobacteria* and a decline in the abundance of beneficial spore-forming *Firmicutes* species that play a dominant role in gut health.[5] The loss of Gram-positive *Firmicutes* leads to microbe-associated changes which support favorable conditions for the spore germination and bacterial growth of *C. difficile*.[5]

After recovering from initial CDI, individuals may get recurrent CDI.[2] Risk factors for recurrent CDI include age 65 years and older, recent antibiotic use, renal insufficiency, history of previous CDIs, prolonged hospital stays, proton pump inhibitor use, and lack of sufficient immune response to *C.difficile* toxins.[4]

Recurrent CDI is defined by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.[6] Approximately 20% of patients will experience an initial recurrence, and rates of further recurrences continue to increase significantly to greater than 40% after each episode.[5,7] For the first recurrence of CDI, 10-day oral vancomycin regimen or a 10-day course of fidaxomicin is recommended if vancomycin was used for the initial episode.[6] For non-severe CDI in children, either weight-based metronidazole or oral vancomycin dosing is recommended for an initial episode or first CDI recurrence.[8] For severe CDI in children, oral vancomycin is recommended over metronidazole by IDSA/SHEA (2017).[8]

Bezlotoxumab, an anti-toxin B monoclonal antibody, received FDA-approval in 2016 for prevention of CDI recurrence in combination with CDI SOC antibiotics (oral vancomycin or fidaxomicin). Bezlotoxumab is not indicated for the treatment of CDI. It is only approved for use in combination with antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg intravenous (IV) infusion.[9] The evidence for the safety and efficacy of bezlotoxumab was reviewed by the P & T Committee at the May 2018 meeting. Considering the high cost of bezlotoxumab and the minimal benefits over placebo in patients at low risk of recurrent CDI, the American College of Gastroenterology (ACG) 2021 guidance recommends bezlotoxumab be considered for patients in whom the observed benefits in clinical trials were greatest, including those aged 65 years or older with at least one of the following additional risk factors: experiencing a second episode of CDI within the past 6 months, immunocompromised, or severe CDI (conditional recommendation, moderate-quality evidence).[7] The IDSA/SHEA 2021 guidance is similar to ACG guidance and recommends bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone for patients with a recurrent CDI episode within the last 6 months (conditional recommendation, very low certainty of evidence).[6] Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited as most patients in clinical trials of bezlotoxumab received vancomcyin.[6]

If there are 2 or more CDI recurrences despite appropriate antibiotic treatments, fecal microbiota transplant (FMT) is recommended by IDSA/SHEA (2017).[8] Transplantation occurs by instillation of processed stool donated by a healthy volunteer via nasogastric/nasoduodenal tube, colonoscopy, enema, or capsule.[10] An important barrier to the integration of FMT into regular clinical practice is the heterogeneity of administration routes and lack of standardization of FMT guidance.[10] Standardization of the methodological components of FMT includes: donor screening, stool preparation, storage, and instillation route.[10] The efficacy of FMT after SOC antibiotics for preventing recurrent CDI has been described in numerous case series and RCTs.[7] There have been a few trials comparing the effectiveness of different FMT delivery modalities.[7] The choice of the most appropriate route of instillation should be driven partly by the options available to the provider, the preferences of the patient, and the clinical circumstances.[7] Its not clear how current FMT processes will change with 2 FDA-approved products commercially available.

A 2018 joint guideline developed by the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) provided recommendations for best practices for the provision of FMT in adults with CDI before commercial products were available.[11] Strength of recommendations and quality of evidence for which patients are the best candidates for FMT are as follows:

- FMT should not be administered as initial treatment for CDI (strong recommendation, low-quality evidence).[11]
- FMT should be offered to patients with recurrent CDI who have had at least 2 recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong recommendation, high-quality evidence).[11]
- FMT should be considered in cases of severe CDI (strong recommendation, moderate-quality evidence).[11]

The ACG 2021 guidance includes a recommendation that patients experiencing their second or more recurrence of CDI be treated with FMT to prevent additional recurrences (strong recommendation, moderate-quality evidence).[7] This recommendation is supported by the United Kingdom's National Institute for Health and Care Excellence (NICE) 2022 guidance.[12]

In June 2019, the FDA released a statement warning of the risks associated with FMT due to transmission of multi-drug resistant organisms.[13] Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E. Coli)*; of the 2 adults, one of the individuals died.[13] Another warning was issued March 2020, reporting 6 additional cases of transmission of antibiotic-resistant organisms (enteropathogenic *E. coli* in 2 cases and Shigatoxin-producing *E. coli* in 4 cases) via FMT.[14] In April 2020, the FDA issued a safety alert requiring testing of stool donors for SARS-CoV-2 virus due to possible risk of viral transmission from donor to recipient.[15] In August 2022, a similar safety alert regarding possible transmission of monkeypox virus via FMT was published to recommend additional donor screening parameters.[16]

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

Clinical Efficacy:
Fecal microbiota spores, live-brpk (VOWST) oral capsules received FDA approval April 2023. This is the second fecal microbiota product approved by the FDA and the first that is administered orally. Oral fecal microbiota capsules are indicated to prevent the recurrence of CDI in adults aged 18 years and older following completion of SOC antibacterial treatment for recurrent CDI.[1] Oral fecal microbiota capsules are not indicated for treatment of CDI.[1] The product is composed of live purified *Firmicutes* bacterial spores in a suspension manufactured from human fecal matter sourced from qualified donors.[1,3] Live purified *Firmicutes* bacterial spores are theorized to limit *C. difficile* spore germination.[3] Sustained clinical responses are associated with the engraftment of *Firmicutes* bacteria.[5] Donors are screened via a questionnaire, physical examination, and blood and stool testing for pathogens of concern.[4] Stool donations are processed with an ethanol solution to kill fecal organisms that are not spores.[4] Unlike most vegetative organisms, spores are resistant to gastric acid, heat, and a range of chemical and physical changes, exhibiting exceptional stability during manufacturing and drug product storage.[5]

The recommended dose of oral fecal microbiota is 4 capsules taken by mouth once daily on an empty stomach prior to the first meal of the day for 3 consecutive days.[1] Prior to taking the first dose, the GI tract should be cleared of residual antibiotic with the administration of 296 mL of magnesium citrate the day before and 8 hours prior to taking the first dose of fecal microbiota capsules.[1,3] In clinical studies, people with impaired renal function received 250 mL of polyethylene electrolyte solution.[1] The manufacturer also recommends patients not eat or drink, except for a small amount of water, for at least 8 hours before taking the first dose.[1] The mechanism of action of fecal microbiota has not been established, although it is hypothesized that replacement of healthy gut microbiome will help prevent recurrent CDIs.[5]

ECOSPOR III was a Phase 3, double-blind, placebo-controlled, RCT of 182 adults with 3 or more CDI episodes who were randomized to receive either oral fecal microbiota or placebo (4 oral capsules daily for three days) following completion of SOC antibiotic treatment (oral vancomycin or fidaxomicin). The RCT was conducted at 56 sites in the United States and Canada.[3] The recurrence of CDI was defined by investigators as diarrhea (3 or more unformed stools per day) for at least 2 consecutive days, a positive stool *C. difficile* toxin test, and resolution of symptoms after receiving 10 to 21 days of SOC antibiotic therapy.[3]

Before donating stool, 4 donors underwent an extensive health examination, including personal and family medical history, laboratory chemical and hematologic screening, urinalysis, and viral, bacterial, and parasite testing of blood and stool to generate 4 lots of fecal microbiota.[3] Donated stool was obtained before the onset of the COVID-19 pandemic.[3] Because vancomycin and fidaxomicin can persist in the gastrointestinal tract for up to 5 to 7 days after discontinuation, 296 mL of magnesium citrate was administered the night before fecal microbiota treatment to limit inactivation of species of bacteria present in the fecal microbiota regimen.[3] Patients who could not take magnesium citrate due to renal impairment were given 250 mL of polyethylene glycol electrolyte solution.[3] Patients were contacted weekly via telephone by investigators to assess onset of adverse events or diarrhea. Patients were asked to complete a daily diarrhea log when they

experienced 1 or more daily episodes of diarrhea. If more than 3 unformed stools per day over 2 consecutive days recurred, patients were instructed to return to the clinic for stool testing at a central laboratory and clinical evaluation. Investigators determined recurrence of CDI after completing a patient assessment. Of the 182 enrolled patients, 149 (82%) completed 8 weeks of follow-up.[3] Five of the 89 patients (6%) in the oral fecal microbiota group and 28 of 93 (30%) in the placebo group withdrew before week 8.[3] The most common reason for withdrawal from the trial was CDI recurrence, which was more common in the placebo group than in the oral fecal microbiota group (24% and 3%, respectively).[3]

The primary efficacy outcome was CDI recurrence up to 8 weeks after initiation of treatment.[3] CDI recurrence was defined as onset of more than 3 watery stools per day over 2 days, positive stool *C.difficile* toxin assay, and persistence of diarrhea until initiation of antibiotic treatment.[3] Patients who were lost to follow-up, discontinued participation in the trial prematurely, or died without a recurrence of *C. difficile* infection before 8 weeks after treatment were defined as having a *C. difficile* infection recurrence.[3] Low-quality evidence showed CDI recurrence was lower in patients who received oral fecal microbiota compared to placebo-treated patients (12% vs. 40%; difference: 28%; RR, 0.32; 95% CI 0.18 to 0.58; p<0.001; NNT=4).[3] Administration of fecal microbiota led to less frequent CDI recurrence than placebo in analyses stratified according to age (age <65 years: RR, 0.24; 95% CI, 0.07 to 0.78 and age ≥65 years: RR, 0.36; 95% CI, 0.18 to 0.72) and antibiotic received (oral vancomycin: RR, 0.41; 95% CI, 0.22 to 0.79 and fidaxomicin: RR, 0.09; 95% CI, 0.01 to 0.63).[3] Most recurrence events occurred rapidly, with onset as early as day 4 after randomization.[3] Of the 48 recurrences that occurred in the overall trial population by week 8, a total of 36 (75%) occurred within 2 weeks and 41 (85%) occurred within 4 weeks after administration of oral fecal microbiota or placebo.[3] In The secondary analysis of percent of patients with recurrent CDI at 24 weeks, the rate of recurrence in the active comparator arm had almost doubled to 21% vs. 47% in the placebo-treated arm (RR, 0.46; 95% CI 0.30 to 0.73; p<0.001).[3]

Limitations of this trial include the very low representation of non-White patients. Considering the extent of CDI in the United and States and Canada, the population recruited for this study was small. Stool specimens were not obtained before antibiotic treatment, so the full effect of fecal microbiota on the pre-antibiotic microbiome is unknown.[3] Efficacy and safety of oral fecal microbiota have not been established in pediatric patients.

Details for the RCT which contributed to the safety and efficacy data of oral fecal microbiota capsules to prevent recurrent CDI are described in **Table 3**.

Clinical Safety:
Adverse events that were related to, or possibly related to, fecal microbiota or placebo occurred in slightly more than half of the patients in each group in the RCT (51% vs. 52%).[3] The most common adverse events were GI disorders (i.e., flatulence, abdominal pain, abdominal distension, constipation, diarrhea), most of which were mild to moderate in nature.[3] Three deaths occurred in the fecal microbiota group, none of which were deemed by the blinded investigators to be drug-related.[3] Adverse effects reported in the RCT are summarized in **Table 1**.

Table 1. Adverse reactions reported in 5% or more of patients treated with fecal microbiota oral capsules compared with placebo[1]

Adverse Reaction	Fecal Microbiota Oral Capsules (n=90)	Placebo (n=92)
Solicited: recorded by participants in a diary for 7 days after completing a 3-day regimen of study drug or placebo		
Abdominal Distension	31.1%	29.3%
Fatigue	22.2%	21.7%
Constipation	14.4%	10.9%
Chills	11.1%	7.6%
Unsolicited: recorded by investigator queries during visits over 8 weeks after first dose of study drug		
Diarrhea	10.0%	4.3%

Look-alike / Sound-alike Error Risk Potential: No results available

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Resolution of CDI-associated diarrhea without CDI recurrence within 8 weeks
2) Sustained treatment response (no CDI 6 months after last dose)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Treatment success (absence of CDI diarrhea within 8 weeks of treatment)

Table 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Not established: theoretical supposition that biotherapeutic product repopulates and restores diversity of gut microbiome to suppress *C. difficile* overgrowth
Oral Bioavailability, Distribution, and Protein Binding	Not Applicable
Elimination, Half-Life and Metabolism	

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Feuerstadt P, et al.[3] ECOSPOR III Phase 3, DB, MC, PC, RCT	1. Fecal microbiota: 4 capsules PO once daily x 3 days 2. Placebo: 4 capsules PO once daily x 3 days *All patients received 296 mL of magnesium citrate (or 250 mL of polyethylene glycol for patients with renal impairment) the night before treatment.	Demographics: -Mean age: 65.5 yo -Race: White: 93% Black: 4% Asian: 1% Other: 3% -Female: 60% -Outpatient: 99% -3 rCDI episodes: 60% -Greater than 4 rCDI episodes: 40% -Previous antibiotic regimen: Vancomycin: 73% Fidaxomicin: 27% Key Inclusion Criteria: - Adults ≥18 yo with ≥ 3 episodes of rCDI within previous 12 mos - Positive *C. difficile* stool toxin assay - Completion of 10 to 21 days of PO vancomycin or fidaxomicin with resolution of diarrhea Key Exclusion Criteria: -Toxic megacolon and/or small bowel ileus, history of IBS or active inflammatory bowel disease - Currently receiving ≥ 20 mg of prednisone or equivalent for > 2 weeks - Prior receipt of FMT	ITT: 1. 89 2. 93 Attrition: 1. 5 (6%) 2. 28 (30%)	Primary Endpoint: Percent of patients with rCDI at 8 weeks 1. 11 (12%) 2. 37 (40%) Difference: 28% RR 0.32; 95% CI 0.18 to 0.58; P<0.001 Secondary Endpoints: Percent of patients with rCDI at 12 weeks 1. 16 (18%) 2. 43 (46%) RR 0.40; 95% CI 0.24 to 0.65; P<0.001 Percent of patients with rCDI at 24 weeks 1. 19 (21%) 2. 44 (47%) RR 0.46; 95% CI 0.30 to 0.73; P<0.001	28%/4 28%/4 26%/4	Any AE 1. 84 (93%) 2. 84 (91%) TEAE 1. 46 (51%) 2. 48 (52%) Serious AE 1. 7 (8%) 2. 15 (16%) GI-related AE 1. 79 (88%) 2. 80 (87%) 95% CI NR for all	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IRS to active drug or placebo. Stratified by antibiotic regimen and age (< 65 yo or ≥ 65 yo). Baseline characteristics balanced between groups except for gender (53% females enrolled in placebo arm vs. 67% enrolled in active comparator arm). Performance Bias: Low. Participants and investigators blinded to treatment assignment. Detection Bias: Low. Placebo capsules matched fecal microbiota capsules in appearance. Blinded investigators determined if patients experienced rCDI. Attrition Bias: High. Attrition rates were higher in the placebo group, due to higher rates of rCDI in this group. Data missing for patients who withdrew early was imputed as rCDI. Reporting Bias: Low. Protocol available online. All outcomes reported as described. Other Bias: Unclear. Research supported by manufacturer. Many of the investigators report financial support or grants from the manufacturer. **Applicability**: Patient: Enrolled adults were primarily White. No data for pediatric patients. Intervention: FDA-approved regimen used. Comparator: Placebo was used to establish efficacy. Comparison to non-FDA approved fecal microbiota formulations or fecal microbiota enema for prevention of rCDI is unknown. Outcomes: Treatment success (defined as symptom resolution) at 8 weeks is a clinically relevant endpoint as defined in guidelines for rCDI. Setting: 56 sites in the US and Canada

Abbreviations: AE = adverse event; ARR = absolute risk reduction; CDI = *C. difficile* infection; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; FMT = fecal microbiota transplant; GI = gastrointestinal; HR = hazard ratio; IBS = irritable bowel syndrome; IRS = interactive response system; ITT = intention to treat; mos = months; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo-controlled; PO = oral; PP = per protocol; rCDI = recurrent *C.difficile* infection; RCT = randomized controlled trial; RR = relative risk; TEAEs = treatment-emergent adverse events; yo = years old.

References:

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Appendix 1: Prescribing Information Highlights

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

VOWST (fecal microbiota spores, live-brpk) capsules, for oral administration
Initial U.S. Approval: YYYY

----------INDICATIONS AND USAGE----------
VOWST is indicated to prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI). (1)

Limitation of Use:
VOWST is not indicated for treatment of CDI.

----------DOSAGE AND ADMINISTRATION----------
For oral administration only. (2)
- Prior to taking the first dose:
  - Complete antibacterial treatment for rCDI 2 to 4 days before initiating treatment with VOWST. (2.1)
  - Drink 296 mL (10 oz) of magnesium citrate on the day before and at least 8 hours prior to taking the first dose of VOWST. In clinical studies, participants with impaired kidney function received polyethylene glycol electrolyte solution (250 mL GoLYTELY, not approved for this use). (2.1)
- The dosage of VOWST is 4 capsules taken orally once daily for 3 consecutive days. (2.2)
- Take each dose (4 capsules) on an empty stomach prior to the first meal of the day. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsule. A single dose is 4 capsules. (3)

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

----------ADVERSE REACTIONS----------
Most common adverse reactions (reported in ≥5% of participants) were abdominal distension (31.1%), fatigue (22.2%), constipation (14.4%), chills (11.1%) and diarrhea (10.0%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aimmune Therapeutics, Inc. at 1-833-246-2566 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Antibacterials should not be administered concurrently with VOWST. (7)

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

Revised: M/YYYY

Prevention of Recurrent *Clostridioides difficile*-Associated Infection

Goal(s):

- To optimize appropriate prevention of recurrent *Clostridioides difficile*-associated infection (CDI). Recurrent CDI is defined by Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.

Length of Authorization:

- Bezlotoxumab (ZINPLAVA): One-time infusion
- Fecal microbiota, live-jslm (REBYOTA): One-time rectal administration
- Oral fecal microbiota spores, live-brpk (VOWST): 4 capsules once daily x 3 days (12 capsules total)

Requires PA:

- Drugs approved to prevent recurrence of CDI:
  - Bezlotoxumab for intravenous infusion (physician administered and pharmacy claims)
  - Fecal microbiota, live-jslm suspension for rectal administration (physician administered and pharmacy claims)
  - Oral fecal microbiota spores, live-brpk (pharmacy claims)
  - Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the indication match the FDA-approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for an FDA approved-age?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the request for bezlotoxumab?	**Yes**: Go to #5	**No:** Go to #7
5. Is this recurrent of *Clostridioides difficile*-associated infection (CDI) within 6 months of CDI **OR** Is the patients presenting with a primary CDI episode and has other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host, or severe CDI on presentation)? * *Per 2021 IDSA/SHEA guidance[1]	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient currently receiving vancomycin or fidaxomicin?	**Yes**: Approve one dose	**No**: Pass to RPh. Deny; medical appropriateness
7. Is this the second or more recurrence of a Clostridioides difficile-associated infection? * *Per 2021 ACG and 2022 NICE guidance[2,3]	**Yes:** Go to # 8	**No**: Pass to RPh. Deny; medical appropriateness
8. Will the patient have recently completed a 10-day course of vancomycin or fidaxomicin prior to starting therapy?	**Yes**: Approve for 1 course of treatment (see Length of Authorization)	**No**: Pass to RPh. Deny; medical appropriateness

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Drug Class Review: Immunotherapy Desensitization, non-injectable

Date of Review: August 2023 **End Date of Literature Search:** 03/24/2023

Purpose for Class Review:
Evaluate new evidence for the safety and efficacy of oral peanut allergen powder (PALFORZIA) published since the 2021 Pharmacy and Therapeutics (P & T) Committee review of this product. Review evidence for the safety and efficacy of sublingual immunotherapy (SLIT) tablets in preventing allergic rhinitis associated with an allergy to grass, ragweed, or dust mites. Develop an Oregon Health Plan (OHP) policy to assess medical appropriateness in children and adolescents up the age of 21 years for non-injectable desensitization immunotherapies that are not funded under OHP under Medicaid provisions but may be covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit. In addition, develop a policy for use of desensitization immunotherapies that are funded in the OHP population.

Plain Language Summary:
- Peanut allergies can cause a range of mild to severe symptoms when people are exposed to or consume peanuts. Mild symptoms include tingling of the tongue and lips and can progress to severe, life-threatening symptoms such as tongue swelling or difficulty breathing.
- PALFORZIA capsules and packets received Food and Drug Administration approval in 2020 for patients aged 4 to 17 years with a history of a serious reaction to peanuts and confirmed peanut allergy through testing. This product reduces the severity of symptoms someone with a peanut allergy will experience when exposed to peanuts.
- People who are allergic to grass, ragweed, or dust mites may develop long lasting hay fever symptoms including a runny nose, sneezing and red, itchy eyes. Injecting small amounts of the agents that trigger the allergy, also known as allergy shots, has proven to be an effective way to develop tolerance and reduce these symptoms over time. This is known as desensitization. Allergy shots must be given in a doctor's office so that rare, but serious side effects can be immediately treated, if they occur.
- Tablets that are dissolved under the tongue (known as sublingual tablets) are another treatment option. These tablets can be taken at home and have less risk of serious side effects than allergy shots. Four different products are approved in the United States to help prevent the severity and frequency of allergy symptoms when exposed to grass, ragweed, or dust mites. GRASTEK AND ORALAIR are used in people with a grass allergy. RAGWITEK is approved for people with allergy to ragweed and ODACTRA is used in people with a dust mite allergy.
- Some people notice mild swelling or itching of the lips when first starting allergy therapy. In most cases, these symptoms will decrease over time as people continue taking the tablets. If serious symptoms develop, such as difficulty breathing or throat swelling, medical attention should be immediately received.
- Providers must explain to the Oregon Health Authority why someone needs sublingual immunotherapy before Medicaid will pay for it. This process is called prior authorization.

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Research Questions:

1. Is there new evidence or guidance for the prevention of serious reactions to peanuts using oral powder (PALFORZIA) in people with an allergy to peanuts?
2. What is the evidence for the efficacy of SLIT tablets in the treatment of allergic rhinitis (with or without conjunctivitis) caused by hypersensitivity to grass, ragweed, or dust mites?
3. What is the evidence for the safety of SLIT tablets in the treatment of allergic rhinitis (with or without conjunctivitis) caused by hypersensitivity to grass, ragweed, or dust mites?
4. Are there subpopulations (based on age, gender, ethnicity, or comorbidities) more at risk for efficacy or harm for treatment of allergic rhinitis with immunotherapy?

Conclusions:

Prevention Of Peanut Allergy

- The National Institute for Health And Care Excellence (NICE) published recommendations in February 2022 to guide the utilization of PALFORZIA.[1] Based on clinical trial evidence that shows PALFORZIA improves tolerance to peanut protein compared with placebo in a food challenge test, PALFORZIA is recommended as an option to treat peanut allergy in children aged 4 to 17 years.[1]

Evidence Summary for the Safety And Efficacy Of Sublingual Immunotherapy

- Evidence for the safety and efficacy of SLIT tablets in the treatment of allergic rhinitis and/or conjunctivitis is evaluated in 5 high-quality systematic reviews.[2-6] Three guidelines provide recommendations for the use of SLIT tablets in allergic rhinitis.[7-9] Data for safety of SLIT tablets in patients with asthma and allergic rhinitis are summarized in 3 systematic reviews,[10-12] and recommendations are presented in 2 guidelines.[13,14]

Sublingual Immunotherapy in Patients with Allergic Rhinitis or Conjunctivitis

- A 2010 Cochrane systematic review evaluated the safety and efficacy of SLIT tablets and oral immunotherapy drops for allergic rhinitis with or without conjunctivitis in children and adults.[2] Primary outcomes included symptom scores and use of relevant rescue medications (antihistamines and nasal corticosteroids).[2] Moderate-quality evidence showed a significant reduction in symptoms (standardized mean difference [SMD] -0.49; 95% confidence interval [CI] -0.64 to -0.34, P<0.00001) and rescue medication requirements (SMD -0.32; 95% CI -0.43 to -0.21, P<0.00001) in participants receiving SLIT compared to placebo.[2] Patients reported improved quality of life when allergic rhinitis symptoms such as red, itchy eyes, runny nose and sneezing were alleviated. None of the trials included in this review reported severe systemic reactions or anaphylaxis, and none of the reported systemic reactions required the use of epinephrine.[2]
- A 2011 Cochrane systematic review and meta-analysis of double-blind, placebo-controlled RCTs evaluated the efficacy of SLIT tablets and oral immunotherapy drops for treating allergic conjunctivitis in patients with or without rhinitis.[3] Moderate-quality evidence from 36 RCTs (n=3,399) showed SLIT significantly reduced total ocular symptom scores (SMD, -0.41; 95% CI, -0.53 to -0.28; P<0.00001) when compared with placebo in the targeted population.[3] Individual ocular symptoms scores showed a significant reduction with SLIT versus placebo in patients with allergic conjunctivitis (moderate-quality evidence for all outcomes) for red eyes (SMD, -0.34; 95% CI, -0.45 to -0.22; P<0.00001), itchy eyes (SMD, -0.31; 95% CI, -0.42 to -0.20; P<0.00001) and watery eyes (SMD, -0.23; 95% CI, -0.34 to -0.11; P=0.0001).[3]
- A 2013 Canadian Agency for Drugs and Technologies (CADTH) report evaluated evidence for the safety and efficacy of 5-grass pollen allergen extract (ORALAIR) in managing allergic rhinitis.[7] The 5-grass pollen extract was shown to be superior to placebo for alleviating allergic rhinitis symptoms in 4 double-blind randomized controlled trials (RCTs).[7] Most adverse events reported in the 4 RCTs were mild or moderate in severity.[7] Based on this report, the Canadian Drug Expert Committee (CDEC) recommended the 5-grass pollen allergen extract be listed on the Canadian drug formulary for the seasonal treatment of grass pollen allergic rhinitis if: 1) patients have not adequately responded to, or tolerated, conventional pharmacotherapy and 2) treatment is initiated by an allergist.[7]

- A 2015 CADTH systematic review evaluated evidence for the safety and efficacy of timothy grass allergenic extract (GRASTEK) in patients with allergic rhinitis, with or without conjunctivitis.[4] Seasonal treatment with timothy grass extract sublingually once daily resulted in statistically lower symptom scores and rescue medication use over one grass pollen season compared with placebo.[4] However, the clinical importance of the observed between-treatment differences in symptom and medication scores was uncertain.[4] Based on the conclusions of this systematic review, the CDEC recommended timothy grass allergenic extract not be listed on the Canadian drug formulary.[4]
- A 2020 systematic review and meta-analysis assessed the efficacy of SLIT tablets in the management of grass pollen-induced allergic rhinitis in adults.[5] The primary outcome measure was change in a 4-point symptom score (0=no symptoms and 3=severe symptoms) based on the World Allergy Organization (WAO) guidance in which 6 symptoms were evaluated (nasal obstruction, sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and tearing).[5] In the meta-analysis of 5 studies, SLIT reduced symptoms compared with placebo (SMD, -0.36; 95% CI, -0.46 to -0.25; P<0.00001; moderate-quality evidence).[5] The studies reported only mild, local adverse events related to treatment.[5] Oral pruritus and dyspepsia were the most commonly reported adverse events.[5]
- A 2017 systematic review assessed the effectiveness and safety of allergen immunotherapy in the management of allergic rhinoconjunctivitis.[6] The European Academy of Allergy and Clinical Immunology (EAACI) taskforce based their guideline recommendations on the findings from this systematic review.[8] The primary outcome was effectiveness, as assessed by symptom resolution and rescue medication scores.[6] Pooled data from 58 subcutaneous immunotherapy (SCIT) and SLIT randomized controlled trials (RCTs) suggested a moderate effect on short term (less than 2 years) improvement in symptom scores in favor of immunotherapy versus placebo (SMD, -0.53; 95% CI, -0.63 to -0.42; p<0.0001; low-quality evidence).[6] Data pooled from 15 RCTs showed a small-to-moderate effect in favor of immunotherapy versus placebo on the combined endpoint of symptom and rescue medication scores (SMD, −0.49; 95% CI, −0.69 to −0.30; p<0.001; low-quality evidence).[6] Safety data from 51 SCIT and SLIT RCTs were pooled to provide an overall risk ratio (RR) of experiencing an adverse event of 1.64 with SLIT treatment (95% CI, 1.43 to 1.89; p=0.00; low-quality evidence).[6]
- A 2017 guideline published by EAACI provides recommendations for the use of allergen immunotherapy to manage allergic rhinoconjunctivitis in adults and children.[8] Sublingual immunotherapy with grass pollen tablets or house dust mite (HDM) tablets is recommended to manage allergic rhinitis for short-term and long-term benefit (i.e., 1 year after cessation of treatment) in adults and children (Grade of Recommendation: A; Evidence Level: 1).[8]
- An allergen immunotherapy practice parameter was published by a joint task force of American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) members in 2017.[9] At the time of writing, 3 Food and Drug Administration (FDA)-approved SLIT tablets were available to alleviate allergic rhinitis symptoms associated with ragweed, timothy pollen, and 5-grass pollen.[9] Only FDA-approved SLIT tablets are recommended in this guidance for the treatment of allergic rhinitis and/or rhinoconjunctivitis and not for any other related or unrelated condition. (Strength of Recommendation: Strong; Evidence: A/B).[9]

Safety And Efficacy Of Sublingual Immunotherapy In Patients With Allergic Rhinitis And Asthma

- A 2018 Agency for Healthcare Research and Quality (AHRQ) review evaluated the efficacy and safety of immunotherapy for treating allergic asthma.[10] The majority of studies that met inclusion criteria included patients with mild to moderate asthma and dust mite allergies.[10] Moderate-quality evidence shows decreased use of long-term asthma control medications (specifically inhaled corticosteroids [ICS]) and improvements in forced expiratory volume in one second (FEV_1) with SLIT therapy.[10] Low-quality evidence shows SLIT administration may decrease quick-relief medication use (i.e., short-acting beta agonists [SABAs]), and may improve quality of life.[10] Local and systemic allergic reactions were common but infrequently required changes in immunotherapy treatment.[10] Life-threatening reactions were not commonly reported, with 3 case reports of anaphylaxis and no deaths (moderate-quality evidence) reported.[10]
- A 2020 Cochrane review updated a 2015 review that assessed safety and efficacy of SLIT compared with placebo in adults and children with asthma.[11] Participants were recruited with mild or intermittent asthma, often with comorbid allergic rhinitis.[11] Primary outcomes for this review included asthma exacerbations requiring a visit to the emergency department (ED) or admission to hospital, and all-cause serious adverse events (SAEs). The pooled estimate

from 2 small studies (n=108) suggests the evidence for SLIT in reducing asthma exacerbations compared with placebo or usual care is very uncertain (odds ratio [OR] = 0.35, 95% CI 0.10 to 1.20; very low-quality evidence).[11] An analysis by risk difference (RD) suggests no more than 1 in 100 people with mild or intermittent asthma taking SLIT will have a serious adverse event (RD, −0.0004, 95% CI, −0.0072 to 0.0064; p=0.09; moderate-quality evidence).[11] The findings from this review suggests the role of SLIT for people with asthma requires further evaluation.[11]

- A 2022 systematic review evaluated the efficacy and safety of HDM SLIT tablets in people with allergic asthma.[12] Seven RCTs, 5 studies in allergic asthma (4 in adults and 1 in children), and 2 studies in patients with allergic rhinitis and asthma, met inclusion criteria.[12] Moderate-to high-quality evidence from 3 RCTs showed that dust mite SLIT effectively improved ICS use in adults and adolescents with asthma, but no treatment effect was observed in a group of pediatric patients with very mild asthma.[12] Two RCTs evaluated the efficacy of dust mite SLIT tablets in reducing asthma exacerbations in patients with partially controlled moderate-to-severe asthma, and their results were inconsistent.[12] One study in children with mild-to-moderate asthma found no benefit of SLIT.[12] The percentage of participants reporting at least 1 adverse effect ranged from 39% to 96.4% in the HDM tablet-treated group.[12] Among all adverse effects, local adverse effects were the most common.[12] Of the 7 included studies, only one RCT reported 7 subjects treated with epinephrine due to adverse effects.[12] Three subjects used epinephrine for 12 standard quality (SQ)-HDM-related adverse effects. The other 4 epinephrine administrations were considered unrelated to 12 SQ-HDM, as 3 were related to food/environmental allergies, and 1 (in the placebo group) was related to complex allergy symptoms.[12]
- In 2017 the EAACI taskforce published a guideline to provide recommendations for the use of allergen immunotherapy to prevent comorbidities in patients with allergic rhinitis.[13] In children and adolescents with allergic rhinitis and grass pollen allergy, who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-year course of SCIT or SLIT can be recommended for the short-term (i.e., less than 2 years) prevention of asthma in addition to the sustained effect on allergic rhinitis symptoms and medication use. (Grade of Recommendation: A; Level of Evidence: 1).[13] This is a moderate recommendation based on consistent significant results from 2 moderate and 2 high risk of bias (ROB) RCTs and some controlled before and after studies.[13]
- In 2019 the EAACI taskforce developed a clinical practice guideline providing evidence-based recommendations for the use of HDM allergic immunotherapy as add-on treatment for HDM-driven allergic asthma.[14] To date, only immunotherapy with HDM SLIT tablets has demonstrated a robust effect in adults for critical end points (exacerbations, asthma control, and safety) in 3 RCTs funded by the manufacturer.[14] The EEACI taskforce recommends HDM SLIT tablets as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma to decrease exacerbations and to improve asthma control (conditional recommendation; moderate-quality evidence).[14] The patient's asthma status should be carefully evaluated prior to initiating HDM SLIT-tablets and assessed regularly during immunotherapy treatment.[14]

Recommendations:

- Add GRASTEK, ORALAIR, RAGWITEK, AND ODACTRA sublingual tablets to the Preferred Drug List (PDL) class "immunotherapy desensitization, non-injectable" as non-preferred medications.
- Develop prior authorization (PA) criteria to provide an approval route for unfunded conditions that will be covered under the EPSDT program and to ensure appropriate utilization of SLIT tablets in people with allergic rhinitis caused by exposure to grass, pollen, or dust mite allergens that is complicated by a comorbidity such as asthma.
- Review medication costs in the executive session.

Background:

Peanut Allergy Desensitization

Peanut allergy is estimated to affect approximately 2% of children,[15] and is an important cause of food allergy-related mortality.[16] Currently, the only Food and Drug Administration (FDA)-approved immunotherapy to mitigate severe reactions to peanut exposure is oral peanut allergen powder (PALFORZIA). This product received FDA-approval in 2020 for use in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy. The Oregon Health Plan (OHP) prioritized list includes funding for peanut allergy treatment in Guideline Note 203.[17] Funding for pharmaceutical treatment with medications to reduce severity are included on line 123 when specified criteria are met.[17] Peanut allergy must be diagnosed clinically based on history of serious reaction or anaphylaxis, with skin or serologic testing, and with a double-blind, placebo-controlled food challenge. Any treatment must be by, or in consultation with, an allergist or immunologist.[17] The P & T Committee reviewed the safety and efficacy of PALFORZIA at the February 2021 meeting. Recommendations to create a Preferred Drug List (PDL) class titled "Immunotherapy Desensitization" and designate PALFORZIA (powder capsules/packet) as non-preferred with PA criteria (**Appendix 3**) to ensure appropriate use were approved by the P & T Committee.

Pollen and Dust Mite Desensitization

Allergic rhinitis is divided into seasonal allergic rhinitis, which can be triggered by exposure to grass and ragweed pollens, and perennial allergic rhinitis in which dust mites are the primary trigger.[18] It is characterized by a type I hypersensitivity response, in which repeated allergen exposure results in histamine release by means of mast cell degranulation.[19] Symptoms of allergic rhinitis include sneezing, nasal congestion, nasal and oral pruritus, and rhinorrhea. Associated conditions, such as conjunctivitis, asthma and atopic dermatitis may contribute to the allergic response.[20] Symptom severity varies from mild to severe, with nasal congestion having the largest impact on quality of life.[20] Allergic rhinitis affects about 10% to 30% of adults and 40% of children worldwide.[21] Rhinitis is also a significant cause of decreased work productivity and absenteeism and school performance.[22] Allergic rhinitis can, by itself, introduce significant inattention, impairment of cognition, and decreased daytime school performance.[22] Quality of life issues associated with rhinitis include disturbed sleep; daytime somnolence and fatigue; irritability; depression; impairment of physical and social functioning; and attention, learning, and memory deficits.[22]

Mild-to-moderate allergic rhinitis is managed with intranasal antihistamines, while moderate-to-severe cases require intranasal corticosteroid therapy. The AAAAI 2020 rhinitis guideline suggests clinicians offer intranasal antihistamines as an initial treatment option for patients with seasonal allergic rhinitis (strength of recommendation: strong; high-quality evidence).[22] When selecting monotherapy for persistent allergic rhinitis, intranasal corticosteroids are the preferred medication (strength of recommendation: strong; high-quality evidence).[22] For the initial treatment of moderate- to severe-seasonal allergic rhinitis in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over a leukotriene antagonist (strength of recommendation: strong; high-quality evidence).[22] Initial treatment with intranasal corticosteroid monotherapy in patients 12 years of age and older with symptoms of seasonal allergic rhinitis is preferred over combination therapy with an oral antihistamine and an intranasal corticosteroid (strength of recommendation: strong; moderate-quality evidence).[22]

Seasonal and perennial allergic rhinitis, are not currently funded by OHP, unless these conditions complicate a co-morbidity such as asthma. The nasal allergy inhalers were reviewed by the P & T Committee at the August 2022 meeting. The Committee approved a recommendation to remove PA criteria for preferred intranasal allergy products in children and adolescents with rhinitis up to their 21st birthday to enhance the ability to grow, develop, or participate in school per the EPSDT Medicaid benefit. All intranasal products require PA for OHP funded indications. Fluticasone propionate is the only preferred drug on the preferred drug list (PDL) and all other intranasal corticosteroids are non-preferred and use for OHP-funded conditions is restricted by PA criteria. Non-steroidal intranasal allergy drugs are non-preferred due to lack of evidence for OHP-funded conditions.

Immunotherapy is an alternative therapy for treatment-resistant allergic rhinitis. Allergen immunotherapy involves the repeated administration of allergen extracts to individuals who have symptoms upon allergen exposure and immunoglobulin E (IgE)-sensitization to environmental triggers.[23] Allergen immunotherapy is effective in patients with allergic rhinitis and, unlike antihistamines, leukotriene antagonists, or intranasal corticosteroid nasal sprays, has been shown to modify the underlying immunologic cause of the allergic response.[24] The OHP prioritized list includes funding guidance for allergen testing and treatment in Guideline Note 156.[17] Testing and treatment are funded when the following criteria are met: 1) the allergy affects a diagnosis that appears above the current funding line (e.g., asthma, anaphylactic shock, occupational lung disease, immune disorder); 2) symptoms are not adequately controlled by empiric conservative therapy; 3) testing correlates to the member's history, risk of exposure, and physical findings; and 4) test technique and/or tested allergens have proven efficacy demonstrated through scientifically valid medical studies published in peer-reviewed literature.[17] Treatment is funded when a skin test and/or serologic evidence of IgE-mediated antibody to a potent extract of the allergen has been obtained and hypersensitivity to the allergen cannot be adequately managed by allergen avoidance or appropriate medication therapy.[17]

For many years, subcutaneous allergen immunotherapy was the gold standard to manage allergic rhinitis induced by seasonal exposure to pollen and for perennial disease in patients with dust mite allergy.[24] Due to the risk of severe systemic reactions, SCIT must be administered by a healthcare provider.[18] To maintain immunity, the injections must be administered every 2 to 4 weeks. Sublingual immunotherapy emerged in 2014 as an effective and safe alternative to SCIT due to less risk of systemic adverse events and ease of self-administration via a tablet taken once daily.[24] Sublingual immunotherapy products are available as dissolvable tablets or liquid extracts. Liquid products are used in other parts of the world, but are not approved by the FDA. Sublingual formulations may still result in minor local side effects, such as oropharyngeal swelling and pruritus. Sublingual tablets are FDA-approved to mitigate allergic rhinitis (with or without conjunctivitis) induced by exposure to certain types of pollen or dust mites.[25-28] The allergy must be confirmed by a positive skin test or in vitro testing for pollen-specific IgE antibodies prior to initiating therapy.[25-28] The 4 FDA-approved SLIT products are described in **Table 1**.

Table 1. FDA-Approved Sublingual Immunotherapy Tablets

Product Name (BRAND NAME)	How Supplied	Approved Age Range	When to Initiate Therapy	Common Adverse Events	Notes
Timothy Grass Pollen Allergen Extract (GRASTEK)[25]	2,800 BAU tablet	5 to 65 yo	Start 12 weeks prior to expected onset of grass season and continue through grass season.	Oral, ear and tongue pruritus, throat irritation, and mouth edema	Trials did not allow people with moderate or severe asthma or those requiring daily controller therapy.
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergy Extract (ORALAIR)[27]	100 IR and 300 IR tablets		Start 16 weeks prior to expected onset of respective grass season and continue through grass season.	Oral, ear, and tongue pruritus, throat irritation, mouth edema, cough, oropharyngeal pain, tonsillitis, and oral paresthesias	
Short Ragweed Pollen Allergen Extract (RAGWITEK)[28]	12 Amb a 1-Unit tablet		Start 12 weeks prior to expected onset of ragweed season and continue through ragweed season.	Oral, ear, and tongue pruritus, throat irritation, and oral paresthesias	Trials allowed patients who required low doses of inhaled glucocorticoids to treat asthma.
House Dust Mite Allergen Extract (ODACTRA)[26]	12 SQ-HDM tablet	12 to 65 yo	Start anytime and continue daily administration until discontinued by provider.	Oral and ear pruritus, swelling of lips or tongue, and throat irritation	Trials allowed patients with mild-to-moderate asthma that required, at most, a medium

					daily dose of an inhaled glucocorticoid to treat asthma.
Abbreviations: Amb a = Ambrosia artemisifolia (short ragweed); BAUs = Bioequivalent Allergy Units; FDA = Food and Drug Administration; SQ-HDM = Standardized-Quality House Dust Mite units; IR = Index of Reactivity; SL = sublingual; yo = years old					

All 4 SLIT products contain a black boxed warning regarding the risk of severe allergic reactions, including anaphylaxis and severe laryngopharyngeal restriction, and are contraindicated in patients with severe, unstable, or uncontrolled asthma.[25-28] Additional contraindications are a history of eosinophilic esophagitis or any severe systemic allergic reaction. The first dose should be administered in the provider's office so the patient can be observed for any serious adverse effects for at least 30 minutes. An auto-injectable epinephrine device should be prescribed and the patient or caregiver educated on proper use of the device. None of the SLIT products are indicated for immediate relief of allergic symptoms.[25-28]

Approximately 50% of people with asthma also have environmental allergies.[10] Allergic asthma is triggered by inhaling airborne allergens.[10] Some of the SLIT clinical trials excluded patients with moderate or severe asthma as the risk of severe and fatal adverse events associated with immunotherapy in patients with severe or uncontrolled asthma is a significant contraindication.[25-28] Most of the evidence for use of SLIT in mild to moderate asthma is in patients with asthma complicated by allergic rhinitis induced by dust mite exposure.[29]

Specific allergen immunotherapy improves the control of allergic diseases but does not completely alleviate symptoms in all patients, especially when the allergen load is heavy (e.g., peak pollen season).[30] Therefore, patients should be provided with appropriate rescue medication options such as an oral second-generation H1-antihistamine (once daily), inhaled short-acting beta2 bronchodilator (SABA), ocular H1-antihistamine, intranasal antihistamine, or oral corticosteroid (for short periods in the case of unresponsive/intolerable symptoms).[30]

There are currently no validated genetic or blood biomarkers for predicting or monitoring the efficacy of allergic immunotherapy in patients.[31] In 2007, the World Allergy Organization (WAO) taskforce published recommendations for standardizing allergen immunotherapy clinical trials.[30] Ordinal scales, days free of symptoms, days free of rescue medications, and symptom scores corrected for rescue medications were used as outcome measures in different trials without standardized methodology.[30] The most frequently used approach in SLIT clinical trials is a 4-point rating scale (from 0=absent to 3=severe) applied to each symptom of rhinoconjunctivitis including: nasal obstruction, sneezing, rhinorrhea, nasal itching and ocular itching.[30] Chest tightness, shortness of breath, cough and wheezing should also be considered in patients with concomitant lower airway symptoms.[30] Studies evaluating the symptom response to perennial allergens over a long period have used a visual analogue scale (VAS) to detect changes in symptom severity.[30] A 10-cm line to grade the severity of symptoms from "no symptoms" (0 cm) to "the highest level of symptoms" (10 cm) has been used.[30] In 2009, the WAO proposed a 20% mean reduction in total combined symptom scores (nasal, ocular, and bronchial) be considered a minimal clinically important difference (MCID) in evaluation of immunotherapy efficacy.[32]

For an allergen immunotherapy product to be approved by the FDA, two statistical criteria must be met: 1) point estimate: a difference of 15% in the total combined score (TCS) between active treatment and placebo must be demonstrated and 2) confidence interval: a lower bound of the 95% CI of the difference demonstrating at least a 10% separation between the two treatment groups must be demonstrated.[30] These statistical tests were selected after internal evaluation by the FDA and were mandated to identify and define a statistically significant and clinically meaningful therapeutic effect more clearly when comparing allergen immunotherapy with placebo.[30] For drug approval, the FDA requires demonstration of a statistically significant difference between SLIT and placebo and at least a 15% improvement in the total symptom scoring compared with placebo, while the WAO recommends a 20% improvement in TCS.[30,32]

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 1**, 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:
Cochrane: Sublingual Immunotherapy for Treating Allergic Rhinitis Due to Various Allergens
A 2010 Cochrane systematic review evaluated the safety and efficacy of SLIT tablets and drops for allergic rhinitis with or without conjunctivitis in children and adults with or without allergic asthma.[2] Patients' sensitivity was proven by positive skin prick tests and/or high specific IgE to a particular allergen.[2] This was an update of a 2003 Cochrane publication. Data was searched through August 14, 2009.[2] A total of 60 RCTs met inclusion critiera.[2] Forty-nine were suitable for pooling in meta-analyses (n = 4589).[2] Most trials evaluated SLIT in patients with allergy to grass pollen (23 studies).[2] Other allergens included: stinging nettle (5 trials), ragweed (2 trials), trees (9 trials), HDM (8 trials) and cat dander (one trial).[2] Thirty-four studies were performed in adults and 15 studies were in children.[2] Treatment lasted for less than 6 months in 17 studies; 6 to 12 months in 16 studies and longer than 12 months in 16 studies.[2] Sublingual tablets were used in 11 studies (n = 1881) and in 35 studies (n = 2464) patients received sublingual drops.[2]

All 60 studies were double-blind, RCTs of parallel-group design. Concealment of treatment allocation was considered adequate in all studies.[2] Blinding of study subjects and investigators was maintained by the use of identical placebo preparations.[2] However, most investigators reported high levels of minor oral side effects (tingling, itching and swelling beneath the tongue) in actively treated subjects, which could influence blinding.[2]

Primary outcomes included symptom scores and use of relevant rescue medications.[2] Overall, moderate-quality evidence from 49 RCTs (n = 4589) showed a reduction in symptoms (SMD -0.49; 95% CI -0.64 to -0.34, P<0.00001; I^2 = 81%) and rescue medication requirements (SMD -0.32; 95% CI -0.43 to -0.21, P<0.00001; I^2 = 50%), favoring SLIT over placebo.[2] In a subgroup analysis of people with seasonal allergens, 39 RCTs (n = 4084) showed symptom scores were significantly reduced with SLIT compared to placebo; the combined SMD was -0.34 (95% CI -0.44, -0.25, P<0.00001; I^2 = 45%).[2] The 10 RCTS (n = 505) in people with perennial allergen also showed a significant reduction in symptoms with immunotherapy versus placebo (SMD -0.93; 95% CI -1.69 to -0.17; P=0.02; I^2 = 92%).[2] There was significant heterogeneity between all studies.[2]

Six RCTs (n = 251) reported no adverse events with SLIT during the trials.[2] Twenty-two studies reported different reactions observed with SLIT administration including buccal pruritus, lip edema, lip swelling, throat irritation, and gastrointestinal symptoms.[2] None of the trials included in this review reported severe systemic reactions or anaphylaxis, and none of the reported systemic reactions required the use of epinephrine.[2] This 2010 review reinforces the conclusion of the original 2003 Cochrane systematic review that SLIT is effective for allergic rhinitis and is a safe route of administration.[2]

Cochrane: Sublingual Immunotherapy for Treating Allergen-Induced Conjunctivitis

A 2011 Cochrane systematic review evaluated the efficacy of SLIT compared with placebo for treating allergic conjunctivitis, a comorbidity of allergic rhinitis.[3] Literature was searched through January 2011 to identify double-blinded RCTS of sublingual drops or tablets in children and adults with allergic conjunctivitis.[3] Forty-two trials (n = 3958) met inclusion criteria.[3] Heterogeneity among studies was around 50% or below for all endpoints.[3] Thirty-five (88%) of the included studies evaluated the efficacy of seasonal allergens (i.e., grass, pollen) while 7 (12%) trials were in people with perennial allergens (i.e., dust mites).[3] Nineteen trials used grass pollen extracts, 10 evaluated tree pollen extracts, 6 trials evaluated mites, 6 evaluated weeds and one study assessed the efficacy of a standardized cat extract.[3] All studies compared SLIT with placebo in double-blind RCTs.[3] Thirty-one (74%) studies administered the extracts as sublingual drops, 9 (21%) as tablets and 2 (5%) studies examined drops during the build-up phase and subsequently switched to tablets for the maintenance phase.[3] The median duration of therapy was 12 months (range 3 to 36 months).[3] Most studies were of moderate quality due to selection bias (unclear allocation concealment or randomization).[3]

The primary outcome was total ocular symptom scores. Thirty-six RCTs (n=3,399) showed SLIT treatment resulted in a reduction of total ocular symptom scores compared to placebo (SMD -0.41; 95% CI -0.53 to -0.28; P<0.00001; I^2 = 59%; moderate-quality evidence).[3] A subgroup assessment according to the allergen type was also analyzed. Thirty RCTs showed a reduction in total ocular symptom scores in people with seasonal allergies treated with SLIT compared to placebo (SMD -0.38; 95% CI -0.50 to -0.25; P<0.00001; I^2 = 58%; moderate-quality evidence).[3] The 6 RCTs that studied the effect of SLIT treatment on ocular symptoms in people with perennial allergies showed no difference from placebo (SMD -0.52; 95% CI -1.05 to 0.01; P=0.05; I^2 = 70%; low-quality evidence).[3]

Secondary outcomes included individual ocular symptoms scores (redness, itching, watery eyes), use of eye drops, and conjunctival allergen sensitivity. Compared with placebo, moderate-quality evidence showed that SLIT induced a significant reduction in individual ocular symptom scores compared to placebo for red eyes (SMD -0.33; 95% CI -0.45 to -0.22; P<0.00001; I^2 = 27%), itchy eyes (SMD -0.31; 95% CI -0.42 to -0.20; P<0.00001; I^2 = 46%), and watery eyes (SMD -0.23; 95% CI -0.34 to -0.11; P<0.0001; I^2 = 42%).[3] No reduction was observed in the use of ocular eye drops in the 13 RCTs that reported this outcome (SMD -0.10; 95% CI -0.22 to 0.03; P=0.13; I^2 = 34%; moderate-quality evidence).[3] Four RCTs (n=250) evaluated the effect of SLIT on conjunctival immediate allergen sensitivity using a conjunctival allergen provocation test, where topical allergen is applied to the external ocular surface to assess inflammatory response in a suspected sensitized patient.[3] Participants who received SLIT showed an increase in the threshold dose for the conjunctival allergen provocation test compared to placebo (SMD 0.35; 95% CI 0.00 to 0.69; P=0.05; I^2 = 43%; moderate-quality evidence).[3]

This systematic review provides moderate-quality evidence which confirms SLIT reduces both the total and individual ocular symptom scores for red eyes, itchy eyes, and watery eyes in patients with rhinoconjunctivitis when compared to placebo.[3] Moderate-quality evidence showed these reductions were evident with tablets and drops when the studies assessed seasonal allergens but not perennial allergens (low-quality evidence).[3] These differences could be explained by the paucity of studies evaluating perennial allergens (n=6) and the small numbers of participants analyzed for this outcome (n=219).[3] Increasing the duration of treatment beyond 12 months did not affect the treatment effect (12 months or less: SMD -0.43; P<0.0001; I^2 = 58%, and greater than 12 months: SMD -0.43; P<0.01; I^2 = 68%; moderate-quality evidence).[3]

Canadian Agency for Drugs and Technologies: Timothy Grass (Phleum pratense) Allergenic Extract

A 2015 CADTH systematic review evaluated evidence for the safety and efficacy of GRASTEK, also known as *Phleum pratense* allergenic extract (PPAE), in patients with allergic rhinitis, with or without conjunctivitis. [4] Literature was searched through February 7, 2014.[4] Eight placebo-controlled RCTs in adults and children aged 5 years and older met inclusion critieria.[4] Five RCTs involved adults, 2 studies involved pediatric patients, and one study involved a mixed population of adults and children.[4] In most of the studies, PPAE therapy was started 8 weeks before the onset of grass pollen season and continued for 24

weeks.[4] Key efficacy outcomes included symptom relief, use of rescue medications (antihistamines, corticosteroids, decongestants, eye drops, and leukotriene inhibitors), and health-related quality of life.

Daily symptom scores (DSS) were measured using a 4-point rating scale (0 to 3 points) of 6 symptoms (4 nasal symptoms and 2 ocular symptoms). The maximum total score was 18 points. Adjusted mean DSS over the entire grass pollen season were reported in all 8 studies and were lower for PPAE groups (range 2.18 to 5.69) compared with placebo groups (range 2.80 to 6.06).[4] Between-treatment mean differences ranged between –0.37 and –1.29, being statistically significant in 5 studies and non-significant in 3 studies.[4] The Daily Medication Scores (DMS) were based on the use of rescue medications. Protocol-specified rescue medications and scoring systems were different in each study.[4] The maximum possible DMS ranged from 12 to 38 across all 8 RCTs.[4] Adjusted mean DMS over the entire grass pollen season were reported in 8 eight studies and were lower with PPAE groups (range 0.78 to 2.60) compared with placebo groups (range 1.19 to 3.81).[4] Between-treatment differences ranged from –0.4 to –1.2, being statistically significant in 4 studies and non-significant in 4 studies.[4] Seasonal treatment with PPAE sublingually once daily resulted in statistically lower symptom scores and rescue medication use over one grass pollen season.[4] However, the clinical importance of the observed between-treatment differences in symptom and medication scores is uncertain.[4]

The total combined score (TCS) was a sum of the symptom and rescue medication scores. Adjusted mean TCSs over the entire pollen season were reported in 6 studies and were lower with PPAE (range 3.70 to 6.74) compared with placebo (range 4.86 to 7.53).[4] Between-treatment mean differences ranged from –0.8 to –2.3, being statistically significant in 5 studies and non-significant in one study.[4] The corresponding relative percentage differences in mean TCS ranged between –10% and –34%, being 20% or greater in 4 studies.[4] The between-treatment difference of 20% or more for the mean TCS (considered to be clinically meaningful by the WAO) was achieved in 5 of 6 studies reporting this outcome.[4] Although a between-treatment difference in the TCS of 20% or greater was achieved in a number of trials, the absolute differences in the TCS were small.[4] Small absolute differences can translate into large percentage differences when TCS scores are relatively low.[4]

Changes in health-related quality of life, as measured by the Rhinoconjunctivitis Quality Of Life Questionnaire (RQLQ), were not considered clinically meaningful.[4] Although immunotherapy was administered seasonally for several years, only one study examined the effects of PPAE over multiple seasons.[4] Despite findings of continuing efficacy over multiple treatment seasons, the findings are limited by the high (approximately 50%) and differential dropout after the first season.[4] Based on one long-term RCT, the beneficial effects of PPAE appear to be sustained over 3 subsequent years of seasonal treatment, with waning of effect in subsequent untreated years, but the validity of the long-term findings is limited by the large and differential dropout following the first grass pollen season.[4]

In all the included studies, adverse events were higher in the PPAE group compared with the placebo group and were reported as being mild or moderate in severity.[4] The most frequently reported adverse events were those associated with the mouth or throat. The treatment durations were approximately 24 weeks, in most studies, but longer-term data (seasonal treatment over three years) available from an extension study did not reveal additional safety issues.[4] Serious adverse events and withdrawals due to adverse events were few and similar in both groups across the trials.[4] Three studies reported one death each in of the PPAE groups, but these were not considered to be related to PPAE.[4]

In summary, while many of the included studies reported statistically significant improvements with PPAE compared with placebo, in terms of DSS, DMS, and TCS, these scales have not been validated and the clinical significance of the observed differences is unclear.[4] In addition, there are a number of potential sources of bias, which may affect the validity of the above reported results.[4] Potential unblinding due to the more frequent experience of oral or pharyngeal adverse events in the PPAE group may have influenced patients' assessment of symptoms, quality of life, and need for rescue medication.[4] Knowledge of

treatment allocation may also have affected the frequency of diary entries regarding symptoms and medication.[4] The extent of missing data is unclear; however, differential missing data may bias results.[4] A key gap in the evidence for PPAE is the absence of RCTs directly comparing PPAE with other SLIT products.[4] Based on the conclusions of this systematic review, the Canadian Drug Expert Committee did not recommend PPAE be listed on the Canadian drug formulary.[4]

Allergen Immunotherapy for Allergic Rhinoconjunctivitis: A Systematic Review and Meta-Analysis

A 2017 systematic review assessed the effectiveness and safety of allergen immunotherapy in the management of allergic rhinoconjunctivitis in patients of any age.[6] The EAACI taskforce based their guideline recommendations on the findings from this systematic review.[13] Literature was searched through October 31, 2015.[6] One hundred thirty-two international RCTs met inclusion criteria.[6] Sixty-one RCTs evaluated SCIT (n = 6379) and 71 RCTs assessed SLIT (n = 13636 patients).[6]The quality of the SLIT studies was assessed to be low risk of bias (ROB) in 26 studies, high ROB in 16 studies and unclear ROB in 29 studies.[6] Overall, the quality of included SCIT studies was high.[6] Thirty-seven studies were found to be at low ROB, 8 studies at high ROB, and 16 were judged at unclear ROB.[6] The majority of studies only included adults.[6] A range of allergens were assessed including weed, tree and grass pollens, molds, cat and dog dander, and dust mites. A range of protocols were utilized and the overwhelming majority of trials only reported on short-term effectiveness.[6]

The primary outcome was therapy effectiveness, as assessed by symptom and medication scores.[6] Pooled data from 58 RCTS that assessed both SCIT and SLIT versus placebo showed a SMD of -0.53 (95% CI -0.63 to -0.42; p<0.0001; I^2 = 67%; low-quality of evidence) suggesting a moderate effect on short term (less than 2 years) symptom scores in favor of immunotherapy.[6] In a subgroup analysis of seasonal versus perennial allergens (SMD −0.37; 95% CI −0.45 to −0.28; p<0.159; I^2 = 22%; and SMD −0.91; 95% CI −1.47 to −0.36, p<0.0001; I^2 = 73%; respectively), low-quality evidence demonstrated benefit from both approaches.[6] Data pooled from 15 RCTs showed a small-to-moderate effect in favor of immunotherapy versus placebo on a combined endpoint of symptom and rescue medication scores (SMD −0.49; 95% CI −0.69 to −0.30; p<0.001; I^2 = 58%; low-quality evidence).[6] There is a limited body of evidence on the longer-term effectiveness of immunotherapy in improving symptom scores (2 low-quality RCTs).[6]

A secondary outcome was safety as reported by the incidence of adverse events. There was a great variation in reporting of adverse events and a number of grading scales including WAO and EAACI guidelines were used.[6] Some studies reported limited or unclear data on number of adverse events, some studies reported no data on adverse events, and others reported that no adverse events occurred at all through the duration of the trial period.[6] Conversely some studies reported all treatment emergent adverse events. Safety data for 51 SCIT and SLIT RCTs were pooled to give an overall risk ratio (RR) of experiencing an adverse event of 1.64 (95% CI 1.43 to 1.89; p=0.00; I^2 = 91%; low-quality evidence).[6] For SLIT studies (n=19 RCTs), an RR of 1.58 was calculated (95% CI 1.13 to 2.20; p=0.00; I^2 = 79%) of experiencing an adverse effect and for SLIT studies (n = 32 RCTs) an RR of 1.68 (95% CI 1.44 to 1.98 p=0.00; I^2 = 79%), suggesting a comparable safety profile for both modes of immunotherapy (low-quality evidence).[6]

Heterogeneity in outcome assessment approaches limited the effectiveness of this review as authors were unable to pool data from all trials or undertake all the planned subgroup analyses.[6] Furthermore, studies for which data was pooled also showed heterogeneity which may be related to the diverse populations studied, protocols followed, products used and duration of trial periods.[6] For the subgroup analyses, there was in some cases imprecision which impacted the ability to draw clear conclusions.[6] These subgroup analyses were indirect comparisons between SCIT and SLIT and the findings should therefore be cautiously interpreted.[6] Greater standardization of trial designs and reporting techniques would improve the research base underpinning immunotherapy.[6]

Sublingual Immunotherapy for Treating Grass Pollen-Induced Allergic Rhinitis

A 2020 systematic review and meta-analysis assessed the efficacy of SLIT in the management of adults with grass pollen-induced allergic rhinitis or allergic rhinoconjunctivitis.[5] Only sublingual tablets were included in the search; sublingual drops were excluded. Literature was searched through May 9, 2019. Of the

412 studies identified, 6 studies (n = 1971) met inclusion critiera.[5] Three studies evaluated GRASTEK and 3 studies assessed ORALAIR.[5] The risk of selection bias was high in 3 of the studies.[5] Overall, there was a low risk of bias for deviations from the intended interventions, missing outcome data and in selection of the reported result in all 6 RCTs.[5] There was some concern surrounding the method of randomization and allocation concealment process due to insufficient information in one RCT.[5] Another RCT resulted in high risk of bias due to issues with treatment adherence.[5]

The primary outcome measure was a 4-point symptom score (0 = no symptoms and 3 = severe symptoms) based on the WAO guidance on trial standardization in which 6 symptoms were evaluated (nasal obstruction, sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and tearing).[5] All studies reported an improvement in symptoms with SLIT compared to placebo, with 5 RCTs reaching statistical significance ($P<0.05$).[5] The adjusted mean difference ranged from -1.96 to -0.80 in the 5 RCTs that reported statistical significance.[5] In the meta-analysis, SLIT showed a significant reduction in symptoms compared with placebo (SMD -0.36; 95% CI -0.46 to -0.25; $P<0.00001$; $I^2 = 48\%$; moderate quality evidence).[5]

Participants in 4 studies withdrew due to adverse events in both active and placebo groups.[5] In the active group, the highest and lowest reported withdrawal was 7.2% and 0%, respectively, compared with 3.5% and 0% for the highest and lowest reported withdrawals in the control group, respectively.[5] Adverse events were limited to localized and mild pruritus and swelling of the mouth, tongue or eyes.[5] Oral pruritus was the most commonly reported adverse event.[5] Dyspepsia was reported in 22% of the active group participants.[5] Five studies reported only mild, local adverse events related to treatment.[5]
In summary, SLIT is generally safe with only minor adverse events. Meta-analysis of 5 RCTs shows that SLIT is associated with statistically significant improvement in symptom scores versus placebo.[5]

Agency for Healthcare Research and Quality: The Role of Immunotherapy in the Treatment of Asthma
A 2018 AHRQ review evaluated the efficacy and safety of SCIT and SLIT for treating allergic asthma.[10] Literature was searched through May 8, 2017.[10] Fifty-four RCTs met inclusion criteria for efficacy: 31 assessed SCIT and 18 assessed SLIT and 5 RCTS compared SCIT versus SLIT.[10] Seventy-five studies met inclusion criteria for the safety analysis: 26 RCTs and 18 non-RCTs for SCIT, 20 RCTs and 10 non-RCTs for SLIT and one non-RCT on SCIT versus SLIT.[10] The majority of studies that met inclusion criteria included adults with mild to moderate asthma with dust mite allergies.[10] The reviewers found insufficient evidence about the efficacy of SLIT in children.[10]

Moderate quality evidence shows SCIT reduces the use of long-term control medication.[10] Subcutaneous immunotherapy may improve quality of life, reduce the use of quick-relief medications (i.e., SABAs), reduce the need for systemic corticosteroids, and improve FEV_1 (low-quality evidence).[10] There was insufficient evidence regarding the effect of SCIT on asthma symptoms and health care utilization in adults.[10] There was insufficient evidence about the efficacy of SCIT in pediatric patients.[10] Local reactions to SCIT were frequent; however reactions also occurred with placebo (risk differences ranged from -0.317 to 0.4) and local reactions infrequently required a change in SCIT dosing (quality of evidence not reported).[10] Systemic allergic reactions to SCIT were frequently reported (risk differences ranged from 0 to 0.319; quality of evidence not reported).[10] The majority of systemic allergic reactions were mild, and only a small number was consistent with anaphylaxis and required treatment with epinephrine.[10] There was insufficient evidence to draw conclusions about whether SCIT increased risk of anaphylaxis, primarily because anaphylaxis was not directly measured.[10] There was one case report of a death determined possibly to be caused by SCIT.[10] High-quality evidence shows SLIT improves asthma symptoms as measured by validated instruments.[10] Moderate-quality evidence shows decreased use of long-term asthma control medication (specifically ICS) and improvements in FEV_1 with SLIT therapy.[10] Sublingual immunotherapy may decrease the use of SABAs and may improve quality of life (low-quality evidence).[10] There is insufficient evidence about the effect of SLIT on systemic corticosteroid use and health care utilization.[10] Local and systemic allergic reactions were common but infrequently required changes in treatment.[10] Life-threatening reactions were not

commonly reported, with 3 case reports of anaphylaxis and no deaths (moderate-quality evidence) reported.[10] There was insufficient evidence about the efficacy of SLIT in children.[10]

There was insufficient evidence to draw conclusions about the comparative effects of SCIT versus SLIT or for differential effects of immunotherapy based on patient age, setting of administration, or type of allergen.[10] Overall, SLIT and SCIT were beneficial for the majority of asthma-related outcomes assessed in this report.[10] Local and systemic allergic reactions were common but infrequently required changes in treatment.[10] Life-threatening events (such as anaphylaxis) were rarely reported.[10]

Cochrane: Sublingual Immunotherapy for Asthma
A 2020 Cochrane review updated a 2015 review that assessed safety and efficacy of SLIT compared with placebo in adults and children with asthma.[11] The literature search for this updated publication was conducted through October 29, 2019.[11] Trials that evaluated SLIT versus placebo, or as an add-on to standard asthma management were included in the search.[11] The target population was children and adults with asthma, rhinitis, or both, providing at least 80% of trial participants had a diagnosis of asthma.[11]

Sixty-six studies met the inclusion criteria for this update (n = 7944), including 52 studies from the original 2015 review.[11] Most studies were double-blind and placebo-controlled, varied in duration from one day to 3 years, and recruited participants with mild or intermittent asthma, often with comorbid allergic rhinitis.[11] Twenty-three studies recruited adults and teenagers; 31 studies recruited only children; 3 recruited both; and 9 did not specify the age of included population.[11] Patients with severe asthma were excluded from most of the studies, resulting in a study population consisting largely of participants with intermittent or mild symptoms.[11] Forty-seven studies examined dust mite allergy and 6 studies focused on grass pollen.[11] Other studies examined tree pollen, cockroach exposure or cat dander.

Reporting of primary efficacy outcomes to measure the impact of SLIT on asthma exacerbations and quality of life was infrequent, and selective reporting may have had a serious effect on the completeness of the evidence; 16 studies did not contribute any data, and a further 6 studies could only be included in a post-hoc analysis of all adverse events.[11] Allocation procedures were generally not well described; about a quarter of the studies were at high risk of performance or detection bias (or both); and participant attrition was high or unknown in around half of the studies.[11] About a quarter of the studies were at high risk for blinding because they used open-label study designs.[11]

Primary outcomes were asthma exacerbations requiring a visit to the ED or admission to hospital, validated measures of quality of life, and SAEs. The primary outcome in most studies did not align with those of interest to the review (mostly asthma or rhinitis symptoms), and only 2 small studies (n = 108) reported the primary outcome of exacerbations requiring an ED or hospital visit.[11] The pooled estimate from these studies suggests the evidence for SLIT in reducing asthma exacerbations is not statistically significant and is very uncertain (OR 0.35, 95% CI 0.10 to 1.20; very low-quality evidence).[11] Nine studies reporting quality of life could not be combined in a meta-analysis and, while the direction of effect mostly favored SLIT, the effects were often uncertain and small.[11]

In total, 56 of 3,086 SLIT-treated patients and 34 of 1,724 placebo-treated patients experienced an SAE.[11] In an analysis using risk differences suggests no more than 1 in 100 people with mild or intermittent asthma taking SLIT will have a serious adverse event (RD, −0.0004, 95% CI −0.0072 to 0.0064; p=0.90; n = 4810; 29 studies; moderate-quality evidence).[11] Twenty-seven studies (n=4,251) reported all adverse events, and 17 RCTs contributed to the meta-analysis.[11] Pooled results showed increased risk of experiencing an adverse event in the SLIT group compared with the placebo group (OR 1.99, 95% CI 1.49 to 2.67; high-quality

evidence), but events were usually reported to be transient and mild and rarely led to withdrawal from the trial.[11] The most frequently reported adverse events included oral discomfort, oral pruritis, and mouth edema.[11]

Secondary outcomes were asthma symptom scores, exacerbations requiring systemic corticosteroids, response to provocation tests, and dose of inhaled steroids. Asthma symptom and medication scores were mostly measured with non-validated scales, which prevented meaningful meta-analysis or interpretation, but there was a general trend of SLIT benefit over placebo.[11] Changes in ICS use (MD, −17.13 mcg/d, 95% CI −61.19 to 26.93; n = 778; 4 studies; low-quality evidence), exacerbations requiring oral steroids (2 studies; no events), and bronchial provocation (SMD 0.99, 95% CI 0.17 to 1.82; low-quality evidence) were not often reported.[11] Results were imprecise and included the possibility of important benefit or little effect and, in some cases, potential harm from SLIT.[11]

In summary, the evidence for important outcomes such as exacerbations and quality of life remains too limited to draw clinically useful conclusions about the efficacy of SLIT for people with asthma.[11] Trials mostly recruited mixed populations with mild and intermittent asthma and/or rhinitis and focused on non-validated symptom and medication scores.[11] The findings from this review suggest the role of SLIT for people with asthma requires further evaluation.[11]

Efficacy and Safety of House Dust Mite Sublingual Immunotherapy Tablets in Allergic Asthma
A 2022 publication reviewed the efficacy and safety of HDM SLIT tablets in people with allergic asthma.[12] Literature was searched through September 30, 2021.[12] Seven RCTs, 5 studies in allergic asthma (4 in adults and 1 in children), and 2 in allergic rhinitis with asthma, met inclusion criteria.[12] Six studies were double-blinded RCTs, and one was an open-label RCT. Five studies included patients with mild-to-moderate asthma, and 2 studies included patients with moderate-to-severe asthma.[12] Six studies used standardized quality (SQ)-HDM tablets, and 1 study used index reactivity (IR)-HDM tablets. Two studies were classified as having low risk of bias, 4 studies were classified as having some concerns of bias, and one study was rated as having a high risk of bias due to suspicion of selective results reporting.[12]

The primary outcome of interest was asthma control during ICS reduction after initiating HDM tablets.[12] Secondary asthma outcomes included: asthma exacerbation, Asthma Control Questionnaire (ACQ) score, Asthma Quality of Life Questionnaire score (AQLQ), the use of SABAs during follow-up, lung function scores, nasal symptoms, and adverse effects.[12]

A high-quality, double-blinded RCT in 604 patients aged 14 years or older with mild-to-moderate asthma concomitant with HDM allergic rhinitis was conducted to evaluate the effect of 6 SQ-HDM tablets in decreasing the use of ICS while maintaining asthma control.[12] The recruited patients were treated according to steps 1 to 3 of the GINA guideline and all the patients were taking similar daily doses of inhaled budesonide.[12] The primary end point was the lowest ICS dose needed to maintain asthma control. The difference in reducing the daily ICS dose between HDM tablets and placebo was 81 mcg (95% CI, 27 to 136 mcg/day; P=0.004).[12] Mean and median reductions from baseline in ICS dose were 42% and 50% for HDM tablets and 15% and 25% for placebo, respectively.[12] No statistically significant differences were observed for the other assessed asthma parameters, reflecting the intended controlled status of the trial subjects.[29] After 1 year of treatment, 34% of the patients in the HDM tablet group could completely discontinue ICS compared with 21% of those in the placebo group.[12]

A moderate quality, 8-month, double-blinded RCT in 111 children aged 5 to 15 years with asthma evaluated the effect of 300 IR-HDM tablets versus placebo.[12] Seventy-three and 36 patients had mild and moderate asthma, respectively.[12] At baseline, 50% of the patients had no asthma symptoms, and the use of SABAs was low, indicating that most patients in this study had well-controlled mild asthma.[12] The ICS dose was stepped-down after 5 months, 9 months, and

12 months of treatment by reducing the ICS dose of 20% to 30% at each stage, based on individual asthma status.[12] There was no significant difference detected between HDM tablets and placebo in improving ICS and SABA used, asthma symptoms scores, lung function, and rhinitis symptom score.

Another high-quality, multicenter, double-blinded RCT compared the efficacy between the 6 SQ- and 12 SQ-HDM tablets and placebo in 834 partially controlled moderate-to-severe asthmatic patients 18 years or older with concomitant dust mite-induced allergic rhinitis.[12] During the last 6 months of the trial, the HDM tablets significantly reduced the risk for a moderate or severe asthma exacerbation while reducing the ICS dose by 50% with a hazard ratio (HR) of 0.72 (95% CI 0.52 to 0.99; P=0.045) for the 6 SQ-HDM group, and HR of 0.69 (95% CI 0.50–0.96; P=0.03) for the 12 SQ-HDM group.[12] There was no significant treatment effect difference between the 2 doses of HDM tablets, and no significant improvement in ACQ or AQLQ was found for either dose.[12] In a similar RCT, 826 Japanese patients with asthma not well controlled by ICS (judged by ACQ score of 1.0 to 1.5) and HDM-induced allergic rhinitis were administered 6 SQ- and 12 SQ-HDM tablets to assess asthma control.[12] No significant difference was found among the 6 SQ-HDM, 12 SQ-HDM, and placebo in all asthma outcomes, including exacerbation, ICS use, asthma symptoms, ACQ, AQLQ, and lung function.[12]

The percentage of participants reporting at least 1 AE ranged from 39% to 96.4% in the HDM tablet-treated group.[12] Among all adverse effects, local adverse effects were the most common.[12] The symptoms include local swelling of the mouth, lips, tongue, or ear along with pruritus and some degree of gastrointestinal discomfort.[12] Of the 7 included studies, only one RCT reported 7 subjects treated with epinephrine due to adverse effects.[12] Three subjects used epinephrine for 12 SQ HDM-related adverse effects. The other 4 epinephrine administrations were considered unrelated to 12 SQ-HDM, 3 related to food/environmental allergies, and 1 (in the placebo group) related to complex allergy symptoms.[12]

In summary, moderate- to high-quality evidence from 3 RCTs review showed that SLIT effectively improved ICS use in adults and adolescents with mild-to-moderate or partially controlled moderate-to-severe asthma, but had no treatment effect in pediatric patients with very mild asthma.[12] Two RCTs evaluated the efficacy of house dust mite SLIT in reducing asthma exacerbation in partly controlled moderate-to-severe asthma, and their results were inconsistent.[12] One study in children with mild-to-moderate asthma found no benefit of SLIT.[12] Adverse events were primarily local, and anaphylaxis treated with epinephrine was reported in 3 patients.[12]

This systematic review has several limitations. First, the number of high-quality RCTs addressing the clinical questions was small.[12] In addition, each RCT also focused on different primary end points or different aspects of asthma control.[12] Finally, although the contrast groups were similar and seemingly comparable across studies, the reported outcomes varied substantially.[12] Only 2 studies reported the intended primary outcome of interest.[12] The measurements of asthma outcomes, asthma severity, and level of asthma control of the recruited population differed among studies, leading to a limitation in conducting quantitative synthesis and concluding clinical benefit.[12]

After review, 5 systematic reviews were excluded due to poor quality (e.g., network meta-analyses),[33-36] wrong study design of included trials (e.g., observational),[37] comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

Peanut Allergy

National Institute for Health And Care Excellence: PALFORZIA For Treating Peanut Allergy In Children And Young People

A recommendation for the use of PALFORZIA in children with a peanut allergy was published by NICE in February 2022.[1] The goal of treatment for peanut allergy is preventive, to reduce the frequency and severity of allergic reactions and improve quality of life, reduce anxiety, and to normalize activities of daily living.[1] The main preventive strategy for peanut allergy is strictly avoiding peanuts and being ready to respond to an emergency.[1] Clinical trial evidence shows that PALFORZIA improves tolerance to peanut protein compared with placebo when precise amounts are used in a food challenge test.[1] It is uncertain how long people would continue treatment beyond 24 months and the effect of stopping treatment on maintaining clinical efficacy has not been evaluated.[1]

NICE Recommendation: PALFORZIA is recommended as an option for treating peanut allergy in children aged 4 to 17 years. It can be continued in people who turn 18 years while on treatment. PALFORZIA should be used with a peanut-avoidant diet.[1]

Grass, Pollen and House Dust Mite Allergies

Canadian Agency for Drugs and Technologies: Grass Pollen Allergen Extract

A 2013 CADTH report evaluated evidence for the safety and efficacy of 5-grass pollen allergen extract (ORALAIR) in allergic rhinitis.[7] The 5-grass pollen extract SLIT was shown to be superior to placebo for management of allergic rhinitis in 4 double-blind RCTs.[7] Most adverse events reported in the 4 RCTs were mild or moderate in severity.[7] Oral pruritus, throat irritation, and mouth edema were reported more frequently with SLIT compared with placebo.[7] Serious adverse events were rare. Compared with placebo, a larger proportion of patients treated with 5-grass pollen extract experience at least one SAE during the first year of treatment (3.4% vs. 0.%) in one RCT.[7] In the other 3 RCTs the proportion of patients with at least one SAE was similar between 5-grass pollen extract and placebo (0.6% vs 0%; 1.4% vs. 1.4%; and 0.9% vs 1.7%, respectively).[7] There is no comparative evidence to evaluate the safety and efficacy of 5-grass pollen extract tablets with SCIT. The CDEC recommended the 5-grass pollen allergen extract be listed on the Canadian drug formulary for the seasonal treatment of grass pollen allergic rhinitis if: 1) patients have not adequately responded to, or tolerated, conventional pharmacotherapy, and 2) treatment is initiated by an allergist.[7]

European Academy of Allergy and Clinical Immunology (EAACI): Guidelines on Allergen Immunotherapy for Allergic Rhinoconjunctivitis

A 2017 guideline published by EAACI provides recommendations for the use of allergen immunotherapy for allergic rhinoconjunctivitis in adults and children.[8] The evidence for the efficacy of immunotherapy in children younger than 5 years of age is limited.[8] A 2017 systematic review (previously summarized above) informed the recommendations developed by the taskforce.[6] Members of the EACCI taskforce represented 18 countries and a range of clinical backgrounds including pediatricians, primary care specialists, ophthalmologists, pharmacists, immunologists, nurses, and patient representatives.[8]

Most clinical studies evaluating the efficacy of immunotherapy follow participants for 1 or 2 years on therapy.[8] The European Medicine Agency currently recommends an experimental, randomized, controlled design involving 3 years of therapy with a 2-year follow-up period off treatment.[8] These studies demonstrate a sustained benefit for 3 years of SLIT-tablet grass pollen therapy for 2 years off therapy.[8] There are some data from one RCT to suggest that HDM SLIT tablets give sustained benefit for at least 1 year after 1 year of therapy.[8] More data are required for HDM, and evidence is required on the optimal duration of therapy.[8] The EAACI taskforce recommends that to achieve long-term benefits, immunotherapy should be continued for a minimum of 3 years.[8]

Recommendations for SCIT and SLIT are provided in the EAACI publication. In general, the meta-analysis suggested both SCIT and SLIT are effective to manage allergic rhinitis.[8] There is insufficient data to determine which of SCIT and SLIT are most effective.[8] Severe adverse effects with SLIT appear to be much less likely than with SCIT although the overall rate of any adverse reactions is similar in both SCIT and SLIT formulations.[8] Specific SLIT recommendations are summarized in **Table 2**. Grade A recommendations are based on Level 1 evidence (systematic reviews, meta-analysis, and RCTs).[8] Grade B recommendations are based on Level 2 evidence (two groups, non-randomized [cohort or case-control] studies) or Level 3 evidence (one group, non-randomized study).[8] Grade C recommendations are based on Level 4 evidence (descriptive studies) or extrapolation of Level 2 or 3 evidence.[8]

Table 2. EAACI Recommendations for Treatment of Allergic Rhinoconjunctivitis with SLIT[3]

Recommendation	Adults		Children and Adolescents		Strength of Recommendation
	Evidence Level	Grade of Recommendation	Evidence Level	Grade of Recommendation	
Seasonal Allergic Rhinitis					
Pre-pollen or coseasonal pollen SLIT is recommended for seasonal allergic rhinitis for short-term benefit.	1	A	1	A	Strong recommendation based on high-quality adult and pediatric studies
Continuous SLIT during pollen season can be recommended for seasonal allergic rhinitis for short-term benefit.	1	A	1	A	Moderate-to-strong recommendation based on low and high ROB adult studies plus low, moderate and unclear ROB pediatric studies. Some heterogeneity between studies particularly pediatric ones, low risk of severe systemic allergic side-effects.
SLIT with grass pollen tablets is recommended for allergic rhinitis short-term benefit.	1	A	1	A	Strong recommendation based on low ROB adult and pediatric studies. Non-important heterogeneity between studies, low risk of severe systemic allergic side-effects.
Grass pollen SLIT tablets with continuous therapy during pollen season is recommended for allergic rhinitis for long-term benefit (at least 1 year after cessation of SLIT course).	1	A	1	A	Strong recommendation for adults based on low risk of bias studies. One low risk of bias pediatric study. Effective up to 2 years after cessation in adults. One pediatric study was designed to look at prevention of asthma.
Perennial Allergic Rhinitis					
SLIT with HDM tablets is recommended for allergic rhinitis for short-term benefit.	1	A	1	A	Strong recommendation based on low ROB adults and mixed adult/pediatric studies. Nonimportant heterogeneity between studies, low risk of severe systemic allergic side-effects.
HDM SLIT tablet with continuous therapy can be recommended to manage allergic rhinitis for long- term benefit (at least 1 year after cessation of SLIT course).	1	B	-	C (no pediatric data, extrapolated from adult data)	Moderate recommendation based on one large, low ROB study. No pediatric data. One study demonstrates effectiveness for one year post-treatment; data require replication especially as 3-year therapy required for grass pollen.
Abbreviations: EAACI= European Academy of Allergy and Clinical Immunology; HDM = house dust mite; ROB = risk of bias; SLIT = sublingual immunotherapy					

General contraindications for SLIT in managing allergic rhinoconjunctivitis include patients with: uncontrolled or severe asthma; active, systemic autoimmune disorders; or active malignant neoplasia.[8] Immunotherapy initiation during pregnancy is also contraindicated; although ongoing treatment is permissible if it has been well tolerated by the patient in the past.[8]

American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology: Sublingual Immunotherapy Guidance

A focused allergen immunotherapy practice parameter update was published by a joint task force of AAAAI and ACAAI members in 2017.[9] At the time of writing, 3 FDA-approved SLIT tablets were available: short ragweed, timothy grass pollen, and 5-grass pollen.[9] The primary focus of the SLIT practice parameter is to provide guidance for effective, safe, and appropriate administration of the FDA-approved SLIT formulations.[9] Both the Timothy grass SLIT tablet and the 5-grass tablet have demonstrated clinical benefits beginning in the first year of a 3-year treatment.[9] Significant improvement in the combined symptom and medication scores over placebo were observed through 2 additional grass pollen seasons after discontinuation of 3 years of continuous treatment with the Timothy grass SLIT tablet and throughout 3 years of pre- and co-seasonal treatment with the 5-grass SLIT tablet.[9] There are insufficient studies that directly compare SCIT and SLIT, precluding a definitive statement regarding efficacy comparison of these forms of immunotherapy.[9] Immunotherapy should be initiated at least 12 to 16 weeks before the relevant season for pre-seasonal and co-seasonal therapy to achieve optimal efficacy.[9] Localized symptoms (e.g., oromucosal itching and swelling) are common during the first week of SLIT treatment, whereas systemic allergic reactions can occur but are rare.[9]

Recommendations:

- Only use FDA-approved SLIT products for the treatment of allergic rhinitis/rhinoconjunctivitis and not for any other related or unrelated condition. (Strength of Recommendation: Strong; Evidence: A/B)**.[9]** There are no FDA-approved study indications for SLIT for the treatment of oral allergy syndrome, food allergy, latex allergy, atopic dermatitis, or venom allergy.**[9]**
- The physician should be aware that SLIT may not be suitable in patients with certain medical conditions, particularly those that may reduce the patient's ability to survive a systemic reaction or the resultant treatment of the systemic reaction. (Strength of Recommendation: Strong; Evidence: D).[9] The FDA-approved SLIT tablet prescribing information lists the following contraindications: severe, unstable, or uncontrolled asthma; any history of a severe systemic reaction to any form of immunotherapy; a history of any severe local reaction to SLIT; a history of eosinophilic esophagitis; or hypersensitivity to any of the inactive ingredients of the preparation. SLIT may not be suitable in patients with medical conditions that may reduce their ability to survive a serious systemic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, or uncontrolled hypertension. SLIT may not be suitable for patients who are taking medications that could potentiate or inhibit the effect of epinephrine should it be required.[9]
- Use FDA-approved SLIT products very cautiously in the pregnant or breastfeeding patient because there are insufficient data regarding the safety of initiating or continuing SLIT during either pregnancy or breastfeeding. (Strength of Recommendation: Weak; Evidence: C).[9]
- Administer the patient's first dose of SLIT in a medical facility under the supervision of a physician or other health care professional with experience in the diagnosis and treatment of anaphylaxis. The patient should be observed in the clinic or medical facility for 30 minutes after the administration of the SLIT dose. (Strength of Recommendation: Strong; Evidence: D).[9]
- Prescribe epinephrine (either an autoinjector or other form for self-injection) to patients receiving SLIT tablets. Patients should be trained how to use the device, instructed on how to recognize and manage adverse reactions and missed doses, and advised on when to contact their physician or other health care professional. Recommendations for when to withhold the SLIT tablet dose to avoid potential situations when systemic allergic reactions may be more likely should also be provided. (Strength of Recommendation: Strong; Evidence: D).[9]

European Academy of Allergy and Clinical Immunology: Allergen Immunotherapy to Prevent Allergic Comorbidities

In 2017 the EAACI taskforce published a guideline to provide evidence-based recommendations for the use of allergen immunotherapy to prevent comorbidities in patients with established allergic conditions.[13] Heterogeneity in the populations under study, methods employed, and outcomes studied made it challenging to interpret the evidence.[13] More evidence is needed for the use of SLIT or SCIT prevention in individuals with allergic rhinitis triggered by dust mites or pollen

and for the prevention of allergic sensitization, the first allergic disease, or for the prevention of allergic comorbidities in those with other allergic conditions.[13] Evidence for the preventive potential of immunotherapy as disease-modifying treatment exists but there is a need for more high-quality clinical trials.[13]

Recommendations and strength of evidence are summarized below. The grading of evidence is described above in the initial EAACI guidance. Based on limited evidence, some of the following recommendations were downgraded to Grade D recommendations and are based on Level 5 evidence (case reports and expert opinion).[13] Recommendations:

- In children and adolescents with allergic rhinitis and grass pollen allergy, who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-year course of SCIT or SLIT can be recommended for the short-term (i.e., less than 2 years post-treatment) prevention of asthma in addition to the sustained effect on allergic rhinitis symptoms and medication use. (Grade of Recommendation: A; Level of Evidence: 1). Moderate recommendation based on consistent significant results from 2 moderate and 2 high ROB RCTs and some controlled before and after (CBA) studies.[13]
- In children with atopic dermatitis, no recommendations can currently be made in favor of or against the use of immunotherapy for the prevention of onset of later allergic manifestations. (Grade of Recommendation: B; Level of Evidence: 1). Weak recommendation based on one small moderate ROB study.[13]
- In individuals at all ages with other early atopic manifestations, e.g., food allergy, no recommendations can currently be made in favor of or against the use of immunotherapy for the prevention of onset of other allergic manifestations. (Grade of Recommendation: D; Level of Evidence: V). Expert opinion due to the lack of studies.[13]
- In healthy individuals with or without sensitization, immunotherapy cannot currently be recommended for the prevention of onset of allergic diseases. (Grade of Recommendation: A; Level of Evidence: 1).[13] Weak recommendation: based on 1 low and 1 high ROB RCT.[13]

European Academy of Allergy and Clinical Immunology: House Dust Mite-Driven Allergic Asthma

In 2019 the EAACI taskforce developed a clinical practice guideline providing evidence-based recommendations for the use of HDM allergic immunotherapy as add-on treatment for HDM-driven allergic asthma.[14] The proportion of asthmatic patients with allergen sensitization varies between 30% and 79% in children and from 30% to 60% in adults, depending on the end points evaluated (sensitization or symptomatic allergic disease).[14] Dust mite immunotherapy was separately evaluated by route of administration (SCIT, SLIT drops and SLIT tablets) in pediatric and adult populations.[14] The important prerequisites for successful treatment with HDM immunotherapy are: 1) selection of patients most likely to respond to treatment and 2) use of allergen extracts and desensitization protocols of proven efficacy.[14] To date, only immunotherapy with HDM SLIT-tablet has demonstrated a robust effect in adults for critical endpoints (exacerbations, asthma control, and safety) in 3 RCTs funded by the manufacturer.[14] Most of the safety data are derived from allergic rhinitis studies enrolling patients with controlled asthma and with FEV_1 greater 70% predicted.[14] Limited data for adverse events are available for patients only with allergic asthma or for patients with moderate or severe asthma.[14] Thus, it is recommended as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma to decrease exacerbations and to improve asthma control (conditional recommendation, moderate-quality evidence).[14] The patient's asthma status should be carefully evaluated prior to initiating HDM SLIT tablets and assessed regularly during immunotherapy treatment.[14] Due to lack of evidence, no recommendation could be provided for the use of HDM SLIT tablets in children.[14] Uncontrolled asthma is the major independent risk factor for both severe and fatal adverse reactions and is therefore a major contraindication for HDM SLIT tablets.[14]

Additional Guidelines for Clinical Context:

Global Initiative for Asthma Strategy

The 2021 GINA report provides guidance for asthma management and prevention.[38] Personalized asthma management includes guidance for adding HDM SLIT if asthma is not well-controlled.

Recommendation:

- For adult patients with allergic rhinitis and sensitized to dust mites, with suboptimally controlled asthma despite low to high dose ICS, consider adding SLIT provided FEV_1 is greater than 70% of predicted value (evidence level B: limited body of data from RCTs and systematic reviews).[38]

Randomized Controlled Trials:

A total of 168 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alert[39]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Peanut (*Arachis hypogaea*) Allergen Powder-dnfp	PALFORZIA	5/2021	REMS Document	Modified the REMS document and materials to allow the first dose of each Up-Dosing level to be dispensed from either the Office Dose Kit or the Daily Dose Pack and require prescribers and healthcare settings to report anaphylaxis including suspected cases managed as anaphylaxis to the REMS Program using the Anaphylaxis Adverse Event Reporting Form.

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Appendix 1: Medline Search Strategy

A. Environmental Allergens

Ovid MEDLINE(R) <1996 to March Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to March 24, 2023>

1	exp Desensitization, Immunologic/	7897
2	Rhinitis, Allergic/	5008
3	Administration, Sublingual/ or Sublingual Immunotherapy/	3144
4	1 and 2 and 3	302
5	ragweed.mp. or Ambrosia/	1391
6	house dust mite.mp. or Pyroglyphidae/	5313
7	grass.mp. or Poaceae/	28874
8	5 or 6 or 7	34823
9	4 and 8	165
10	limit 9 to (english language and humans)	144

B. Food Allergens

Ovid MEDLINE(R) 1996 to March Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to March 24, 2023

1	Administration, Sublingual/ or Sublingual Immunotherapy/	3144
2	Peanut Hypersensitivity/	1699
3	1 and 2	25
4	limit 3 to (english language and humans)	24

Appendix 2: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
peanut allergen powder-dnfp	PALFORZIA	ORAL	CAP SPRINK	N
peanut allergen powder-dnfp	PALFORZIA	ORAL	POWD PACK	N
grass pollen-timothy, standard	GRASTEK	SUBLINGUAL	TAB SUBL	
mite,D.farinae-D.pteronyssinus	ODACTRA	SUBLINGUAL	TAB SUBL	
gr pol-orc/sw ver/rye/Kent/tim	ORALAIR	SUBLINGUAL	TAB SUBL	
weed pollen-short ragweed	RAGWITEK	SUBLINGUAL	TAB SUBL	

Peanut (arachis hypogaea) Allergen Powder-dnfp (Palforzia)

Goal(s):
- To ensure appropriate use of desensitization products in patients with peanut allergies

Length of Authorization:
- 12 months

Requires PA:
- Peanut (arachis hypogaea) allergen powder-dnfp (Palforzia) (both 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 by, or in consultation with, an allergist or immunologist?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for continuation of current therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for an FDA-approved indication and age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a history of serious peanut allergy or anaphylaxis?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity

Approval Criteria		
6. Is there baseline documentation of number of epinephrine administrations and hospital/emergency department visits (if any) in past 12 months which were caused by presumed peanut exposure.	**Yes:** Go to #7 Epi administrations:_____ Hospital/ED visits:_____	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have a history of severe peanut reaction that included circulatory shock or need for mechanical ventilation?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the patient have a peanut-specific positive IgE of ≥ 0.35 kU_a/L OR a skin prick test wheal of ≥ 3 mm?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have a peanut allergy confirmed with a double-blind, placebo-controlled food challenge?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the patient have uncontrolled asthma, history of eosinophilic esophagitis, or other eosinophilic gastrointestinal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Are the healthcare setting and the prescriber certified in the Palforzia REMS program AND will the patient be enrolled in the REMS program upon PA approval?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for the full 300 mg daily maintenance dose of peanut allergen powder?	**Yes**: Go to #3	**No:** Go to #2

Renewal Criteria		
2. Is the patient new to OHA FFS and has the patient not yet completed the initial dose titration prior to FFS enrollment?	**Yes:** Approve for 12 months; Document baseline epinephrine use and hospital/emergency department visits	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient had a reduced number of allergic attacks since beginning peanut allergen powder as evidenced by either: • Absence of, or reduction in the number of needed epinephrine administrations due to presumed peanut exposure OR • Absence of, or reduction in the number of hospital/emergency department visits due to presumed peanut exposure	**Yes**: Approval for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/23 (DM); 2/21 (SF)
Implementation: 3/1/21

Sublingual Immunotherapy Tablets

Goal(s):

- Restrict use of sublingual immunotherapy tablets for conditions funded by the OHP and where there is evidence of benefit. Treatment for allergic rhinitis is funded by the Oregon Health Plan only if there is a comorbidity such as asthma.
- Allow case-by-case review for members covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program.

Length of Authorization:

- Up to 12 months

Requires PA:

- All FDA-approved sublingual immunotherapy tablets (physician administered and pharmacy claims).

Covered Alternatives:

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

Table 1. FDA-Approved Sublingual Immunotherapy Tablets

Product Name (BRAND NAME)	How Supplied	Approved Age Range	When to Initiate Therapy
Timothy Grass Pollen Allergen Extract (GRASTEK)	2,800 BAU tablet	5 to 65 yo	Start 12 weeks prior to expected onset of grass season and continue through grass season.
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergy Extract (ORALAIR)	100 IR and 300 IR tablets		Start 16 weeks prior to expected onset of respective grass season and continue through grass season.
Short Ragweed Pollen Allergen Extract (RAGWITEK)	12 Amb a 1-Unit tablet		Start 12 weeks prior to expected onset of ragweed season and continue through ragweed season.
House Dust Mite Allergen Extract (ODACTRA)	12 SQ-HDM tablet	12 to 65 yo	Start anytime and once daily administration until discontinued by provider.

Abbreviations: Amb a = Ambrosia artemisiifolia (short ragweed); BAUs = Bioequivalent Allergy Units; FDA = Food and Drug Administration; SQ-HDM = Standardized-Quality House Dust Mite units; IR = Index of Reactivity; SL = sublingual; yo = years old

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication ?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for continuation of current therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Does patient have co-morbid conditions funded by the OHP and listed in HERC guidance? • Uncontrolled Mild to Moderate Asthma	**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

Approval Criteria		
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 #7	**No**: Pass to RPh. Deny; medical necessity.
6. If the patient has asthma, have they tried and failed to receive adequate benefit from or have a contradiction to a low to high dose orally inhaled corticosteroid treatment?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient tried and failed to receive adequate benefit from or have a contraindication to oral antihistamines and/or nasal corticosteroids to manage allergic rhinitis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical necessity.
8. Does the patient meet the FDA-approved age range outlined in **Table 1**?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the request by, or in consultation with, an allergist or immunologist?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the patient have severe, unstable, or uncontrolled asthma, a history of eosinophilic esophagitis, or other severe systemic allergic reaction?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Has the patient undergone a properly performed skin test and/or is there serologic evidence of IgE-mediated antibody to a potent extract of the allergen?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a prescription on file for an epinephrine autoinjector in case of an adverse event?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
13. Will the first dose be administered under medical supervision?	**Yes**: Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Does the provider attest that patient's symptoms have improved with sublingual immunotherapy treatment and not experienced any adverse effects?	**Yes**: Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 8/23 (DM)
Implementation: TBD

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OHSU Drug Effectiveness Review Project Summary Report – Gene Therapies for Hemophilia A and B (Feb 2023) Gene Therapies for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia (Nov 2022)

Date of Review: August 2023

Date of Last Review: n/a
DERP Literature Search: Hemophilia A and B, database inception to 09/22/22
Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia, database inception to 07/26/22

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

Plain Language Summary:

- This is a summary of 2 different research reports from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). The reports studied gene therapies which are Food and Drug Administration (FDA) approved for beta-thalassemia and hemophilia B. Gene therapies are currently being studied for 2 other conditions, sickle cell anemia and hemophilia A, but are not included in this report summary.
- Beta thalassemia is an inherited blood disorder where there is not enough hemoglobin made in the body, resulting in decreased production of healthy red blood cells (RBCs.) Hemophilia B is another inherited disorder that results in uncontrolled bleeding and mostly affects males assigned at birth.
- Gene therapies are a newer type of medication that usually involve getting just one dose. Most conditions being studied for gene therapy are uncommon. Studies for these treatments are often small and do not have a "placebo" group (a group that does not get the active therapy) to compare how safe and how well the drug works. This can make it difficult to understand how well these treatments work and what side effects they may have. We do not know how long the effect of gene therapies last.
- Betibeglogene autotemcel (ZYNTEGLO) is approved for adult and pediatric patients with beta-thalassemia who must have frequent red blood cell transfusions. Transfusions are when a person is given blood that came from a blood donor. Most patients who have received this gene therapy do not require as many red blood cell transfusions, and many no longer need red blood cell transfusions. We do not know if this improvement will last more than 2.5 years, but studies are happening now to answer this question. Many patients experienced adverse events when getting this treatment. Nearly every patient had mucositis (inflammation of mucosa such as the mouth), and it was significant in more than half of the patients. At least one in five patients had each of these: febrile neutropenia (fever in a person who has a low number of the blood cells that fight infections), vomiting, fever, hair loss, nose bleed, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder (changing of the

color of skin), and itching. The most common severe adverse reactions were low counts of the different kinds of blood cells. This gene therapy requires treatment to destroy the bone marrow (inner part of the bone that includes stem cells and makes different kinds of blood cells) before it can be given. Patients must stay in the hospital for many weeks because they are at very high risk of bleeding and infections after getting this type of treatment.

- Etranacogene dezaparvovec (HEMGENIX) is approved for adult patients with severe forms of hemophilia B. Data show that patients who receive this therapy have fewer bleeding episodes each year than they did before receiving this therapy. Some patients no longer need to take other therapies to prevent bleeding such as the blood product known as Factor IX ("Factor 9"). We do not know if this improvement will last more than 18 months, but studies are happening now to answer this question. Some patients who received this medication had side effects, including reactions when the drug was being infused, and signs of damage to their liver. Some patients needed to take certain medications, called steroids, for many months while they had signs of inflammation in the liver after getting this medicine.
- Drug Use Research and Management (DURM) recommends that doctors who prescribe one of these medicines to a person enrolled in the Oregon Health Plan must show that certain criteria have been met to ensure the medicine is used safely and correctly before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the effectiveness of gene therapies for beta-thalassemia and hemophilia B?
2. What are the harms of gene therapies for beta-thalassemia and hemophilia B?
3. Are there any important subgroups of patients where these gene therapies have not been studied?

Conclusions:

Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia[1]

- Three non-controlled, open-label studies with 5 total publications for participants with transfusion dependent beta thalassemia (TDT) receiving betibeglogene were identified by DERP. The primary publications reported results for 45 total participants. Additional presentation abstracts provided quality of life (QoL) and long-term follow-up outcomes for participants enrolled in the primary studies. The studies were rated as having a *high* Risk of Bias (RoB) due to lack of a control group. All outcomes are rated very low certainty of evidence due to risk of bias, imprecision, and indirectness in 3 non-randomized studies. The primary efficacy endpoint of NORTHSTAR-2 was transfusion independence defined as a hemoglobin(Hb) of $\geq$ 9 g/dL starting 60 days after the last transfusion in patients who had not received RBC transfusions in 12 months or longer.
- Transfusion frequency was reduced and many patients achieved transfusion independence up to 29.5 months. NORTHSTAR-2 found transfusion independence was achieved in 91% (20 of 22) of patients with an average Hb level of 11.7 g/dL (range 9.5 to 12.8 g/dL), the two patients who did not achieve transfusion independence had a 67.4% and 22.7% reduction in transfusion volume.[1]
- Transfusion independence was achieved in 79.5% (35 of 44) of all evaluated patients in the combined study populations, and 3 of 9 (33%) of patients with the β^0/β^0 genotype. The β^0/β^0 genotype was excluded from NORTHSTAR-2.
- A high incidence of adverse events (AEs) occurred with betibeglogene, most often around the time of infusion. More than 20% of patients experienced each of the following at any severity: mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus.[2] Severe adverse events were common, including febrile neutropenia (51%) and mucositis (63%).[2] No deaths were reported.

Etranacogene dezaparvovec for Hemophilia B[3,4]

- Two non-controlled, open-label studies with 4 total publications in participants with hemophilia B were identified by DERP. The largest study was the phase 3, HOPE-B study which enrolled 54 participants with interim results reported via abstract. The full study was published after the DERP report was completed and was reviewed and graded by DURM. The second study, a phase 2b trial, enrolled 3 participants. Both are rated as having a *high* RoB and all conclusions are very low certainty of evidence due to high risk of bias and indirectness.
- Etranacogene reduced the annualized bleeding rate (ABR) in the phase 3 study from 4.19 (95% confidence interval [CI] 3.22 to 5.45) at baseline to 1.51 (95% CI 0.81 to 2.82) during months 7 to 18 post treatment vs. the 6 month baseline period ($P < 0.01$).
- Factor IX (FIX) replacement use decreased significantly by -248,825.0 IU (95% CI -291,149.9 to -206,500.1) during months 7 to 18 post treatment compared to the 6 month baseline period in the HOPE-B study ($P < 0.01$). Baseline unadjusted mean annualized exogenous factor IX consumption was 257,339±149,013 IU/year.
- Etranacogene administration resulted in improved FIX activity at 6 months (least-squares mean [LSM] 36.2%; 95% CI 31.4% to 41.0%) and 18 months (LSM 34.3%; 95% CI 29.5 to 39.1) after treatment.
- Elevations in liver enzymes was a common AE. Alanine aminotransferase (ALT) was elevated for 20% of patients and 17% of patients were given glucocorticoid treatment for weeks to months.

Recommendations:

- Designate betibeglogene autotemcel and etranacogene dezaparvovec as non-preferred on the preferred drug list (PDL)
- Apply prior authorization (PA) to ensure clinically appropriate utilization.

Summary of Prior Reviews and Current Policy

- Gene therapies are a relatively new type of medication. Many currently available agents fall under the Oncology Policy, and several others have drug-specific prior authorization criteria. These 2 therapies are being reviewed by the Pharmacy and Therapeutics (P & T) committee for the first time and are the first gene therapy agents available for beta-thalassemia and hemoglobin B.
- Gene therapies are extremely costly and some have been introduced with prices of several million dollars for a one-time treatment, in addition to costs for necessary supportive care.
- Gene therapies often target relatively rare or uncommon conditions which have a clear genetic cause. Consequently, many of the conditions disproportionately affect those of a specific race or sex. For example, hemophilia B is more common in males assigned at birth with XY chromosomes because it is X-linked. Beta-thalassemia most prevalent in Asia and in the Mediterranean basin.

Methods:

The November 2022 drug class report on Gene Therapies for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia and the February 2023 drug class report on Gene Therapies for Hemophilia A and B by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon P & T Committee members upon request.

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

Summary Findings:
Gene therapy is a developing field of therapeutics. The Food and Drug Administration (FDA) has approved a number of gene therapies for oncology and non-oncology uses.[5] Data from recent Drug Effectiveness Review Project (DERP) reports will be summarized for the recent approvals of betibeglogene autotemcel (ZYNTEGLO) for use in certain beta-thalassemia patients and etranacogene dezaparvovec-drlb (HEMGENIX) for specific hemophilia B patients.[1,3]

Beta Thalassemia
Beta thalassemia is an inherited, genetic blood disorder where there is insufficient production of β-hemoglobin (β+) or an absence of β-globin (β°), resulting in decreased production of healthy RBCs. This may result in anemia and based on the severity of phenotype, beta thalassemia can be labeled as transfusion dependent beta thalassemia (TDT) or transfusion nondependent. There are different genotypic forms of this disease. Individuals with severe forms of the disease can require regular transfusions of packed RBCs, which can result in iron overload and the need for concomitant iron chelation therapy.[1]

A complete blood count is generally required to diagnose beta thalassemia. It is most prevalent in Asia and the Mediterranean basin, but is estimated to have increased 7.5% over the last 50 years in the United States. Migration was considered as an important factor for this higher trend in beta thalassemia prevalence.[1] Global incidence of symptomatic disease is approximately 1 in 100,000 and can vary greatly geographically.[6]

Treatment options for TDT include splenectomy, hematopoietic stem cell transplant (HSCT), and FDA-approved drug therapies such as luspatercept. Donor matching, reduced survival rate for adults, and risk of graft versus host disease (GVHD) are concerns when HSCT is used to treat people with beta thalassemia.[1] While HSCT is potentially curative, it is generally most successful in younger children with an HLA-identical sibling donor.[7] The FDA approved the first gene therapy for beta thalassemia in the form of betibeglogene autotemcel in August 2022.[2] Other gene therapies are currently under investigation. Outcomes used when caring for patients with TDT or researching interventions include hemoglobin levels, frequency of transfusions, fatigue, and QoL.[1] There are no clear minimum clinically important differences (MCID) for these outcomes. An evaluation by the National Institute for Health and Excellence (NICE) discussing the methodological challenges in evaluating gene therapy products was published in 2021 and reviewed the initial NORTHSTAR results.[7] The NICE recommendation was that "betibeglogene autotemcel is not recommended, within its marketing authorisation, for treating TDT in patients aged ≥12 years who do not have a $beta^0/beta^0$ genotype, when HSCT is appropriate, but an HLA- matched related hematopoietic stem cell donor is not available".[8] The conditional EU and UK marketing authorization was for those with TDT who do not have the $beta^0/beta^0$ genotype and when HSCT would be appropriate but there is not suitable donor.[9] The manufacturer withdrew its marketing application from the Medicines and Healthcare products Regulatory Agency in 2021 and the European Medicines Agency in 2022.[10,11]

Efficacy
Betibeglogene Autotemcel (ZYNTEGLO) is an autologous hematopoietic stem cell-based gene therapy indicated for treatment of adult and pediatric patients with beta-thalassemia who require regular RBC transfusions.[2] Efficacy and safety were evaluated in 3 non-randomized, single arm studies. The β^0/β^0 genotype or the IVS1-110 mutation was found in 9 of 22 patients of patients in the NORTHSTAR trial (which is a pooled summary of 2 phase 1-2 studies), while the NORTHSTAR-2 trial excluded patients with the β^0/β^0 genotype.[1] The ongoing NORTHSTAR-3 Study does allow the β^0/β^0 genotype in its inclusion parameters.[1] Published studies (N=45 patients) are at high risk of bias due to lack of control group, and GRADE ratings for confidence of evidence in relevant outcomes is very low.[1] The phase

1/2 NORTHSTAR study focused on engraftment, while the phase 3 NORTHSTAR-2 study primary efficacy endpoint was transfusion independence defined as a Hb of $\geq$ 9 g/dL starting 60 days after the last transfusion in patients who had not received RBC transfusions in 12 months or longer.[1] The median age across trials was 13 years and most patients were Asian.[2] While one study allowed inclusion up to 50 years of age, the combined age ranges for those enrolled in the studies are 4 to 34 years. Those under 5 years had to meet a minimum weight threshold of 6 kg to reasonably provide the minimum number of cells for the product manufacturing process.[1] Patients in all studies required a history of transfusion of at least 100 mL/kg/year of packed RBCs in the 2 years before enrollment, or at least 8 transfusions of packed RBCs/year in the past 2 years for those 12 years in older.[1,7] NORTHSTAR-2 found transfusion independence was achieved in 91% (20 of 22) patients with an average Hb level of 11.7 g/dL (range 9.5 to 12.8 g/dL), the two patients who did not achieve transfusion independence had a 67.4% and 22.7% reduction in transfusion volume.[1] NORTHSTAR found transfusion independence in 68% (15 of 22) of patients with a median Hb level of 11.2 g/dL.[1] Of those with the β^0/β^0 genotype or the IVS1-110 mutation, 3 of 9 (33%) achieved transfusion independence.[1,7]

Harms

Overall survival during study follow-up was 100% in published studies. The most common adverse events experienced in at least 20% of patients were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. Grade 3 or higher febrile neutropenia (51%) or mucositis (63%) were common.[2] Serious adverse events were experienced by 37% of patients. The most common serious adverse events were pyrexia, thrombocytopenia, liver veno-occlusive disease, febrile neutropenia, neutropenia, and stomatitis.[2] The median duration of hospitalization from conditioning though discharge (N=30) was 44 days (range 29 to 92 days).[1] No deaths were reported.[1] Study characteristics can be found in **Table 1** and complete demographics and results can be found in the full report.[1] The package insert states there is a potential risk for insertion oncogenesis after treatment and that patients should be monitored lifelong for hematologic malignancies with a complete blood count at months 6, 12, and then annually for at least 15 years, in addition to an integration site analysis at months 6, 12 and then as warrented.[2]

Table 1. Study Characteristics of Betibeglogene for Transfusion-Dependent Beta Thalassemia[1]

Author, Year **Trial Number** **Trial Name**	**Participants**	**Treatment Protocol**	**Study Design**	**Follow-up**	**Risk of Bias**
Thompson et al., 2018 HGB-204 NCT01745120 HGB-205 NCT02151526 NORTHSTAR	N = 22 n = 18, HGB-204 n = 4, HGB-205	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 1/2 study	26 months	High

Locatelli et al., 2022 HGB-207 NCT02906202 NORTHSTAR-2	N = 23	Single infusion of autologous CD34+ hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector Target Dose: at least 5.0 million CD34+ cells per kilogram of body weight	Single-arm, open label, phase 3 study	29.5 months	High
Kwiatkowski et al., 2021 Kulozik et al., 2021 HGB-207 NCT02906202 NORTHSTAR-2 HGB-212 NCT03207009 NORTHSTAR-3	N = 30	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 3 studies	24 months	Not performed (conference abstract)
Yannaki et al., 2021 LTF-303 NCT02633943	N = 44	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, long-term follow-up study	45.6 months	Not performed (conference abstract)

Hemophilia B

Hemophilia B is a recessive, X chromosome-linked bleeding disorder mainly affecting males assigned at birth. Hemophilia B represents a deficiency in factor IX (FIX) and affects 1 in 25,000 live male births. Females assigned at birth are more likely to experience mild or moderate hemophilia than severe hemophilia B. Bleeding most often occurs in large joints, leading to hemophilic arthropathy, which results in significant pain and physical disability. Physical activity can greatly increase the risk for weight-bearing joint bleeds, and many affected people with hemophilia avoid sports, exercise, and physical activities. Risk of bleeding associated with physical activity and frequent infusions of on-demand and prophylactic clotting factor concentrates (CFCs) contribute to the reduced QoL in individuals with hemophilia B. The severity of hemophilia B, defined by percent of normal clotting factor level, is detailed in **Table 2**. Factor IX activity of over 5% of normal is associated with a lower risk of spontaneous bleeding than those with moderate or severe hemophilia and is generally the target level for routine prophylactic therapy to prevent or reduce the incidence of spontaneous bleeds.[3]

Table 2. Hemophilia B Disease Severity by Factor IX Levels[3]

Percent of Normal Factor IX activity	Disease Severity
<1%	Severe
1-5%	Moderate
5-40%	Mild

The current standard of care for hemophilia B is regular administration of prophylactic CFCs or other hemostasis products to prevent bleeding. This prophylaxis is recommended prior to the age of 3 years to prevent both acute bleeds and the long-term development of hemarthroses and joint disease.[3] Many CFCs have a short half-life, leading to breakthrough bleeding as factor levels fall close to baseline between intravenous administration of FIX.[3] Newer formulations of CFCs with an increased half-life and the use of monoclonal antibodies allow for extended intervals between administrations.[3] Outcomes used when caring for patients and researching interventions for hemophilia B tend to include annualized bleeding rate (ABR), response to treatment (e.g., number of CFC infusions or dose required to resolve a bleed or time from last infusion to bleeding episode), need for other therapies, and quality of life. There are no clear MCIDs for these. The Haem-A-Qol is a common questionnaire used for assessment of health-related quality of life.[12] It has been validated in adult patients ≥ 17 years old with hemophilia.[12] Questions use a 5-point Likert-type frequency scale (1= never, 2=rarely, 3=sometime, 4=often, 5=all the time).[12] Higher total scores indicate more impairment and the maximum score is 100.[12] There are 10 different domains (e.g., physical health, sports & leisure, work & school) with varying numbers of items in each domain.[12]

Efficacy

Etranacogene dezaparvovec-drlb (HEMGENIX) is an adeno-associated virus vector-based gene therapy.[13] It is indicated for adults with hemophilia B who currently use FIX prophylaxis therapy; or have current or historical life threatening bleeding; or have repeated, serious spontaneous bleeding episodes.[13] It was evaluated in 2 non-randomized, single arm studies. HOPE-B study was a phase 3, open-label study, using intra-subject comparison as the control (n=54).[3,4] Patients had 18 months of post-treatment follow-up.[4] Patients were observed for FIX prophylaxis during the ≥ 6 month lead-in period (baseline) and had a 64% reduction in ABR (all bleeds, primary endpoint) from 4.19 (95% CI 3.22 to 5.45) at baseline to ABR 1.51 (95% CI 0.81 to 2.82; $P < 0.01$) during months 7 to 18 after etranacogene was administered.[4] The adjusted ABR ratio was 0.36 (95% CI 0.20 to 0.64), meeting predetermined criteria for non-inferiority (primary endpoint) and superiority (secondary endpoint) compared to lead-in period.[4] The mean FIX activity increase was 39.0 ± 18.7% (range 8.2 to 97.1%) at 6 months, most patients had <1% FIX activity at diagnosis. These were sustained at 12 and 18 months.[4] Baseline unadjusted mean annualized exogenous factor IX consumption was 257,339±149,013 IU/year. Factor IX annualized consumption decreased by 248,825.0 IU/year (95% CI -291,149.9 to -206,500.1).[4] Fifty-two of 54 participants (96.3%) stopped prophylactic FIX infusions.[4] One non-responder received a subtherapeutic dose equivalent to approximately 10% of the intended dose, and the other non-responder was noted to have an adeno-associated virus serotype 5 (AAV5) neutralizing antibody titer of 3,212.[4] Clinical thresholds for this titer are unknown and being assessed with further research.[13] The Haem-A-QoL showed a total mean score of 25.56 compared with 20.06 in the lead-in and post-treatment periods, respectively, resulting in a 21.5% score improvement ($P < 0.01$).[3,4] The FDA noted that with the single-arm open label trial design that reliable assessments of patient-reported outcomes cannot be made and the information would not be in the label.[14] Study characteristics can be found in **Table 3** and complete demographics and results can be found in the full report.[3]

Von Drygalski and colleagues reported efficacy outcomes for etranacogene in 3 participants in the phase 2b study. All participants had a baseline FIX activity of less than 1%. Mean FIX activity increased to 31% at 6 weeks, 38% at 12 weeks, and 47% at 26 weeks. No bleeds or FIX administration was reported during the study period (26 weeks).

Table 3. Study Characteristics of Etranacogene for Hemophilia B[3,4]

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment Protocol	Study Design	Follow-up	Risk of Bias
Miesbach et al., 2022 Pipe et al., 2022 Pipe et al., 2023 NCT03569891 HOPE-B	Men ≥ 18 years with FIX coagulant activity ≤ 2% who had received continuous prophylaxis for ≥ 2 months N = 54	2 x 10 vg/kg	Open-label, multicenter, non-randomized, phase 3 study	18 months	High
Von Drygalski et al., 2019 NCT03489291	Men ≥ 18 years with moderate to severe hemophilia B (FIX coagulant activity ≤ 2%) receiving either prophylactic FIX or on-demand FIX with ≥ 4 bleeds/year or chronic hemophilic arthropathy N = 3	2 x 10 vg/kg	Open-label, multicenter, non-randomized study	Interim assessment at 26 weeks published; planned 52 weeks; additional long-term follow-up assessments over 4 years	High
Abbreviations: FIX: factor IX; vg/kg: vector genomes per kilogram.					

Harms

The HOPE-B study includes safety information for etranacogene in 54 participants in the phase 3 study. There were 92 treatment-related adverse events (TRAEs) affecting 69% of participants.[3,4] Of these TRAEs, 74 (80.4%) were mild, 16 (17.4%) were moderate, and 2 (2%) were severe.[3,4] An increase in alanine aminotransferase (ALT) was noted in 9 participants (16.7%), all of whom received corticosteroid treatment (mean duration = 79 days ± 26.6, range 51 to 130 days) and maintained FIX expression.[3,4] Additional TRAEs include headache (n = 8; 14.8%), influenza-like illness (n = 7; 13%), infusion-related reaction (n = 7; 13%), AST increase (n = 5; 9.3%), increase in blood creatine phosphokinase (n = 4; 7.4%), fatigue (n =4; 7.4%), nausea (n = 4; 7.4%), and arthralgia (n = 3; 5.6%).[3,4] Two SAEs were reported, these included 1 death related to cardiogenic shock and 1 case of hepatocellular carcinoma, neither of which were determined to be related to etranacogene.[4] The follow-up time was 18 months. No patients developed FIX inhibitors.[4]

Von Drygalski and colleagues reported harm outcomes for etranacogene in 3 participants in the phase 2b study.[3] Two adverse events possibly related to etranacogene were reported in 1 participant, including a self-limited headache on day 1 and a mild increase in C-reactive protein on day 14, neither of which required intervention.[3] Changes in liver transaminase concentrations were not determined to be clinically significant. One participant required prednisone at 50 mg daily for 5 days at day 94 for bronchitis.[3] No serious adverse events (SAEs) were reported.[3] **Table 4** summarizes adverse events reported in the 2 trials.

Table 4. Adverse events from Etranacogene for Hemophilia B Studies[3,4]

Author, Year Study Name Study Name	Adverse Events	Serious Adverse Events

Miesbach et al., 2022 Pipe et al., 2022 Pipe et al., 2023 NCT 03569891 HOPE-B	• Alanine aminotransferase increase: n=9 (16.7%) • Headache: n=8 (14.8%) • Influenza-like illness: n=7 (13%) • Infusion-related reaction: n=7 (13%) • Aspartate aminotransferase increase: n=5 (9.3%) • Blood creatinine kinase increase: n=4 (7.4%) • Fatigue: n=4 (7.4%) • Nausea: n= 4 (7.4%) • Arthralgia: n=3 (5.6%)	• Death: n=1; cardiogenic shock unrelated to study treatment • Hepatocellular carcinoma: n=1; unrelated to study treatment
Von Drygalski et al., 2019 NCT03489291 Not applicable	• Headache: n=1 • Elevation in C-reactive protein: n=1	

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Appendix 1: Current Preferred Drug List

PDL unassigned

Generic	Brand	Route	Form	PDL
etranacogene dezaparvovec-drlb	HEMGENIX	IV	VIAL	
etranacogene dezaparvovec-drlb	HEMGENIX	IV	KIT	
betibeglogene autotemcel	ZYNTEGLO	IV	PLAST. BAG	

Betibeglogene Autotemcel

Goal(s):
- Approve Betibeglogene Autotemcel (ZYNTEGLO) for conditions supported by evidence of benefit

Length of Authorization:
- Once in a lifetime dose.

Requires PA:
- Betibeglogene Autotemcel (billed as pharmacy or physician administered claim)

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
3. Has the patient ever received another gene therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness	No: Go to #4
4. Does patient have confirmed Beta-thalassemia?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the genotype documented?	**Yes:** Go to #6 Genotype_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient transfusion dependent, defined as requiring in each of the past 2 years: • 100 mL/kg/year or more of packed red blood cells (any patient age) OR • 8 transfusions or more of packed red blood cells per year (patients 12 years and older)	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient between 5 years and 35 years old?	**Yes**: Go to #9	**No:** Go to #8
8. Is the patient younger than 5 years old and weighs at least 6 kg?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have cirrhosis or advanced liver disease?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the patient have any of the following viral infections: HIV, Hepatitis B, or Hepatitis C?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Does the prescriber attest that the patient's general health and comorbidities have been assessed and that the patient is expected to safely tolerate myeloablation?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient (and/or guardian, if applicable) been educated on the risk of insertional oncogenesis and need for lifelong monitoring (bloodwork) at least annually?	**Yes**: Approve one lifetime dose.	**No**: Pass to RPh. Deny; medical appropriateness

Etranacogene dezaparvovec

Goal(s):

- Approve Etranacogene dezaparvovec (HEMGENIX) for conditions supported by evidence of benefit

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Etranacogene dezaparvovec (billed as pharmacy or physician administered claim)

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 it the FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient ever received another gene therapy for any diagnosis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Does the patient require continuous routine factor IX prophylaxis?	**Yes**: Go to #7	**No:** Go to #5
5. Does the patient have a history of repeated, serious spontaneous bleeding OR current or historical life threatening hemorrhage?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Did these events occur during adherence to physician recommended and maximally adjusted factor IX therapy (including routine factor IX prophylaxis, if indicated) AND adherence to appropriate lifestyle precautions?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Send to Medical Director for review.
7. Does patient have congenital hemophilia B with: • Severe Factor IX deficiency (<1% plasma factor IX activity) OR • Moderately-Severe Factor IX deficiency (1 to 2% plasma factor IX activity) with a severe bleeding phenotype?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Send to Medical Director for review.
8. Is the patient 18 years or older?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have a history of Factor IX inhibitors?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Has the patient had a Factor IX inhibitor test within the past 3 months?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Was the Factor IX inhibitor test negative?	**Yes:** Go to #13	**No:** Go to #12
12. Was the Factor IX inhibitor retest negative? Note: retest should be performed within approximately 2 weeks of original test.	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Has this patient had a liver health assessment including all of the following: AST, ALT, ALP, total bilirubin, hepatic ultrasound, elastography, and recent (previous 3 months) screening for hepatitis B and C?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
14. Were all hepatic enzymes and hepatic radiological tests normal AND were hepatitis B and C screenings negative? Note: Enzyme elevations which are transient and mild (less than twice the upper limit of normal) may answer “Yes” to this question.	**Yes**: Go to #16	**No:** Go to #15
15. Has the patient been evaluated and cleared for gene therapy treatment by a gastroenterologist or hepatologist?	**Yes**: Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Does the patient have HIV that is uncontrolled (CD4 count ≤ 200/μL)?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #17
17. Has the provider discussed enrollment in a study to measure pre-existing anti-AAV5 neutralizing antibodies with patient? Note: study details and contact information in gene therapy package insert.[1]	**Yes:** Approve one lifetime dose.	**No:** Pass to RPh. Deny; medical appropriateness

1. Hemgenix (etranacogene dezaparvovec-drlb) package insert.uniQure, Inc Lexington, MA: https://www.fda.gov/media/163467/download. November 2022.

P&T/DUR Review: 8/23 (SF)
Implementation: TBD

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Drug Class Update: Gonadotropin-Releasing Hormone Agonists

Date of Review: August 2023

Date of Last Review: December 2021
(fibroids/endometriosis focused review on GNRH antagonists) March 2019 (Endometriosis); Nov 2019 (Elagolix); Jan 2019 (Hormone replacement); May 2015 (GnRH Agonists)
Dates of Literature Search: 01/01/2015 – 06/20/2023

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

Plain Language Summary:

- This review looks at new evidence for using medications to treat early onset puberty also called central precocious puberty. This rare condition means females will begin menstruating, develop breasts, or develop pubic hair before 8 years of age. Males will develop enlarged testicles, deepen their voice, or grow pubic hair before 9 years of age. This condition can be stressful for a child that is experiencing physical changes before their peers.
- This review also looks at new evidence for using medications to manage gender dysphoria. Gender dysphoria is a sense of unease a person may have because of a difference between their biological sex at birth and their gender identity. This discomfort can cause anxiety, depression, and thoughts of suicide. Medical management of gender dysphoria is covered under the Oregon Health Plan.
- Medicines that stop the production of hormones which cause changes during puberty are used to treat central precocious puberty and manage gender dysphoria. These medicines are called gonadotropin-releasing hormone agonists and include goserelin, histrelin, leuprolide, nafarelin, and triptorelin.
- Medicines should only be used for a short time (3 years) to stop puberty in children with central precocious puberty. Once the child has reached the age of 11 or 12 years, the medicines can be stopped and puberty will begin again within 12 to 18 months.
- Positive outcomes associated with using these medicines in children are less depression, less anxiety, and improved growth to normal height as an adult.
- Adverse events associated with use of these medicine include slowed growth, increased mood swings, and decreased bone turnover.
- Providers must explain to the Oregon Health Authority why someone needs goserelin, histrelin, leuprolide, nafarelin, and triptorelin before Medicaid will pay for it. This process is called prior authorization.

Purpose for Class Update:

- Examine recently published evidence for safety and efficacy of gonadotropin-releasing hormone (GnRH) agonists (e.g., goserelin, histrelin, leuprolide, nafarelin, triptorelin) for management of pediatric patients with central precocious puberty (CPP) and off-label use of GnRH agonists for puberty suppression in adolescents with gender dysphoria.

Author: Deanna Moretz, PharmD, BCPS

Research Questions:

1. What is the evidence of efficacy and safety for GnRH agonists when used to manage CPP or suppress puberty in adolescents with gender dysphoria?
2. Are there any subgroups of patients who, based on age, ethnicity, comorbidities, disease duration or severity, would particularly benefit or be harmed by a specific GnRH agonist?
3. What is the most current guidance for use of GnRH agonists to manage CPP or gender dysphoria?

Conclusions:

- Two high-quality systematic reviews[1,2] and 2 high-quality clinical practice guidelines[3,4] have been published since the GnRH agonists were last reviewed for CPP and gender dysphoria. No evidence was identified that directly compared on GnRH agonist with another agonist for either CPP or gender dysphoria.
- A 2020 systematic review with meta-analysis examined the effects of long-acting GnRH agonist treatment (triptorelin or leuprolide) on adult height in females with precocious puberty (onset before 10 years of age).[1] Adult height, duration of the treatment, and age at the start of treatment were analyzed.[1] Adult height increased in females who received GnRH agonists compared to those who did not receive treatment (mean difference [MD] 3.2 cm; 95% confidence interval [CI] 1.3 to 5.1 cm, I^2 = 84%; low QoE).[1] Mean height difference in females who started treatment before 8 years of age was 5.1 cm compared to 2.5 cm in females who started treatment at 8 years of age or older.[1] In females who were treated for less than 3 years, adult height was increased by an average of 0.4 cm compared to 5.9 cm in those who were treated for more than 3 years.[1] Duration of treatment was associated with greater height (p=0.005) than age at start of treatment (p=0.084) when compared with females who were not treated (low QoE).
- A 2021 systematic review investigated the long-term efficacy and safety of GnRH agonist treatment in children with CPP.[2] GnRH agonists leuprolide, triptorelin, nafarelin, goserelin, and histrelin were used in studies. Primary outcomes included in the studies were final adult height, body mass index (BMI), incidence of polycystic ovary syndrome (PCOS) in females and androgen excess in males.[2] Compared with no treatment, GnRH agonists increased final adult height and decreased BMI in females with CPP (low QoE).[2] GnRH agonists did not increase the risk of PCOS in females with CPP (low QoE).[2] Evidence was insufficient to make conclusions about androgen excess in males.[2]
- In 2017, the international Endocrine Society published guidance for endocrine treatment of persons with gender dysphoria.[3] They recommend puberty suppression with long-acting GnRH agonists in adolescents with gender dysphoria who have entered puberty at Tanner Stage 2.[3] The primary risks of pubertal suppression in gender-dysphoric adolescents may include adverse effects on bone mineralization, compromised fertility, and unknown effects on brain development.[3]
- An update of World Professional Association for Transgender Health (WPATH) Standards of Care was published in 2022.[4] They recognize that the body of evidence to support the effectiveness of early medical intervention is growing but is still limited, and there are few studies that follow youth into adulthood.[4] WPATH recommends health care professionals use GnRH agonists in eligible transgender and gender diverse people for whom suppressing puberty is indicated.[4] The adolescent should have reached Tanner stage 2 of puberty for pubertal suppression to be initiated with GnRH agonists.[4]
- No populations were identified based on age, race, ethnicity, or comorbidities who would particularly benefit or be harmed from treatment with a specific GnRH agonist.
- In June 2023 House Bill 2002-C was enacted to modify provisions relating to protections for individuals receiving gender-affirming health services.[5] The bill specifies criteria for medical necessity and requires that any denial of services be reviewed and approved by a provider with experience providing or delivering gender-affirming treatment.

Recommendations:

- No changes to the Oregon Health Plan (OHP) Preferred Drug List (PDL) are recommended based on review of the clinical evidence.
- Revise clinical prior authorization (PA) criteria to include Early and Periodic Screening, Diagnostic and Treatment (EPSDT) assessment and alignment with Health Evidence Review Commission (HERC) Guideline Note 127 for management of gender dysphoria with GnRH agonists and recently enacted state legislation.
- Review costs in the executive session.

Summary of Prior Reviews and Current Policy:

- Puberty suppression in adolescents with gender dysphoria is a funded under the OHP Prioritized List of Health Services. In April 2015, the Pharmacy and Therapeutics (P&T) Committee approved use of GnRH agonists in adolescents with documented gender dysphoria at the beginning of puberty.
- The GnRH modulators were last reviewed by the P&T Committee in December 2021 in a review focused on fibroids and endometriosis treatments. Clinical PA criteria for GnRH modulators were separated into two PA documents for GnRH agonists and GnRH antagonists (see **Appendix 3**).
- The PDL status of each GnRH agonist is presented in **Appendix 1**. All GnRH agonists are non-preferred and require PA in patients under 18 years of age to ensure appropriate use for conditions funded under OHP.

Background:

Central Precocious Puberty

Central precocious puberty is defined as the full activation of the hypothalamic-pituitary-gonadal (HPG) axis before 8 years of age in females and before 9 years of age in males.[6] In a population-based study of data from Danish national registries from 1993 to 2001, the incidence of precocious puberty was 20 per 10,000 females and less than 5 per 10,000 males.[7] Although usually idiopathic in females, CPP can be induced by head trauma, neoplasm, radiation, or genetic conditions.[8] Pathologic causes due to physical injury of the central nervous system are more common in males with CPP.[8] In contrast, peripheral precocious puberty occurs when hormonal influences originating outside of the HPG axis (e.g., androgen-secreting tumor, estrogen secreting-tumor, congenital adrenal hyperplasia) produce incomplete, atypically sequenced or rapid pubertal progression.[8]

Central precocious puberty is characterized by sequential maturation of breasts and pubic hair in females and of testicular and penile enlargement and pubic hair in males.[6,8] Tanner stages are used to evaluate pubertal development.[9] Children are rated on a scale of 1-5 with 1 being preadolescent and 5 being fully developed.[9] The onset of puberty is marked by breast development in females (Tanner stage 2 breast development) and testicular enlargement in males (Tanner stage 2 genital development).[10,11] Children with CPP have accelerated linear growth for age, advanced bone age, and pubertal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[8] An LH level of more than 0.3 IU/L is the most reliable laboratory finding for CPP.[8,12] CPP may result in premature cessation of growth and short stature as an adult.

The goal of CPP therapy is to halt pubertal progression and delay epiphyseal maturation, which leads to improvement of final adult height.[13] GnRH agonists are indicated in idiopathic CPP.[6] They work by providing continuous stimulation of the pituitary gonadotrophs, leading to desensitization and decreases in the release of LH and FSH.[14] In open-label, noncomparative, longitudinal studies, the use of GnRH agonists consistently resulted in the regression or stabilization of pubertal symptoms.[15,16] The duration of GnRH agonist therapy should be long enough to optimize final adult height, yet still allow progression of pubertal characteristics at an age that is concurrent with the individual's peers.[17] When GnRH agonist therapy with monthly depot preparations is stopped, normal puberty returns, on average, within 12 to 18 months.[17] Adverse effects with GnRH agonist treatment are rare, but may include allergic reactions, sterile abscess

formation after injection, fracture of implant upon removal, vaginal bleeding, hot flashes, and seizures.[12] Medications approved by FDA for puberty suppression in children with CPP are presented in **Table 1.**

Table 1. Gonadotropin-Releasing Hormone Agonists for Central Precocious Puberty.[18]

Drug/Formulation	Age and Weight (if appropriate)	Dose
Histrelin (SUPPRELIN LA) SC Implant	≥ 2 years	50 mg implant surgically inserted SC every 12 months
Leuprolide (FENSOLVI) 6-month 45 mg SC Suspension	≥ 2 years	45 mg SC every 6 months; discontinue at the appropriate age of puberty onset
Leuprolide (LUPRON DEPOT-PED) 1-month IM Suspension (7.5 mg, 11.25mg, 15 mg)	≥ 1 years and ≤ 25 kg	7.5mg IM once a month; discontinue at the appropriate age of puberty onset
	≥ 1 years and > 25 kg to 37.5 kg	11.25 mg IM once a month; discontinue at the appropriate age of puberty onset
	≥ 1 years and > 37.5 kg	15 mg IM once a month; discontinue at the appropriate age of puberty onset
Leuprolide (LUPRON DEPOT-PED) 3-month IM Suspension (11.25 mg and 30 mg)	≥ 1 years	11.25 mg IM every 3 months or 30 mg IM every 3 months; discontinue at the appropriate age of puberty onset
Leuprolide (LUPRON DEPOT-PED) 6-month IM Suspension (45 mg)	≥ 1 years	45 mg IM every 6 months; discontinue at the appropriate age of puberty onset
Nafarelin (SYNAREL) Nasal Spray	Initiate before 8 years of age in females and before 9 years of age in males	2 sprays (400 mcg) into each nostril twice daily (total daily dose = 1600 mcg)
Triptorelin (TRIPTODUR) 6-month IM Suspension	≥ 2 years	22.5 mg IM every 6 months
Abbreviations: IM = intramuscular; kg = kilograms; mcg = microgram; mg = milligram; SC = subcutaneous		

Gender Dysphoria

Gender dysphoria is the distress experienced by an individual when their gender identity and their gender assigned at birth are discordant.[19] Gender dysphoria is more specifically defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association) as a diagnosis.[20] Gender dysphoria can result in psychologic dysfunction, depression, and suicidal ideation.[20] The prevalence of gender dysphoria is difficult to determine in the general population. Previously, the prevalence in adults was thought to range from 0.005% to 0.014% for people assigned male gender at birth and 0.002% to 0.003% for people assigned female gender at birth.[20] More recent studies suggest that 0.39% to 0.60% of adults identify as transgender, with an increasing prevalence over the past decade.[21] Youth may present to providers stating overtly that they are transgender and requesting a gender assessment, or they may present less overtly with a mood disorder, anxiety or depressive traits, or a caregiver may have concern about social problems such as a change in academic performance or school truancy.[19] Not all children and youth who report gender identities different from their gender assigned at birth will experience persistent gender dysphoria. Retrospective studies suggest gender dysphoria persists from childhood into adulthood in the range of 12% to 27%.[22]

The Oregon Health Authority's Health Evidence Review Commission (HERC) Guideline Note 127 provides guidance on the treatment of gender dysphoria in OHP members.[23] Treatment with GnRH agonists is funded under the OHP if used to delay the onset of puberty.[23] The HERC recommends therapy be initiated at first physical signs of puberty, confirmed by pubertal hormone levels, but no earlier than Tanner stages 2-3.[23] Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and have a comprehensive mental health evaluation.[23] Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.[23]

The World Professional Association for Transgender Health (WPATH) Standards of Care recommend regimens for hormone therapy in adolescents with gender dysphoria that are substantially different from those used in adults. These regimens are adapted to account for the somatic, emotional and mental development that occurs throughout adolescence.[4] Although none of the GnRH agonists are approved by FDA for gender dysphoria, evidence from the use of GnRH agonists in treating CPP is oftentimes extrapolated to individuals with gender dysphoria to delay puberty.[24] GnRH agonists are covered under the OHP medical benefit for management of gender dysphoria. Compendial dosing information for GnRH agonists studied in gender dysphoria is presented in **Table 2**.

Table 2. Gonadotropin-Releasing Hormone Agonists Studied in Gender Dysphoria[18]

Drug/Formulation	Off-Label Dose
Goserelin (ZOLADEX) SC Implant	3.6 mg SC every month
Leuprolide (LUPRON) Suspension	3.75 mg IM every month
Leuprolide (LUPRON DEPOT-PED) 1-month or 3-month IM Suspension	3.75 mg IM every month 11.25 mg IM every 3 months
Triptorelin (TRELSTAR) IM Suspension	3.75 mg IM every month
Abbreviations: IM = intramuscular; kg = kilograms; SC = subcutaneous	

2023 Oregon Legislative Update

In June 2023 House Bill 2002-C was enacted to modify provisions relating to protections for providers and individuals receiving reproductive or gender-affirming health services. The bill specifies criteria for medical necessity and requires that any denial of services be reviewed and approved by a provider with experience providing or delivering gender-affirming treatment. Section 24 states: "Gender-affirming treatment means a procedure, service, drug, device or product that a physical or behavioral health care provider prescribes to treat an individual for incongruence between the individual's gender identity and the individual's sex assignment at birth. The Oregon Health Authority or a coordinated care organization may not: a)Deny or limit coverage under the plan for gender-affirming treatment that is: 1) medically necessary as determined by the physical or behavioral health care provider who prescribes the treatment; and 2) prescribed in accordance with accepted standards of care; b) Deny or limit gender-affirming treatment unless a physical or behavioral health care provider with experience prescribing or delivering gender-affirming treatment has first reviewed and approved the denial of or the limitation on access to the treatment."[5] This legislation will take effect 1/1/24.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) that assessed clinically relevant outcomes of GnRH agonists 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 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 clinical practice guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Adult Height After GnRH Agonist Treatment in Female Children with Precocious Puberty

A 2020 meta-analysis examined the effects of long-acting GnRH agonist treatment on adult height in female children younger than 10 years of age with precocious puberty.[1] Studies published from 1980 through 2018 were identified.[1] Of the 14 studies that met inclusion criteria, 9 were from Europe, 4 were from the Middle East, and one was from Asia.[1] Leuprolide was assessed in one study, either triptorelin or leuprolide were assessed in another study, and triptorelin was assessed in all of the other studies.[1] The GnRH agonist was administered every 28 days in almost all of the studies except two studies which used 21- to 25-day intervals.[1] The mean duration of treatment ranged from 1.9 to 4.2 years.[1] Only 2 studies were randomized. One study used a historical control.[1] The RoB was evaluated as follows: randomization of sequence generation (high RoB), allocation sequence concealment (high RoB), blinding of participants and personnel (high RoB), blinding of outcome assessors (moderate RoB), incomplete outcome data (low RoB), and selective outcome reporting (low RoB).[1]

A total of 608 treated and 395 untreated females were included in the meta-analysis.[1] The age in each study ranged from 6.3 to 9.0 years.[1] Adult height, duration of the treatment, and age at the start of treatment were analyzed.[1] The adult height increased in the females who were treated with GnRH agonists compared to those who did not receive treatment for early puberty.[1] The meta-analysis showed a pooled mean difference in adult height of 3.2 cm between treated and untreated individuals (95% CI 1.3 to 5.1 cm, I^2=84%; low QoE).[1] The mean height difference in the females who started the treatment before 8 years of age was 5.1 cm (95% CI 0.4 to 9.8, I^2=94%; low QoE).[1] In a subgroup of females older than 8 years of age at start of treatment, the mean height difference was smaller at 2.5 cm (95% CI 0.9 to 4.0, I^2=53%; low QoE).[1] In females treated for less than 3 years, differences in adult height were not statistically significant, with an average increase of 0.4 cm versus those who were not treated (95% CI −1.8 to 2.7, I^2=74%). In females treated for more than 3 years, adult height was increased by an average of 5.9 cm versus those who were not treated (95% CI 3.7 to 8.1, I^2=77%; low QoE).[1]

This systematic review provides low-quality evidence that the adult height achieved with puberty suppression with GnRH agonists is associated with duration of treatment (p=0.005) but does not provide evidence that the age at treatment initiation improves the adult height achieved (p=0.084).[1]Use of an GnRH agonist for more than 3 years increased adult height; however, this meta-analysis did not find that treatment for less than 3 years had an effect on adult height achieved.[1] However, significant heterogeneity was identified between the studies in this meta-analysis, so there is high uncertainty of the effects found and more studies are needed.[1]

Long-Term Efficacy and Safety of GnRH Agonist Treatment in Children with Central Precocious Puberty

A 2021 systematic review investigated the long-term efficacy and safety of GnRH agonist treatment in children with CPP.[2] Literature was searched through November 2019.[2] Ninety-eight studies with a total of 5475 individuals (98.5% were female) met inclusion critieria.[2] The average age of CPP onset in each study ranged from 4.5 to 8 years, and the average age of GnRH agonist treatment initiation in each study ranged from 5 to 9.3 years.[2] The GnRH agonists used in the studies included leuprolide, triptorelin, nafarelin, goserelin, and histrelin.[2] Of the 98 total studies, 18 were RCTs (n=1303) with moderate to high RoB and the remaining 81 (n=4172) were single-arm studies with high RoB.[2] Thirteen studies (n=1047) compared GnRH agonist treatment with no treatment, and six studies

(n=310) compared GnRH agonist treatment with GnRH agonist plus growth hormone.[2] Treatment duration in the studies ranged from 3 months to 5 years.[2] Selection bias and attrition bias were the primary concerns for the RCTs.[2] The QoE for each outcome were graded as very low to moderate.[2]

The primary efficacy outcome was final adult height. Harm outcomes included BMI, the incidence of polycystic ovary syndrome (PCOS) among females and androgen excess among males.[2] The RCTs showed that GnRH agonist treatment increased final adult height compared to no treatment by a mean difference [MD] of 4.83 cm (95% CI 2.32 to 7.34; I^2 = 49%; 4 studies; n=242; low QoE).[2] Lower BMI was observed in females treated with GnRH agonists compared with no treatment (MD −1.01 kg/m^2; 95% CI −1.64 to −0.37; I^2 = 0%; 3 studies; n=334; low QoE).[2] The incidence of PCOS was not found to be impacted by GnRH agonist treatment (RR 1.21; 95% CI 0.46 to 3.15; I^2 = 48%; 3 studies; n=179; low QoE).[2] There is insufficient evidence to know the effects of GnRH agonists on androgen excess in males.[2]

Compared with no treatment, there is low QoE that GnRH agonists increase final adult height.[2] GnRH agonists did not increase the risk of PCOS or obesity in females with CPP (low QoE).[2] Evidence regarding other key long-term outcomes (such as infertility and malignant or metabolic diseases) was considered insufficient to make conclusions.[2]

After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[25-31]

New Clinical Practice Guidelines:

Endocrine Society Clinical Practice Guideline: Gender Dysphoria

In 2017, the global Endocrine Society updated a 2009 practice guideline titled “Endocrine Treatment of Transsexual Persons” and renamed the guidance as “Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons”.[3] This nomenclature change reflects updated medical perspectives on management of gender dysphoria. This publication was co-sponsored by the American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and WPATH.[3] Gender incongruence is an umbrella term used when the gender identity or gender expression differs from what is typically associated with the designated gender.[3] Not all individuals with gender incongruence have gender dysphoria or seek treatment.[3] Two systematic reviews supported the evidence-based recommendations developed by the guideline task force.

The guideline recommends treatment of gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage 2 by suppression with long-acting GnRH agonists.[3] An advantage of using GnRH agonists is the reversibility of the intervention.[3] If the individual no longer desires transition, they can discontinue pubertal suppression.[3] A benefit of pubertal suppression at early puberty may be better psychological and physical outcomes compared with starting gender-affirming treatment long after the first phases of puberty.[3] Although there is sparse evidence regarding the use of GnRH agonists in adolescents with gender dysphoria; in adolescents with CPP spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH agonists.[3]

The primary risks of pubertal suppression in gender-dysphoric/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development.[3] Few data are available on the effect of GnRH agonists on bone mineral density (BMD) in adolescents with gender-dysphoric/gender incongruence.[3] In children with CPP, treatment with GnRH agonists has been found to result in a decrease of BMD during treatment by some, but not others.[3] Recommended monitoring for individuals taking GnRH agonists includes Tanner staging, blood pressure, height and weight measurements every 3 to 6 months;

LH, FSH, estradiol (transgender females), and testosterone levels (transgender males) every 6 to 12 months; and BMD using dual-energy X-ray absorptiometry (DEXA) every 1 to 2 years.[3]

Clinicians may add gender-affirming hormones to induce puberty (oral or transdermal estradiol in transgender women and intramuscular or subcutaneous testosterone in transgender men) after a multidisciplinary team has confirmed the persistence of gender dysphoric/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment.[3] Most adolescents have this capacity by age 16 years old.[3] There may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age.[3] The care of peripubertal youths and older adolescents, should be cared for by an expert multidisciplinary team comprised of medical professionals and mental health professionals.[3] The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents.[3]

Specific graded recommendations and the quality of evidence regarding use of GnRH agonists in children and adolescents are summarized below:

- Recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with gender-dysphoric/gender incongruence. (Strong Recommendation, Moderate QoE).[3]
- Suggest that adolescents who meet diagnostic criteria for gender-dysphoric/gender incongruence who are requesting treatment, and fulfill criteria for treatment, initially undergo treatment to suppress pubertal development. (Weak Recommendation, Moderate QoE).[3]
- Recommend that where indicated, long-acting GnRH agonists are used to suppress pubertal hormones. (Strong Recommendation, Moderate QoE).[3]
- Suggest that clinicians begin pubertal hormone suppression after first signs of physical changes of puberty. (Weak Recommendation, Moderate QoE).[3]

<u>World Professional Association for Transgender Health</u>

An update of WPATH Standards of Care was published in 2022 due to growing scientific evidence for the care of transgender and gender diverse people.[4] This professional organization was founded in 1979 to create an international community of providers committed to understanding the treatment of gender dysphoria. Recommendations were based on data derived from systematic literature review.[4] Most of the research and experience in this field comes from a North American and Western European perspective.[4] The term gender incongruence is recognized as a condition in the International Classification of Diseases and Related Health Problems, 11th Version of the World Health Organization (ICD-11) and will replace the term gender dysphoria in subsequent publications.[4]

A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical and surgical treatments over time.[4] Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood.[4] WPATH recommends health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:

- The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care.[4]
- The experience of gender diversity/incongruence is marked and sustained over time.[4]
- The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.[4]
- The adolescent's mental health is assessed and any concerns that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed.[4]
- The adolescent has been informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.[4]

- The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.[4]
- WPATH recommends health care professionals use GnRH agonists to suppress endogenous sex hormones in eligible transgender and gender diverse people for whom puberty blocking is indicated.[4]
- WPATH recommends health care professionals prescribe GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy.[4]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alert[32]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Histrelin	SUPPRELIN LA	4/22	Warnings and Precautions	Pseudo tumor cerebri (idiopathic intracranial hypertension) have been reported in pediatric patients receiving GnRH agonists. Monitor patients for signs and symptoms of pseudo tumor cerebri, including headache, papilledema, blurred vision, diplopia, loss of vision, pain behind the eye or pain with eye movement, tinnitus, dizziness, and nausea.
Leuprolide	LUPRON DEPOT-PED, FENSOLVI			
Nafarelin	SYNAREL			
Triptorelin	TRIPTODUR			

Randomized Controlled Trials:

A total of 46 citations were manually reviewed from the initial literature search. After further review, 46 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
histrelin acetate	SUPPRELIN LA	KIT	IL	N
histrelin acetate	SUPPRELIN	KIT	SQ	N
leuprolide acetate	LUPRON DEPOT-PED	KIT	IM	N
leuprolide acetate	LUPRON DEPOT	SYRINGEKIT	IM	N
leuprolide acetate	LUPRON DEPOT	SYRINGEKIT	IM	N
leuprolide acetate	LUPRON DEPOT (LUPANETA)	SYRINGEKIT	IM	N
leuprolide acetate	LUPRON DEPOT-PED	SYRINGEKIT	IM	N
leuprolide acetate	LEUPROLIDE ACETATE	KIT	SQ	N
leuprolide acetate	ELIGARD	SYRINGE	SQ	N
leuprolide acetate	FENSOLVI	SYRINGE	SQ	N
leuprolide acetate	LEUPROLIDE ACETATE	VIAL	SQ	N
leuprolide mesylate	CAMCEVI	SYRINGE	SQ	N
leuprolide/norethindrone acet	LUPANETA PACK	KT SYR TAB	MC	N
nafarelin acetate	SYNAREL	SPRAY	NS	N
triptorelin pamoate	TRELSTAR	VIAL	IM	N
triptorelin pamoate	TRIPTODUR	VIAL	IM	N

Appendix 2: Medline Search Strategy

Search # 1: Ovid MEDLINE(R) 1996 to November Week 2 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to **November 17, 2022**

1. central precocious puberty.mp. or exp Puberty, Precocious/	2688
2. exp Gender Dysphoria/	842
3. exp Goserelin/	1098
4. exp Leuprolide/	2241
5. exp Nafarelin/	129
6. Gonadotropin-Releasing Hormone/ or histrelin.mp.	16174
7. Triptorelin Pamoate/	1242
8. 1 or 2	3527
9. 3 or 4 or 5 or 6 or 7	18895
10. 8 and 9	784
11. limit 10 to (english language and humans and yr="2015 -Current")	279
12. limit 11 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study 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")	41

Search # 2: Ovid MEDLINE(R) 1996 to June Week 2 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to **June 19, 2023**

1	central precocious puberty.mp. or exp Puberty, Precocious/	2790
2	exp Gender Dysphoria/	909
3	exp Goserelin/	1106
4	exp Leuprolide/	2266
5	exp Nafarelin/	129
6	Gonadotropin-Releasing Hormone/ or histrelin.mp.	16530
7	Triptorelin Pamoate/	1247
8	1 or 2	3696
9	3 or 4 or 5 or 6 or 7	19275
10	8 and 9	824
11	**limit 10 to (english language and humans and yr="2022 -Current")**	70
12	limit 11 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study 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")	5

Gonadotropin-Releasing Hormone Agonists

Goals:

- Restrict use of gonadotropin-releasing hormone (GnRH) agonists to medically appropriate conditions funded under the Oregon Health Plan.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Up to 6 months

Requires PA:

- All Non-preferred -GnRH agonists (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 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 diagnosis central precocious puberty or other endocrine disorder?	Yes: Go to #5	No: Go to #6
5. Is the prescriber a pediatric endocrinologist?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh; deny for medical appropriateness.
6. Is the diagnosis gender dysphoria?	**Yes:** Approve for 1 year	**No:** Go to #7

Approval Criteria			
~~7.~~ • ~~Diagnosis of gender dysphoria made by a health professional with experience in gender dysphoria~~ • ~~Onset of puberty confirmed by physical changes and hormone levels, but no earlier than Tanner Stages 2.~~ • ~~The prescriber agrees criteria in the Guideline Note* of the OHP List of Prioritized Services have been met.~~ ~~*From Guideline Note 127: To qualify for cross-sex hormone therapy, the patient must:~~ ~~A) have persistent, well-documented gender dysphoria;~~ ~~B) have the capacity to make a fully informed decision and to give consent for treatment;~~ ~~C) have any significant medical or mental health concerns reasonably well controlled; and~~ ~~D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).~~	~~**Yes:** Approve for up to 6 months.~~	~~**No:** Deny; Medical Appropriateness~~	
~~8.~~7. Is the patient of childbearing potential and pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness		**No:** Go to #9
~~9.~~8. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to # 10		**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~10.~~9. Is this request for treatment of breast cancer or prostate cancer?	**Yes:** Approve up to 1 year	**No:** Go to #11
~~11.~~10. Is this request for leuprolide for the management of preoperative anemia due to uterine fibroids (leiomyoma)?	**Yes:** Approve for up to 3 months	**No:** Go to #12
~~12.~~11. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
~~13.~~12. Has the patient tried and failed an adequate trial of at least 1 of the preferred first line endometriosis therapy options for at least 3 months including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Approve for 6 to 12 months, depending on selected medication. *Note maximum recommended duration of therapy for nafarelin and goserelin is 6 months. Leuprolide therapy should not exceed 12 months. If requesting continuation of therapy beyond FDA-approved duration, pass to RPh. Deny; medical appropriateness.	**No:** Go to #14 *First-line therapy options such as hormonal contraceptives or progestins do not require PA
~~14.~~13. RPh only: All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.		

P&T / DUR Review: *8/23 (DM); 12/21 (DM); 3/19 (DM); 5/15*
Implementation: *1/1/24; 1/1/22; 5/1/19*

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Prior Authorization Criteria Update: Estrogen Replacement (oral, topical, vaginal); Androgens (oral, topical, parenteral)

Plain Language Summary:

- The Oregon legislature recently passed a bill to ensure individuals receiving gender-affirming care have access to health care services.

Purpose of Update:

- The purpose of this update is to evaluate pharmacy utilization of drugs that can be used for gender-affirming care and review requirements in recently passed state legislation.

Conclusions:

- New legislation specifies that the Oregon Health Authority may not deny or limit coverage under the plan for gender-affirming treatment that is medically necessary and prescribed in accordance with accepted standards of care. Before denying gender-affirming treatment a provider with experience prescribing or delivering gender-affirming treatment must first review and approve the denial of or the limitation on access to the treatment.
- In an analysis of members with paid or denied FFS claims from 10/1/22 to 12/31/22, members were prescribed estrogen (n=318 members), testosterone (n=195), progesterone products (n=243), and gonadotropin-releasing hormone (GnRH) agonists (n= 11; e.g., leuprolide). Members with claims for more than one product within the same drug class or in different drug classes may be counted more than once.
- Most members with claims for estrogen or progesterone had initial paid claims which is consistent with the current policy where preferred products are available without prior authorization for many members. Denied claims were more common for vaginal estrogen products which are generally prescribed for diagnoses other than gender-affirming treatment.
- Claims for testosterone were initially paid for only 29% of members and paid within 90 days of an initial denial for 18% members. Fifty-three percent of members prescribed testosterone had an initial denied claim without any subsequent paid claims for a comparable product (n=105). Most of these members with denied claims for testosterone were enrolled in a CCO or had other insurance in the 90 days following an initial denial, which may be why claims were not paid by FFS. Only 8% of members had a denied prior authorization (PA) for testosterone and 17% of members had no PA submitted.
- The majority of requests for GnRH agonists were approved. Only 11 members had claims for GNRH agonists, and all but 1 member ultimately had a claim paid by FFS within 90 days following the first claim.

Recommendation:

- Update PA criteria for estrogen and testosterone products to align with recently passed state legislation **(Appendix 1**).

Background

2023 Oregon Legislative Update

In June 2023, House Bill 2002-C was enacted to modify provisions relating to protections for providers and individuals receiving gender-affirming health services. Section 24 states: "Gender-affirming treatment means a procedure, service, drug, device or product that a physical or behavioral health care provider prescribes to treat an individual for incongruence between the individual's gender identity and the individual's sex assignment at birth.

The Oregon Health Authority or a coordinated care organization may not:

a) Deny or limit coverage under the plan for gender-affirming treatment that is:

1) medically necessary as determined by the physical or behavioral health care provider who prescribes the treatment; and

2) prescribed in accordance with accepted standards of care;

b) Deny or limit gender-affirming treatment unless a physical or behavioral health care provider with experience prescribing or delivering gender-affirming treatment has first reviewed and approved the denial of or the limitation on access to the treatment."[1]

A review of the estrogen and androgen replacement PA criteria resulted in additional language for requests of either agent to support gender-affirming therapy.

Brief Drug Use Evaluation

This brief drug use evaluation assessed members with paid or denied claims for drugs that can be used for gender-affirming care. Drug classes included androgens, estrogens, progestational agents, and GNRH agonists. Currently all androgens and GnRH agonists require prior authorization to ensure use for a funded and medically appropriate indication. Because estrogens are commonly used for other indications such as symptoms of menopause, PA is only required for members under 18 years of age. Preferred progesterone products are available without PA.

Members were included if they had paid or denied fee-for-service (FFS) claims for these drugs from 10/1/22 to 12/31/22. Members were categorized based on whether the IE was paid or denied and based on subsequent claims and enrollment status changes in the 90 days following the IE.

Table 1 shows initial claim status for members with paid or denied claims based on drug class. If members had claims in multiple drug classes or denied claims for more than one product, they may be counted more than once. The most commonly prescribed classes included androgens and oral estrogens. Paid claims were more common for estrogens and progestational agents which are available without PA for preferred products for many members. Denied claims were more common for androgens and GnRH agonists which require PA for all products. A paid claim in the subsequent 90 days generally indicates that a PA was submitted and approved based on clinical criteria. While the majority of these members had a paid claim within 30 days of the initial denial, this demonstrates a delay in care for these members. Eighteen percent (n=35) of members with claims for testosterone had an initial denial but subsequent claim paid by FFS. The number of members with claims for GnRH agonist was smaller, but a large proportion (36%, n=4) had a subsequent paid claim. More than half of members with claims for androgens (53%) had an initial denial and no subsequent paid claim within 90 days. Diagnoses available in medical claims in the 6 months prior to or during the evaluation window are listed in **Table 2**. About 75% of members with no subsequent paid FFS claims were enrolled in a CCO, lost eligibility, or had other primary insurance coverage within 90 days of the initial denial which may account for the lack of paid FFS claims (**Table 3**). A PA for testosterone was denied for 8 members (8%) and not requested for 17 members (16%).

Table 1. Members with paid or denied claims for drugs used in gender affirming treatment

	Initially Paid		Initially Denied & Paid Within 90 days		No Drugs Paid Within 90 Days		Total
	#	%	#	%	#	%	
Androgens, Topical & Parenteral	57	29%	35	18%	105	53%	195
Estrogen Replacement, Oral	169	93%	2	1%	10	6%	181
Estrogen Replacement, Topical	67	93%	1	1%	4	5%	72
Estrogen Replacement, Vaginal	52	80%	9	14%	4	6%	65
GnRH Agonists	5	45%	4	36%	1	18%	11
Progestational Agents	237	98%	5	2%	1	0%	243

Table 2. Diagnoses for members in the 6 months prior to or during the evaluation window

	Initially paid		Initially Denied & Paid Within 90 days		No Drugs Paid Within 90 days	
N=	522	%	54	%	125	%
Gender identity disorders (F64x)	74	14%	22	41%	39	31%
Testicular dysfunction (E29x)	11	2%	4	7%	28	22%
Menopausal and other perimenopausal disorders (N95x)	81	16%	3	6%	1	1%
Excessive, frequent and irregular menstruation (N92x)	46	8%	2	4%	4	3%
Other abnormal uterine and vaginal bleeding (N93x)	41	7%	4	7%	0	0%

Table 3. Enrollment and PA status for members with no paid claims after an initial denial

	Enrolled in CCO		Lost Eligibility		Has Other Insurance		PA Approved		PA Denied		PA Not Requested		Total #
	#	%	#	%	#	%	#	%	#	%	#	%	
Androgens, Topical & Parenteral	37	35%	3	3%	39	37%	1	1%	8	8%	17	16%	105
Estrogen Replacement, Oral	3	30%	1	10%	4	40%	0	0%	0	0%	2	20%	10
Estrogen Replacement, Topical	0	0%	0	0%	4	100%	0	0%	0	0%	0	0%	4
Estrogen Replacement, Vaginal	1	25%	0	0%	1	25%	0	0%	0	0%	2	50%	4
GnRH Agonists	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	1
Progestational Agents	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1

References:

1. Oregon Legislature 2023 Updates. https://olis.oregonlegislature.gov/liz/2023R1/Downloads/MeasureDocument/HB2002/Enrolled. Accessed June 28, 2023.

Appendix 1. Proposed Prior Authorization Criteria

Estrogen Derivatives

Goal(s):

- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred estrogen derivatives
- ~~All estrogen derivatives for patients <18 years of age~~

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.	
~~Is the estrogen requested for a patient ≥18 years old?~~	~~**Yes:** Go to #3~~	~~**No**: Go to #4~~
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require prior authorization • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class ~~and approve for up to 12 months.~~	**No:** Go to #3 ~~Approve for up to 12 months.~~

Approval Criteria		
3. Is the request for a funded diagnosis?	**Yes**: Approve for up to 6 months	**No:** If non-funded and current age ≥21 years: Deny; not funded by the OHP If non-funded and current age < 21 years: Go to #4
~~Is the medication requested for gender-affirming care?~~	~~**Yes:** Go to #5~~	~~**No:** Go to #6~~
~~3. Have **all** of the following criteria been met?~~ ~~• Patient has the capacity to make fully informed decisions and to give consent for treatment; and~~ ~~• If patient <18 years of age, the prescriber is a pediatric endocrinologist~~ ~~• The prescriber agrees criteria in Guideline Notes on the OHP List of Prioritized Services have been met.~~ ~~See: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-127.docx~~	~~**Yes:** Approve for up to 6 months~~	~~**No**: Pass to RPh; Deny; medical appropriateness.~~
~~Is the medication requested for hypogonadism?~~	~~**Yes:** Approve for up to 6 months~~	~~**No**: Go to #7~~
~~RPh only: All other indications need to be evaluated to see if funded under the OHP.~~	~~If funded and prescriber provides supporting literature: Approve for up to 12 months.~~	~~If non-funded and current age ≥21 years: Deny; not funded by the OHP~~ ~~If non-funded and current age < 21 years: Go to #8~~
4. 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 #~~9~~5	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
5. Is the request for: a) an FDA approved indication AND b) for a preferred product or has the patient failed to have benefit with, or have contraindications or intolerance to the preferred products?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *8/23 (SS); 8/22 (KS), 1/17 (SS); 11/15 (KS)*
Implementation: *TBD; 4/1/17; 1/1/16*

Testosterone

Goal(s):

- Restrict use to medically appropriate conditions funded under the Oregon Health Plan (use for sexual dysfunction or body-building is not covered)
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 months

Requires PA:

- All testosterone 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. Is the medication requested for AIDS-related cachexia?	**Yes:** Go to #~~8~~7	**No:** Go to #3

Approval Criteria		
3. Is the medication requested for one of the following diagnoses? • Primary Hypogonadism (congenital or acquired): defined as testicular failure due to such conditions as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, trauma, or toxic damage from alcohol or heavy metals OR • Hypogonadotropic Hypogonadism (congenital or acquired): as defined by idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma or radiation	**Yes:** Go to #4	**No:** Go to #6
4.Is there documentation of 2 morning (between 8 a.m. to 10 a.m.) tests (at least 1 week apart) demonstrating low testosterone levels at baseline as defined by the following criteria: • Total serum testosterone level less than 300ng/dL (10.4nmol/L); OR • Total serum testosterone level less than 350ng/dL (12.1nmol/L) AND free serum testosterone level less than 50pg/mL (or 0.174nmol/L)	**Yes:** Go to #5	**No:** Deny; medical appropriateness

Approval Criteria		
5.Is there documentation based on submitted chart notes of any of the following diagnoses: • A recent major cardiovascular event (i.e., myocardial infarction, stroke or acute coronary syndrome) within the past 6 months • Heart failure with uncontrolled symptoms (i.e., NYHA Class III-IV, presence of edema, or evidence of fluid retention) • Benign prostate hyperplasia with uncontrolled symptoms or presence of severe lower urinary tract symptoms (i.e., frequent symptoms of incomplete emptying, increased frequency, intermittency, urgency, weak stream, straining, or nocturia) • Breast cancer • Prostate cancer (known or suspected) or elevated PSA with prior use of testosterone • Untreated obstructive sleep apnea with symptoms • Elevated hematocrit (>50%)	**Yes:** Deny; medical appropriateness	**No:** Go to #8
6. Is the medication requested for gender-affirming care?	**Yes:** Go to #7	**No:** Go to #~~9~~8
~~7. Have **all** of the following criteria been met?~~ ~~• Patient has the capacity to make fully informed decisions and to give consent for treatment; and~~ ~~• If patient <18 years of age, the prescriber is a pediatric endocrinologist; and~~ ~~• The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.~~ ~~See: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-127.docx~~	~~**Yes:** Go to #8~~	~~**No**: Pass to RPh. Deny; medical appropriateness.~~

Approval Criteria		
7. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a co-pay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
8. RPh only: all other indications need to be evaluated to see if funded under the OHP. Note: Testosterone should not be prescribed to patients who have any contraindicated diagnoses listed in question #5.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If not funded: Current age ≥ 21 years: Deny; not funded by the OHP Current age < 21 years: prescriber provides documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) AND supporting literature then approve for up to 12 months.

P&T Review: *8/23 (SS); 11/18 (SS); 11/15; 2/12; 9/10; 2/06; 2/01; 9/00*
Implementation: *TBD; 1/1/19; 5/1/16; 1/1/16; 7/31/14; 5/14/12, 1/24/12, 1/1/11, 9/1/06*