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, December 7th, 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	T. Douglass (OHA)
1:30 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)

A. Quarterly Utilization Report
B. Ycanth™ (cantharidin) Abbreviated Drug Review
C. Oncology Prior Authorization Updates
D. Orphan Drug Policy Updates
    1. Public Comment

1:35 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. Buprenorphine: Place in Therapy for Chronic Pain
2. Update on the Use of SGLT-2 Inhibitors
3. 2023 Global Initiative for Chronic Obstructive Lung Disease Report: Focus on Revised Recommendations for Inhaler Products

IV. DUR NEW BUSINESS

1:55 PM	A. Nexletol® (bempedoic acid) Prior Authorization Update	M. Herink (OSU)

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

2:05 PM	B. Over-the-Counter Policy Proposal 1. Policy Discussion 2. Opill™ (norgestrel) Abbreviated Drug Review 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
	V. PREFERRED DRUG LIST NEW BUSINESS	
2:15 PM	A. Topical Moisturizers Class Review 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
2:30 PM	B. Erythropoiesis Stimulating Agents Literature Scan 1. Literature Scan/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:45 PM	C. Jesduvroq™ (daprodustat) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
3:00 PM	BREAK	
3:15 PM	D. Antidepressants Class Update and New Drug Evaluation 1. Class Update/Safety Edit 2. Zurzuvae™ (zuranolone) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
3:40 PM	E. Filspari™ (sparsentan) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
3:55 PM	F. Oral and Topical Antifungals Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Vivjoa® (oteseconazole) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
4:15 PM	VI. EXECUTIVE SESSION	
5:00 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, October 5th, 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; Patrick DeMartino, MD; Russ Huffman, PMHNP; Cat Livingston, MD; Caryn Mickelson, PharmD; Robin Moody; 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; Trevor Douglass, DC, MPH; Amanda Parish, LCSW; Jennifer Bowen; Dee Weston, JD; Kyle Hamilton; Chris DeMars

Audience: Tara Gonzales, Sobi*; Christine Donahue, CSL Behring*; Rick Kegler, BioMarin*; Lynda Finch, Biogen*; Rochelle Yang, Teva*; Amy Breen, Teva; Cheryl Bondy, Sobi; Jonathan Abdul-Haqq, CSL Behring; Gibby Rodriguez; Madonna McGuire Smith, PNWBD; Kate Ramsay, EOCCO; Cecilia Stewart, EOCCO; Teresa Blair, Ipsen; Katie Vo, Ipsen; Bill McDougall, Biogen; Melissa Snider, Gilead; Melissa Abbott, Eisai; Craig Plauschinat, Eisai; Gary Parenteau, Dexcom; Matt Worthy, OHSU; Tiina Andrews, UHA; Sebastian Branton, student @ UHA; Brandie Feger, Advanced Health CCO; Lori McDermott, Viking HCS; Deron Grothe, Braeburn; Chris Johnson, Biomarin; Georgette Dzwilewski, Indivior; Nirmal Ghuman, Janssen; Susan Lattimore; Michele Sabados, Alkermes; Ann Nelson, Vertex; Alison Bass, CSL Behring; Shauna Wick, Trillium; Jeff White, Sumitomo; Lisa Pulver J&J; Bill Robie, NBDF; Richard Maloy

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

D. Department Update provided by Andrew Gibler, PharmD

II. CONSENT AGENDA TOPICS

A. CMS Annual Report

B. P&T Annual Report

C. Colony Stimulating Factor (CSF) Class Update and New Drug Evaluation (NDE)
Recommendation:
- No PDL changes recommended based on the review of recently published evidence
- Evaluate costs in executive session

D. Opioid Reversal Agents Class Update
Recommendation:
- No PDL changes recommended based on the review of recently published evidence
- Evaluate costs in executive session

E. Substance Use Disorder Literature Scan
Recommendation:
- No PDL changes recommended based on the review of recently published evidence
- Evaluate costs in executive session

F. Parenteral Antipsychotics Literature Scan
Recommendation:
- No PDL changes recommended based on the review of recently published evidence
- Evaluate costs in executive session

G. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Elrexfio (elranatamab-bcmm); Akeega (niraparib and abiraterone acetate); Vanflyta (quizartinib); and Talvey (talquetamab-tgvs) to table 1 in the Oncology Agents prior authorization (PA) criteria

H. Orphan Drug Policy Updates
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Sohonos (palovarotene) and Veopoz (pozelimab-bbfg) based on FDA-approved labeling
ACTION: Motion to approve, 2nd, all in favor

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III. PREFERRED DRUG LIST (PDL) NEW BUSINESS

A. RSV Prior Authorization Update: Kathy Sentena, PharmD
Recommendation:
- Update the clinical PA criteria to align with the Advisory Committee on Immunization Practices (ACIP) recommendations for combination use of prophylactic therapies
Public Comment: Tara Gonzales, Sobi
ACTION: Motion to approve, 2nd, all in favor

B. Gene Therapies for Hemophilia A, Hemophilia B, and Beta-thalassemia DERP Summary & NDE: Sara Fletcher, PharmD
Recommendations:
- Designate betibeglogene autotemcel, etranacogene dezaparvovec, and valoctocogene roxaparvovec-rvox non-preferred on the PDL
- Apply PA to ensure clinically appropriate utilization
Public Comment: Christine Donahue, CSL Behring; Rick Kegler, BioMarin
ACTION: The Committee modified the proposed betibeglogene autotemcel clinical PA criteria to allow for approval in people over 35 years of age with beta thalassemia
Motion to approve, 2nd, all in favor

C. SGLT-2 Inhibitors Class Update: Kathy Sentena, PharmD
Recommendations:
- No PDL changes recommended based on the review of recently published evidence
- Update PA criteria to allow for preferred SGLT2 therapies to be used first-line in treatment of T2D
- Maintain bexagliflozin and sotagliflozin as non-preferred
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

D. Alzheimer's Drugs Class Update and New Drug Evaluation: Dave Engen, PharmD
Recommendations:
- Create a new PDL class: Monoclonal Antibodies for Alzheimer's Disease
- Designate lecanemab as non-preferred on the PDL
- Implement PA criteria for lecanemab and update existing criteria as proposed
Public Comment: Lynda Finch, Biogen
ACTION: The Committee recommended removing the requirement for amyloid imaging in renewal criteria
Motion to approve, 2nd, all in favor

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E. VMAT-2 Inhibitors Class Update: Deanna Moretz, PharmD

Recommendations:

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

Public Comment: Rochelle Yang, Teva

ACTION: After considering input from the Mental Health Clinical Advisory Group (MHCAG), the Committee recommended revising the proposed clinical PA criteria to remove the requirement of a specialist for initial approval and to update the renewal criteria to require a clinically significant reduction in symptoms of tardive dyskinesia from baseline

Motion to approve, 2nd, all in favor

IV. DUR NEW BUSINESS

A. Asthma Rescue Inhalers Drug Use Evaluation: Sara Fletcher, PharmD

Recommendations:

- Implement one-time targeted provider fax notifications requesting SABA therapy reassessment for specific patients as proposed
- Implement targeted RetroDUR to fax provider notification when 3 SABA inhalers are filled within 6 months (Exclude patients with COPD diagnosis)
- Implement a quantity limit of 6 SABA claims in 6 months (Exclude patients with COPD diagnosis)

ACTION: The Committee rejected the proposed SABA quantity limit

Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Tim Langford, PharmD; Cat Livingston, MD; Caryn Mickelson, PharmD; Robin Moody; 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, Dee Weston, JD; Kyle Hamilton

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VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. CSF Class
Recommendation: Make Nyvepria (pegfilgrastim-apgf) non-preferred
ACTION: Motion to approve, 2nd, all in favor

B. Opioid Reversal Agents
Recommendations: Add OTC reversal agents as covered products and make Opvee (nalmefene) and naloxone cartridge preferred
ACTION: Motion to approve, 2nd, all in favor

C. Substance Use Disorder
Recommendations: Make Brixadi preferred and Sublocade Voluntary non-preferred
ACTION: Motion to approve, 2nd, all in favor

D. Parenteral Antipsychotics
Recommendations: Make Uzedy (risperidone) preferred
ACTION: Motion to approve, 2nd, all in favor

E. SGLT-2 Inhibitors
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

F. Alzheimer's Drugs
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

G. VMAT-2 Inhibitors
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: April 2022 - March 2023

Eligibility	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
Total Members (FFS & Encounter)	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	1,375,185	1,381,362	1,389,121	1,341,014
FFS Members	112,522	113,945	111,881	115,910	113,720	117,050	118,585	118,506	120,719	124,278	118,766	122,639	117,377
OHP Basic with Medicare	8,510	8,597	8,424	8,606	8,473	8,710	8,899	8,720	8,696	8,865	8,706	8,797	8,667
OHP Basic without Medicare	10,595	10,601	10,503	10,497	10,255	10,368	10,396	10,140	10,077	10,182	9,945	10,050	10,301
ACA	93,417	94,747	92,954	96,807	94,992	97,972	99,290	99,646	101,946	105,231	100,115	103,792	98,409
Encounter Members	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	1,250,907	1,262,596	1,266,482	1,223,637
OHP Basic with Medicare	90,661	92,068	93,206	94,346	95,446	96,256	97,094	98,309	98,992	99,800	100,627	101,457	96,522
OHP Basic without Medicare	68,580	68,801	68,956	69,022	69,064	68,981	69,116	69,282	69,339	68,751	68,998	68,768	68,972
ACA	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	1,082,356	1,092,971	1,096,257	1,058,144

Gross Cost Figures for Drugs	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	YTD Sum
Total Amount Paid (FFS & Encounter)	$106,389,526	$111,633,595	$113,399,909	$104,297,269	$117,413,950	$108,903,226	$109,922,182	$111,531,474	$112,851,936	$119,544,599	$110,382,879	$126,871,970	$1,353,142,514
Mental Health Carve-Out Drugs	$11,632,498	$12,126,081	$11,928,952	$11,100,725	$11,884,904	$11,155,937	$11,193,862	$11,310,533	$11,529,809	$12,108,470	$11,203,240	$11,197,196	$138,372,206
OHP Basic with Medicare	$11,471	$9,259	$10,001	$7,612	$3,774	$5,976	$4,972	$2,989	$9,065	$11,372	$5,010	$9,726	$91,226
OHP Basic without Medicare	$4,144,754	$4,338,839	$4,413,433	$3,991,902	$4,330,790	$4,140,126	$4,048,426	$4,092,817	$4,210,889	$4,219,724	$3,926,597	$3,924,395	$49,782,691
ACA	$7,388,593	$7,684,437	$7,427,324	$7,020,871	$7,481,537	$6,947,200	$7,073,197	$7,147,126	$7,244,010	$7,806,263	$7,190,676	$7,183,580	$87,594,815
FFS Physical Health Drugs	$5,259,893	$5,495,460	$5,206,008	$4,812,989	$5,619,157	$5,111,558	$5,323,592	$5,284,433	$5,254,519	$5,963,439	$5,193,085	$6,254,560	$64,778,694
OHP Basic with Medicare	$200,383	$210,050	$235,210	$209,818	$229,505	$199,993	$181,167	$189,138	$200,333	$204,982	$177,111	$220,809	$2,458,500
OHP Basic without Medicare	$1,162,612	$1,223,287	$1,192,699	$976,065	$1,218,034	$1,021,988	$1,224,627	$1,088,762	$1,096,219	$1,295,494	$1,166,991	$1,355,154	$14,021,932
ACA	$3,742,419	$3,910,364	$3,647,875	$3,474,072	$3,998,143	$3,736,815	$3,762,340	$3,805,640	$3,719,092	$4,236,238	$3,596,407	$4,435,874	$46,065,278
FFS Physician Administered Drugs	$1,443,145	$1,398,923	$1,691,242	$1,483,129	$1,306,155	$1,508,768	$1,305,565	$1,169,624	$1,300,703	$2,330,941	$1,708,434	$1,633,788	$18,280,418
OHP Basic with Medicare	$141,725	$102,648	$110,943	$180,873	$138,569	$162,401	$156,551	$136,311	$202,246	$121,523	$105,542	$132,109	$1,691,441
OHP Basic without Medicare	$258,113	$319,443	$567,497	$380,931	$105,395	$522,695	$353,004	$124,435	$160,998	$834,656	$336,833	$155,174	$4,119,174
ACA	$555,939	$531,521	$544,064	$390,715	$485,875	$418,826	$403,202	$400,767	$348,817	$647,622	$692,246	$656,422	$6,076,016
Encounter Physical Health Drugs	$69,185,174	$72,400,339	$72,000,843	$67,155,501	$75,674,327	$70,761,290	$71,176,562	$72,019,946	$73,061,241	$75,671,243	$71,380,129	$81,013,448	$871,500,041
OHP Basic with Medicare	$410,018	$426,551	$397,160	$356,096	$412,960	$378,964	$348,029	$388,445	$363,939	$366,974	$369,865	$428,773	$4,647,772
OHP Basic without Medicare	$17,062,334	$17,073,787	$17,309,329	$16,372,446	$17,925,605	$16,774,308	$17,181,041	$16,860,878	$17,243,550	$17,525,480	$16,489,650	$18,781,912	$206,600,320
ACA	$50,676,341	$53,867,814	$53,223,442	$49,215,526	$55,769,355	$51,999,079	$52,212,743	$53,196,114	$53,756,564	$56,069,613	$52,737,631	$59,713,826	$642,438,049
Encounter Physician Administered Drugs	$18,868,816	$20,212,791	$22,572,865	$19,744,925	$22,929,406	$20,365,673	$20,922,600	$21,746,938	$21,705,664	$23,470,505	$20,897,992	$26,772,979	$260,211,155
OHP Basic with Medicare	$962,578	$986,364	$1,170,087	$1,097,856	$1,043,121	$918,538	$893,545	$1,172,862	$955,119	$1,242,253	$958,182	$1,337,898	$12,738,404
OHP Basic without Medicare	$4,463,761	$5,827,970	$4,892,431	$4,568,518	$5,247,676	$4,445,868	$4,687,000	$4,882,571	$5,208,881	$5,172,136	$4,513,112	$5,646,600	$59,556,523
ACA	$13,273,622	$13,216,644	$16,158,467	$13,812,238	$16,264,852	$14,646,121	$14,771,864	$15,181,260	$14,978,929	$16,324,695	$14,968,076	$18,858,098	$182,454,865

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: October 19, 2023

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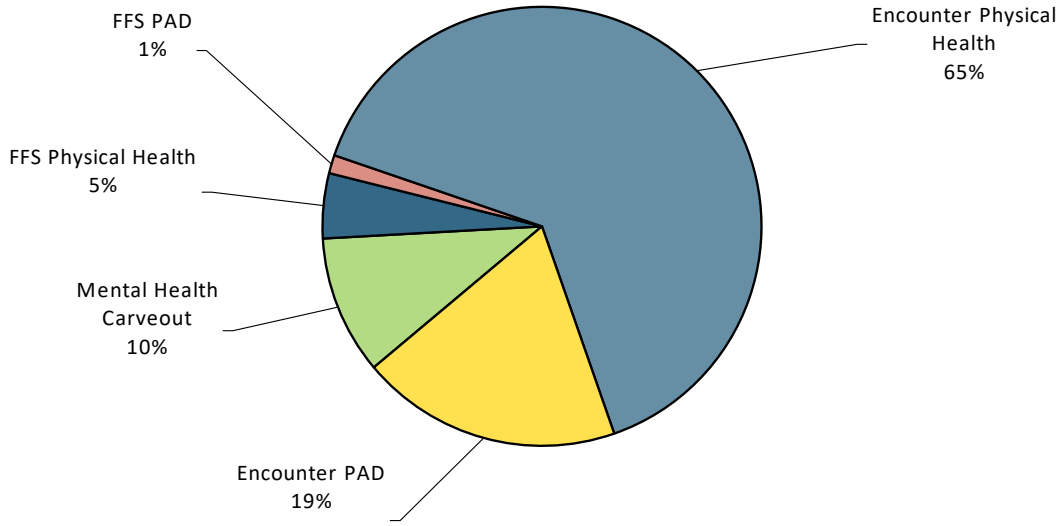
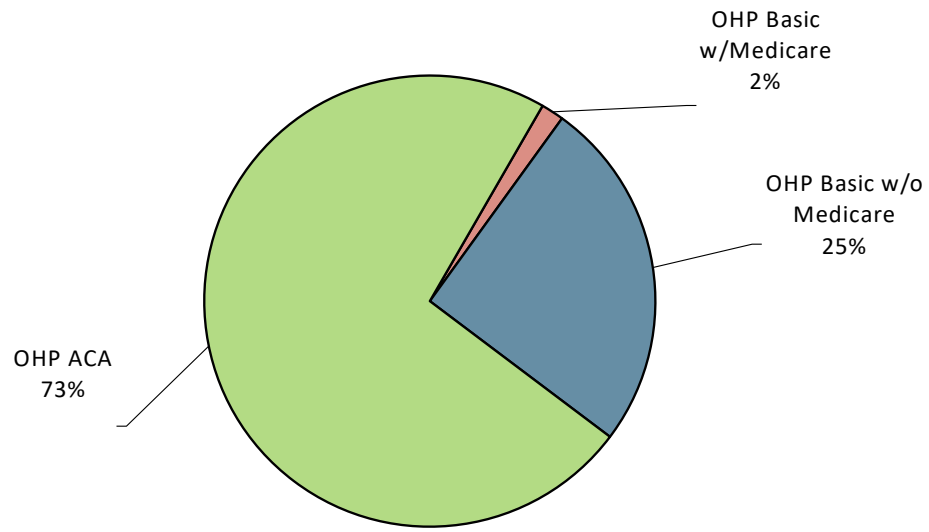
Pharmacy Utilization Summary Report: April 2022 - March 2023

YTD Percent Paid Amounts





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

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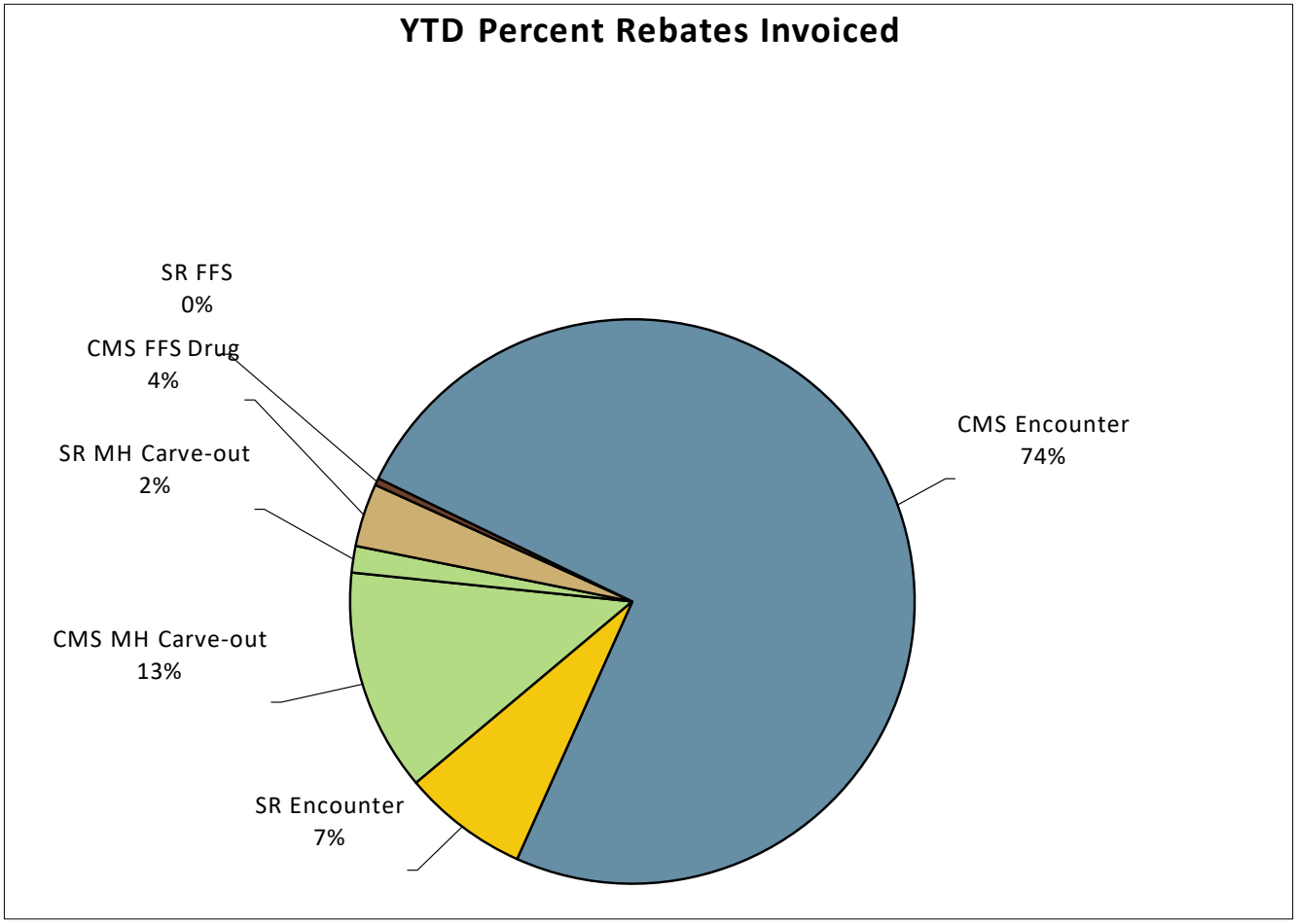
Pharmacy Utilization Summary Report: April 2022 - March 2023

Quarterly Rebates Invoiced	2022-Q2	2022-Q3	2022-Q4	2023-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$121,638,811	$126,351,118	$121,085,405	$142,209,644	$511,284,979
CMS MH Carve-out	$18,154,846	$16,613,290	$15,322,897	$15,103,828	$65,194,862
SR MH Carve-out	$1,715,924	$2,205,460	$1,975,430	$1,870,476	$7,767,290
CMS FFS Drug	$4,601,408	$4,524,904	$3,912,893	$5,478,298	$18,517,503
SR FFS	$508,747	$557,128	$429,720	$582,658	$2,078,253
CMS Encounter	$87,450,265	$91,570,682	$90,711,130	$111,210,720	$380,942,798
SR Encounter	$9,207,621	$10,879,654	$8,733,334	$7,963,663	$36,784,273

Quaterly Net Drug Costs	2022-Q2	2022-Q3	2022-Q4	2023-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$209,784,219	$204,263,326	$213,220,186	$214,589,804	$841,857,535
Mental Health Carve-Out Drugs	$15,816,761	$15,322,816	$16,735,876	$17,534,601	$65,410,055
FFS Phys Health + PAD	$15,384,516	$14,759,725	$15,295,824	$17,023,291	$62,463,356
Encounter Phys Health + PAD	$178,582,942	$174,180,784	$181,188,487	$180,031,912	$713,984,125



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

Last Updated: October 19, 2023

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

Pharmacy Utilization Summary Report: April 2022 - March 2023

Gross PMPM Drug Costs (Rebates not Subtracted)	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$82.40	$86.09	$87.01	$78.87	$88.28	$81.40	$81.77	$82.28	$82.68	$86.93	$79.91	$91.33	$84.08
Mental Health Carve-Out Drugs	$9.01	$9.35	$9.15	$8.39	$8.94	$8.34	$8.33	$8.34	$8.45	$8.80	$8.11	$8.06	$8.61
FFS Physical Health Drugs	$46.75	$48.23	$46.53	$41.52	$49.41	$43.67	$44.89	$44.59	$43.53	$47.98	$43.73	$51.00	$45.99
FFS Physician Administered Drugs	$12.83	$12.28	$15.12	$12.80	$11.49	$12.89	$11.01	$9.87	$10.77	$18.76	$14.38	$13.32	$12.96
Encounter Physical Health Drugs	$58.70	$61.21	$60.43	$55.66	$62.22	$57.96	$58.07	$58.22	$58.72	$60.49	$56.53	$63.97	$59.35
Encounter Physician Administered Drugs	$16.01	$17.09	$18.95	$16.37	$18.85	$16.68	$17.07	$17.58	$17.45	$18.76	$16.55	$21.14	$17.71

Claim Counts	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
Total Claim Count (FFS & Encounter)	1,147,878	1,183,204	1,174,224	1,106,045	1,203,120	1,141,994	1,179,084	1,184,367	1,180,462	1,222,367	1,115,627	1,276,113	1,176,207
Mental Health Carve-Out Drugs	193,127	199,439	197,694	189,732	206,349	194,274	196,536	196,008	197,033	210,567	191,952	218,475	199,266
FFS Physical Health Drugs	36,481	37,555	36,600	34,793	36,905	34,841	35,464	35,608	35,278	38,771	35,315	41,575	36,599
FFS Physician Administered Drugs	10,404	10,513	10,322	10,038	10,244	9,832	10,092	10,096	9,971	11,276	9,964	10,921	10,306
Encounter Physical Health Drugs	787,273	813,485	810,834	758,001	828,572	786,746	818,521	826,540	825,342	842,955	767,971	877,946	812,016
Encounter Physician Administered Drugs	120,593	122,212	118,774	113,481	121,050	116,301	118,471	116,115	112,838	118,798	110,425	127,196	118,021

Gross Amount Paid per Claim (Rebates not Subtracted)	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$92.68	$94.35	$96.57	$94.30	$97.59	$95.36	$93.23	$94.17	$95.60	$97.80	$98.94	$99.42	$95.83
Mental Health Carve-Out Drugs	$60.23	$60.80	$60.34	$58.51	$57.60	$57.42	$56.96	$57.70	$58.52	$57.50	$58.36	$51.25	$57.93
FFS Physical Health Drugs	$144.18	$146.33	$142.24	$138.33	$152.26	$146.71	$150.11	$148.41	$148.95	$153.81	$147.05	$150.44	$147.40
FFS Physician Administered Drugs	$138.71	$133.07	$163.85	$147.75	$127.50	$153.45	$129.37	$115.85	$130.45	$206.72	$171.46	$149.60	$147.31
Encounter Physical Health Drugs	$87.88	$89.00	$88.80	$88.60	$91.33	$89.94	$86.96	$87.13	$88.52	$89.77	$92.95	$92.28	$89.43
Encounter Physician Administered Drugs	$156.47	$165.39	$190.05	$173.99	$189.42	$175.11	$176.61	$187.29	$192.36	$197.57	$189.25	$210.49	$183.67

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$24.00	$24.02	$24.50	$24.45	$24.99	$25.01	$23.65	$23.25	$23.47	$24.03	$24.15	$24.50	$24.17
Mental Health Carve-Out Drugs	$16.63	$16.81	$17.06	$17.21	$17.56	$17.29	$17.35	$17.33	$17.61	$17.83	$17.96	$17.99	$17.39
FFS Physical Health Drugs	$97.49	$99.77	$99.83	$94.81	$103.33	$106.38	$103.98	$105.68	$106.51	$103.78	$98.25	$103.97	$101.98
Encounter Physical Health Drugs	$22.77	$22.66	$23.28	$23.41	$23.73	$23.74	$22.05	$21.46	$21.67	$22.26	$22.61	$22.72	$22.70

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$641.32	$654.32	$666.14	$670.47	$697.77	$643.95	$616.16	$638.82	$672.64	$722.45	$761.93	$754.92	$678.41
Mental Health Carve-Out Drugs	$962.53	$964.18	$1,020.78	$1,085.19	$1,115.96	$1,147.02	$1,155.25	$1,195.37	$1,233.87	$1,241.46	$1,280.19	$1,289.22	$1,140.92
FFS Physical Health Drugs	$372.20	$375.11	$349.65	$348.53	$400.50	$337.78	$367.86	$355.68	$362.10	$424.00	$416.61	$409.06	$376.59
Encounter Physical Health Drugs	$627.27	$641.74	$653.60	$656.11	$682.03	$625.32	$593.06	$616.72	$650.97	$701.74	$744.36	$744.70	$661.47

Generic Drug Use Percentage	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
Generic Drug Use Percentage	90.2%	90.2%	90.5%	90.7%	90.8%	90.2%	89.9%	90.2%	90.5%	91.2%	91.3%	91.5%	90.6%
Mental Health Carve-Out Drugs	95.4%	95.4%	95.7%	96.1%	96.4%	96.4%	96.5%	96.6%	96.6%	96.8%	96.8%	97.4%	96.3%
FFS Physical Health Drugs	83.0%	83.1%	83.0%	82.8%	83.5%	82.6%	82.5%	82.9%	83.4%	84.4%	84.7%	84.8%	83.4%
Encounter Physical Health Drugs	89.2%	89.3%	89.6%	89.7%	89.7%	89.0%	88.6%	89.0%	89.4%	90.1%	90.3%	90.4%	89.5%

Preferred Drug Use Percentage	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Avg Monthly
Preferred Drug Use Percentage	89.88%	89.89%	89.82%	90.49%	90.42%	90.45%	90.65%	90.48%	90.31%	90.44%	90.35%	90.37%	90.3%
Mental Health Carve-Out Drugs	93.33%	93.31%	93.27%	93.24%	93.13%	93.14%	93.07%	92.87%	92.70%	92.58%	92.51%	92.53%	93.0%
FFS Physical Health Drugs	94.66%	94.80%	94.90%	95.64%	95.77%	95.69%	95.65%	95.79%	95.85%	95.20%	95.24%	95.27%	95.4%
Encounter Physical Health Drugs	88.85%	88.86%	88.79%	89.61%	89.54%	89.59%	89.89%	89.72%	89.54%	89.72%	89.63%	89.64%	89.4%

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: October 19, 2023

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	VRAYLAR*	Antipsychotics, 2nd Gen	$4,311,803	11.0%	3,529	$1,222	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$4,241,850	10.8%	1,735	$2,445	Y
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,588,607	6.6%	1,113	$2,326	Y
4	REXULTI*	Antipsychotics, 2nd Gen	$2,515,132	6.4%	1,988	$1,265	V
5	INVEGA TRINZA	Antipsychotics, Parenteral	$1,120,336	2.9%	152	$7,371	Y
6	TRINTELLIX	Antidepressants	$880,913	2.2%	2,053	$429	V
7	CAPLYTA*	Antipsychotics, 2nd Gen	$841,817	2.1%	596	$1,412	V
8	ARISTADA	Antipsychotics, Parenteral	$811,214	2.1%	355	$2,285	Y
9	SERTRALINE HCL	Antidepressants	$597,145	1.5%	61,474	$10	Y
10	BUPROPION XL	Antidepressants	$580,731	1.5%	48,210	$12	Y
11	DULOXETINE HCL	Antidepressants	$569,491	1.4%	38,891	$15	Y
12	FLUOXETINE HCL	Antidepressants	$513,518	1.3%	45,166	$11	Y
13	TRAZODONE HCL	Antidepressants	$508,758	1.3%	49,601	$10	
14	ESCITALOPRAM OXALATE	Antidepressants	$486,369	1.2%	45,225	$11	Y
15	LYBALVI*	Antipsychotics, 2nd Gen	$459,434	1.2%	347	$1,324	V
16	SPRAVATO*	Antidepressants	$379,194	1.0%	344	$1,102	V
17	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$349,077	0.9%	28,995	$12	
18	LAMOTRIGINE	Antiepileptics, Outpatient	$336,568	0.9%	30,712	$11	Y
19	TRIKAFTA*	Cystic Fibrosis	$335,320	0.9%	33	$10,161	N
20	ATOMOXETINE HCL*	ADHD Drugs	$312,472	0.8%	9,070	$34	Y
21	BIKTARVY	HIV	$304,625	0.8%	120	$2,539	Y
22	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$269,000	0.7%	241	$1,116	Y
23	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$265,545	0.7%	20,795	$13	Y
24	BUPROPION XL	Antidepressants	$245,049	0.6%	1,433	$171	V
25	VENLAFAXINE HCL ER	Antidepressants	$243,317	0.6%	19,493	$12	Y
26	LAMOTRIGINE ER	Antiepileptics, Outpatient	$242,050	0.6%	3,850	$63	V
27	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$238,063	0.6%	1	$238,063	
28	Inj Pembrolizumab	Physican Administered Drug	$237,261	0.6%	31	$7,654	
29	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$228,087	0.6%	20,533	$11	Y
30	Elosulfase Alfa, Injection	Physican Administered Drug	$226,773	0.6%	12	$18,898	
31	CONCERTA*	ADHD Drugs	$202,361	0.5%	604	$335	Y
32	INVEGA HAFYERA	Antipsychotics, Parenteral	$199,273	0.5%	11	$18,116	Y
33	HUMIRA(CF) PEN*	Targeted Immune Modulators	$193,112	0.5%	47	$4,109	Y
34	AUVELITY	Antidepressants	$189,645	0.5%	239	$793	V
35	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$177,003	0.5%	6	$29,500	
36	OLANZAPINE*	Antipsychotics, 2nd Gen	$175,729	0.4%	13,460	$13	Y
37	CITALOPRAM HBR	Antidepressants	$175,128	0.4%	19,674	$9	Y
38	MIRTAZAPINE	Antidepressants	$173,817	0.4%	12,647	$14	Y
39	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$164,559	0.4%	17	$9,680	Y
40	AMITRIPTYLINE HCL*	Antidepressants	$155,794	0.4%	14,325	$11	Y
		Top 40 Aggregate:	**$27,045,940**		**497,128**	**$9,065**	
*** Drug requires Prior Authorization**		**All FFS Drugs Totals:**	**$39,307,142**		**738,518**	**$775**	

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: October 19, 2023

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	TRIKAFTA*	Cystic Fibrosis	$335,320	3.4%	33	$10,161	N
2	BIKTARVY	HIV	$304,625	3.1%	120	$2,539	Y
3	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$238,063	2.4%	1	$238,063	
4	Inj Pembrolizumab	Physican Administered Drug	$237,261	2.4%	31	$7,654	
5	Elosulfase Alfa, Injection	Physican Administered Drug	$226,773	2.3%	12	$18,898	
6	CONCERTA*	ADHD Drugs	$202,361	2.0%	604	$335	Y
7	HUMIRA(CF) PEN*	Targeted Immune Modulators	$193,112	1.9%	47	$4,109	Y
8	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$177,003	1.8%	6	$29,500	
9	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$164,559	1.6%	17	$9,680	Y
10	AFINITOR DISPERZ*	Antineoplastics, Newer	$151,888	1.5%	12	$12,657	
11	TRULICITY*	Diabetes, GLP-1 Receptor Agonists and GIP The	$146,079	1.5%	238	$614	Y
12	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$145,468	1.5%	6	$24,245	
13	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$142,510	1.4%	79	$1,804	Y
14	DAYBUE*	STC 99 - Miscellaneous	$142,461	1.4%	3	$47,487	
15	VYVANSE*	ADHD Drugs	$131,436	1.3%	780	$169	Y
16	LANTUS SOLOSTAR*	Diabetes, Insulins	$128,772	1.3%	385	$334	Y
17	Factor Viii Fc Fusion Recomb	Physican Administered Drug	$117,596	1.2%	2	$58,798	
18	STELARA*	Targeted Immune Modulators	$111,123	1.1%	19	$5,849	N
19	ELIQUIS	Anticoagulants, Oral and SQ	$102,323	1.0%	271	$378	Y
20	TIBSOVO*	Antineoplastics, Newer	$96,595	1.0%	3	$32,198	
21	SKYRIZI PEN*	Targeted Immune Modulators	$95,418	1.0%	6	$15,903	N
22	EPIDIOLEX*	Antiepileptics, Outpatient	$94,618	0.9%	60	$1,577	N
23	VILTEPSO*	Duchenne Muscular Dystrophy	$93,119	0.9%	6	$15,520	
24	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	$92,705	0.9%	191	$485	N
25	IBRANCE*	Antineoplastics, Newer	$90,539	0.9%	6	$15,090	
26	METYROSINE	STC 71 - Other Hypotensives	$88,143	0.9%	3	$29,381	
27	Aflibercept Injection	Physican Administered Drug	$78,559	0.8%	143	$549	
28	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$76,369	0.8%	1,311	$58	Y
29	PROMACTA	Thrombocytopenia Drugs	$74,146	0.7%	15	$4,943	Y
30	Injection, Nivolumab	Physican Administered Drug	$72,775	0.7%	12	$6,065	
31	Canakinumab Injection	Physican Administered Drug	$72,399	0.7%	2	$36,200	
32	HEMLIBRA	STC 99 - Miscellaneous	$71,580	0.7%	2	$35,790	
33	CREON	Pancreatic Enzymes	$64,275	0.6%	58	$1,108	Y
34	VERZENIO*	Antineoplastics, Newer	$62,923	0.6%	8	$7,865	
35	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$62,772	0.6%	2,315	$27	Y
36	Etonogestrel Implant System	Physican Administered Drug	$61,766	0.6%	97	$637	
37	LENALIDOMIDE	STC 30 - Antineoplastic	$60,511	0.6%	4	$15,128	
38	ICLUSIG*	Antineoplastics, Newer	$60,421	0.6%	3	$20,140	
39	COSENTYX SENSOREADY (2 PENS)*	Targeted Immune Modulators	$58,872	0.6%	18	$3,271	Y
40	Mirena, 52 Mg	Physican Administered Drug	$54,949	0.6%	62	$886	
		Top 40 Aggregate:	**$4,982,186**		**6,991**	**$17,902**	
		All FFS Drugs Totals:	**$9,985,351**		**108,230**	**$794**	

*** 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: October 19, 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**
motixafortide	APHEXDA
momelotinib	OJJAARA

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 11/07/2023)
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
elranatamab-bcmm	ELREXFIO
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
epcoritamab-bysp	EPKINLY
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
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

Generic Name	Brand Name
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mobecertinib	EXKIVITY
momelotinib	OJJAARA
mosunetuzumab-axgb	LUNSUMIO
motixafortide	APHEXDA
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib and abiraterone acetate	AKEEGA
niraparib tosylate	ZEJULA
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

Generic Name	Brand Name
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
quizartinib	VANFLYTA
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
talquetamab-tgvs	TALVEY
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

Generic Name	Brand Name
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. New orphan drugs

Generic Name	Brand Name
nedosiran	RIVFLOZA

Recommendation:

- PA was modified to include new, recently approved orphan drugs.

Orphan Drugs

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

Length of Authorization:
- Up to 6 months

Requires PA:
- See Table 1 (pharmacy and physician administered claims)

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

Table 1. Indications for orphan drugs based on FDA labeling

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

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

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

			≥ 20 kg Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 yr	Initial: 1 mg/kg SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 3 mo	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 380 mcg/kg once daily after 1 week on initial dose, as tolerated	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Mitapivat (PYRUKYND)	Hemolytic anemia in adults with pyruvate kinase (PK) deficiency.	≥ 18 yr	Initial: 5 mg twice daily Titration: If Hb less than normal range or patient required transfusion in previous 8 weeks, then after 4 weeks increase to 20 mg twice daily, and after another 4 weeks increase to 50 mg twice daily. Max dose: 50 mg twice daily Discontinuation should include down-titration.	Baseline/Ongoing Monitoring • Hgb, transfusion requirement

Nedosiran RIVFLOZA	Lower urinary oxalate levels in those with primary hyperoxaluria type 1 (PH1) and relatively preserved renal function, e.g., eGFR ≥ 30 mL/min/1.73 m^2	≥ 9 yr	Weight ≥ 50 kg: 160 mg once monthly Weight <50 kg and age ≥12 yr: 128 mg once monthly Weight <50 kg and age 9 to 11 yr: 3.3 mg/kg once monthly; max 128 mg.	Baseline/Ongoing Monitoring • eGFR
Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)	≥ 3 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments Max dose: 120 mcg/kg once daily; not to exceed 6 mg	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Olipudase alfa-rpcp (XENPOZYME)	Non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD)	N/A	Initial: Age based dose escalation table per Package insert Maintenance: 3 mg/kg via IV infusion every 2 weeks Weight: • If BMI ≤ 30, use actual body weight • If BMI > 30, use adjusted body weight Adjusted body weight (kg) = (actual height in M)^2 x 30	Baseline Monitoring • Liver function tests (ALT, AST) within 1 month • Pregnancy test (if childbearing potential) Ongoing Monitoring • Liver function tests (ALT, AST) within 72 hours of infusions during dose escalation, then during routine clinical management once at maintenance dose
Palovarotene, (SOHONOS)	Fibrodysplasia ossificans progressive (FOP)	≥ 8 yr females ≥ 10 yr males	≥ 14 years: Daily: 5 mg Flare wk 1-4: 20 mg once daily Flare wk 5-12: 10 mg once daily <14 years weight based: Daily 10-19.9 kg: 2.5 mg 20-39.9 kg: 3 mg 40-59.9 kg: 4 mg ≥ 60 kg: 5 mg	Baseline Monitoring • Pregnancy test (if childbearing potential) • Assessment of skeletal maturity in growing pediatric patients: hand/wrist & knee x-ray, standard growth curves, pubertal staging. • Psychiatric symptoms or signs of depression Ongoing Monitoring • Pregnancy test (if childbearing potential)

			Flare week 1-4 (daily dose) 10-19.9 kg: 10 mg 20-39.9 kg: 12.5 mg 40-59.9 kg: 15 mg ≥ 60 kg: 20 mg Flare week 5-12 (daily dose) 10-19.9 kg: 5 mg 20-39.9 kg: 6 mg 40-59.9 kg: 7.5 mg ≥ 60 kg: 10 mg Week 5-12 flare dosing may be extended in 4-week intervals and continued until symptoms resolve. If marked worsening of original symptoms or another flare occurs during flare-up treatment, may restart 12 week flare-up dosing. (all ages)	• Assessment of skeletal maturity in growing pediatric patients every 6-12 months until skeletal maturity or final adult height. • Spine assessment for bone density • New or worsening psychiatric symptoms or signs of depression
Plasminogen, human-tvmh (RYPLAZIM)	Treatment of patients with plasminogen deficiency type 1 (hypoplasmino-genemia)	N/A	6.6 mg/kg body weight given IV every 2 to 4 days	Baseline Monitoring • Plasminogen activity level (allow 7 day washout if receiving with fresh frozen plasma) • CBC (bleeding) Ongoing Monitoring • Trough Plasminogen activity level 72 hours after initial dose and every 12 wks with ongoing therapy • CBC (bleeding)
pozelimab-bbfg (VEOPOZ)	CD55-deficient protein-losing enteropathy (PLE or CHAPLE disease)	≥ 1 yr	Day 1 loading dose: 30 mg/kg single IV infusion Day 8 and after maintenance dose): 10 mg/kg SC weekly May increase to 12 mg/kg if inadequate response after at least 3 weekly doses Max maintenance dose: 800 mg once weekly	Baseline Monitoring • Meningococcal vaccination at least 2 wk prior to first drug dose unless risks of delayed therapy outweigh risk of meningococcal infection. Ongoing Monitoring • Signs of meningococcal infection
Sodium thiosulfate (PEDMARK)	Decrease ototoxicity associated with cisplatin infusions lasting ≤ 6 hours. Not approved for use with longer infusions.	≥ 1 mo to ≤18 yr	< 5 kg: 10 g/m^2 5-10 kg: 15 g/m^2 >10 kg: 20 g/m^2	Baseline Monitoring • Serum potassium and sodium

Sutimlimab-jome (ENJAYMO)	Decrease need for RBC transfusion due to hemolysis in cold agglutinin disease (CAD)	≥ 18 yr	Dosed IV infusion weekly for two weeks, then every two weeks thereafter. **39 to <75 kg:** 6500 mg **≥75 kg:** 7500 mg	Baseline Monitoring • Vaccination against encapsulated bacteria (*Neisseria meningititides* (any serogroup), *Streptococcus pneumonia,* and *Haemophilus influenza*) at least prior to treatment or as soon as possible if urgent therapy needed
Trientine tetrahydrochloride (CUVRIOR)	Stable Wilson's disease who are de-coppered and tolerant to penicillamine	≥ 18 yr	Total daily dose in transition from penicillamine per table in package insert.	Baseline/Ongoing Monitoring • Serum NCC levels at baseline, 3 months, then roughly every 6 months serum levels or 6 to 12 months with urinary copper excretion
Velmanase alfa-tycv (LAMZEDE)	Treatment of non-central nervous system manifestations of alpha-mannosidosis	N/A	1 mg/kg (actual body weight) once weekly by IV infusion	Baseline and ongoing monitoring • Pregnancy test (if childbearing potential)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase, AST = aspartate aminotransferase; BG = blood glucose; BSA = body surface area; CBC = complete blood count; CrCL = creatinine clearance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycalated hemoglobin; Hgb = hemoglobin; INR = international normalized ratio; IV = intravenous; mo = months; NCC = non-ceruloplasmin copper; RBC = red blood cells; SC = subcutaneously; wks = weeks; yrs = years

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6

Approval Criteria		
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

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

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

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

Ycanth™ (cantharidin)

Indications

- Topical treatment of molluscum contagiosum (MC) in adult and pediatric patients 2 years of age and older.

Dosage

- Apply contents of a single-use ampule (approximately 0.45 ml of a 0.7% cantharidin solution) directly to each lesion every 3 weeks as needed.
- Do not use more than two applicators during a single treatment session.
- Remove with soap and water 24 hours after treatment.

Special Instructions:

- For topical use only. Not for oral, mucosal, or ophthalmic use.
- All healthcare professionals should receive instruction and training prior to preparation and administration.

Background

- A naturally occurring terpenoid compound extracted from blister beetle used medicinally to treat MC for over 70 years but never formally approved by FDA
- Molluscum contagiosum is a viral skin lesion that presents as a painless, flesh-colored 3-5 mm diameter papule that typically resolves in a few months without treatment
- Pharmacologic treatments for molluscum contagiosum are not funded for adults or children (Oregon Prioritized List Line 613)

Efficacy

Approval by the FDA was obtained with data from two identical, phase 3, randomized, double blind, placebo vehicle-controlled, multicenter trials conducted over 12 weeks. The trials included 528 patients at least 2 years of age diagnosed with molluscum contagiosum by physical exam by investigators with appropriate clinical expertise. Those with immunosuppressive conditions (e.g., human immunodeficiency virus) or on systemic immunosuppressive therapy within prior 14 days or had lesions within 10 mm of a mucosal area at baseline were excluded. Patients were to receive a single 24-hour administration of YCANTH or matching placebo vehicle every 3 weeks until complete clearance achieved or for a maximum of 4 treatments. Patients (or caregivers) were to remove study drug with soap and water 24 hours after treatment or if treatment-emergent adverse events (TEAEs) occurred such as significant pain or blistering. The primary efficacy endpoint was the proportion of cantharidin-treated participants achieving complete clearance of all treatable baseline and new molluscum lesions at the end of the study. The secondary endpoint was the proportion of cantharidin-treated participants achieving complete clearance of all treatable baseline and new molluscum lesions at each visit. Patients with missing clearance data at the end of study period (day 84) were considered as not achieving clearance. Baseline characteristics were similar between groups in both trials and both males and females were equally represented. Most participants were aged 2 to 11 (89%), White (91%), had history of atopic dermatitis (AD) (16%) or active AD as determined by concomitant medication (8%), with a mean lesion count of roughly 21.

Table 1. Percentage of Subjects Exhibiting Complete Clearance of Treatable Molluscum Contagiosum Lesions

	Trial 1 (CAMP-1)			Trial 2 (CAMP-2)		
	Cantharidin (N = 160)	Vehicle (N = 106)	Treatment Difference (95% CI)	Cantharidin (N = 150)	Vehicle (N = 112)	Treatment Difference (95% CI)
Day 84	46%	18%	29% (19% to 38%)	54%	13%	40% (30% to 51%)
Day 63	32%	17%	15% (4% to 25%)	28%	5%	23% (15% to 32%)
Day 42	21%	9%	10% (25 to 19%)	13%	4%	9% (3% to 16%)
Day 21	11%	4%	8% (2% to 14%)	5%	2%	3% (-1% to 8%) NS

Key: CI=confidence Interval; NS = non-significant

Safety

Common adverse reactions: vesicles* (96%), pain** (63%), pruritis** (56%), scab** (48%), erythema** (46%), discoloration* (33%), dryness* (21%), edema* (10%), erosion* (7%), contact dermatitis (1%).
Contraindications: none
Warnings and precautions: Avoid application near eyes, mucosal tissue, or healthy skin. Possibilities of life threatening or fatal toxicities with oral use, ocular toxicity with eye contact, and local skin reactions possible with inappropriate administration. Cantharidin is a flammable liquid, even after drying. Avoid fire, flame or smoking near lesion(s) during treatment and after application until removed.
Special Populations: Has not been studied in children <2 years of age, in pregnant women, or in geriatric patients.
Key: *= at application site only; **= generalized and/or at application site

Evidence Gaps/Limitations

- No studies found to support evidence for use in the treatment of Oregon Health Plan (OHP) funded conditions.

Recommendation

- Apply Drugs for Non-funded Conditions prior authorization criteria to limit use to funded indications.

References

1. Ycanth (cantharidin) Prescribing Information. Verrica Pharmaceuticals, Inc. West Chester, PA. July 2023.
2. Eichenfield LF, McFalda W, Brabec B, et al. Safety and Efficacy of VP-102, a Proprietary, Drug-Device Combination Product Containing Cantharidin, 0.7% (w/v), in Children and Adults with Molluscum Contagiosum: Two Phase 3 Randomized Clinical Trials. JAMA Dermatol. 2020;156(12):1315–1323.

Drugs for Non-funded Conditions

Goal:

- Restrict use of drugs reviewed by the Oregon Pharmacy & Therapeutics (P&T) Committee without evidence for use in Oregon Health Plan (OHP)-funded conditions. Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 6 months.

Requires PA:

- A drug restricted by the P&T Committee due to lack of evidence for conditions funded by the OHP.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the drug being used to treat an OHP-funded condition?	**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
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:** Approve for 6 months, or for length of the prescription, whichever is less	**No:** Pass to RPh; Deny; medical necessity.
4. Pass to RPh. The prescriber must provide documentation of therapeutic failure, adverse event, or contraindication alternative drugs approved by FDA for the funded condition. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.		

P&T / DUR Review: *12/22; 4/22 (SS); 11/15*
Implementation *1/1/23; 1/1/16*

ProDUR Report for July through September 2023
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	4	2	0	2	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	1,928	475	0	1,451	1.2%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	8,236	2,515	0	5,714	5.2%	N/A
ER (Early Refill)	**Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)**	**Set alert/Deny claim**	**99,683**	**21,037**	**73**	**78,572**	**63.5%**	**21.1%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	34,968	10,071	3	24,859	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	858	198	0	8,046	0.5%	N/A
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	2	2	0	0	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	773	248	0	521	0.5%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	473	177	0	296	0.3%	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	2	1	0	1	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**17**	**16**	**0**	**1**	**0.0%**	**94.1%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	10,127	3,051	0	7,054	6.4%	N/A
		Totals	**157,071**					

ProDUR Report for July through September 2023
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	7,952	1,466	6,486	83,091	9.6%	18.4%
ER	Prozac (Fluoxetine)	5,646	1,085	4,561	59,712	9.4%	19.2%
ER	Lexapro (Escitalopram)	5,604	1,015	4,588	58,940	9.5%	18.1%
ER	Celexa (Citalopram)	2,093	392	1,701	25,203	8.3%	18.7%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	8,029	1,539	6,490	86,699	9.2%	19.2%
ER	Trazodone	6,949	1,403	5,546	64,982	10.7%	20.2%
ER	Cymbalta (Duloxetine)	5,421	1,035	4,386	51,338	10.5%	19.1%
ER	Effexor (Venlafaxine)	3,092	602	2,490	32,303	9.6%	19.5%
ER	Remeron (Mirtazapine)	1,966	394	1,572	16,712	11.8%	20.0%
ER	Elavil (Amitriptyline)	1,712	373	1,339	18,680	9.1%	21.8%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	4,761	1,192	3,569	33,702	14.1%	25.0%
ER	Abilify (Aripiprazole)	3,983	726	3,257	24,218	12.9%	18.2%
ER	Zyprexa (Olanzapine)	2,708	620	2,088	20,780	13.1%	22.9%
ER	Risperdal (Risperidone)	2,040	476	1,564	13,832	14.9%	23.3%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	3,830	717	3,113	38,729	9.8%	18.7%
ER	Lorazepam	338	114	224	13,230	2.5%	33.7%
ER	Alprazolam	171	45	126	7,405	2.5%	26.3%
ER	Diazepam	98	29	69	4,057	2.4%	29.6%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	6,638	1,415	5,223	48,879	13.6%	21.3%
ER	Intuniv (Guanfacine ER)	1,766	303	1,463	13,846	12.8%	17.2%
ER	Depakote (Divalproex)	1,695	467	1,227	12,639	13.4%	27.6%
ER	Suboxone (Buprenorphine/Naloxone)	92	40	52	2,021	4.7%	43.5%

ProDUR Report for July through September 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	July	4,209	161	243	560	5	3,028	33	0	179
ER	August	4,553	164	284	671	7	3,187	57	0	183
ER	September	4,381	163	264	616	6	3,108	45	0	181
	Total =	**13,143**	**488**	**791**	**1,847**	**18**	**9,323**	**135**	**0**	**543**
	Percentage of total overrides =		**3.7%**	**6.0%**	**14.0%**	**0.1%**	**70.9%**	**1.0%**	**0.0%**	**4.1%**

ProDUR Report for July through September 2023			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
July	DD	12	$ 2,219.86
	ER	58	$ 10,921.25
	ID	15	$ 1,863.35
	LR	2	$ 548.11
	TD	3	$ 181.37
	July Total	**90**	**$ 15,733.94**
August	DC	2	$ 219.98
	DD	14	$ 3,103.63
	ER	57	$ 14,760.59
	HD	1	$ 68.69
	ID	20	$ 2,095.40
	LD	1	$ 4.50
	TD	5	$ 357.89
	August Total	**100**	**$ 20,610.68**
September	DC	1	$ 45.69
	DD	8	$ 1,691.87
	ER	33	$ 3,002.87
	ID	8	$ 1,176.60
	MX	1	$ 23.99
	September Total	**51**	**$ 5,941.02**
		Total 3Q2023 Savings =	**$ 42,285.64**

Drug Use Research & Management Program
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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
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	18	13	12	12
		Unique Patients Identified	18	13	12	12
		Total Faxes Successfully Sent	12	8	8	11
		Prescriptions Changed to Recommended Within 6 Months of Intervention	3	7	2	1
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$4,394	$21,597	$4,710	$154
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	119	103	84	89
		Unique Patients Identified	120	103	86	89
		Total Faxes Successfully Sent	76	83	62	67
		Prescriptions Changed to Recommended Within 6 Months of Intervention	67	56	39	34
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$101,046	$61,738	$23,833	$11,074
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	109	56	383	154
		Unique Patients Identified	110	56	414	155
		Total Faxes Successfully Sent	69	35	257	111
		Prescriptions Changed to Recommended Within 6 Months of Intervention	42	26	141	53
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$11,576	$6,551	$21,797	$4,571

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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	3
		Total Faxes Successfully Sent	1	5	2	2
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent		3		1
		Prescriptions Unchanged after 3 Months of Fax Sent		4	3	
		Safety Monitoring Profiles Identified	2	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0	$844	$0	$163

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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	823
		High risk patients identified	6	9	1	8
		Prescribers successfully notified	6	9	1	2
		Patients with change in antipsychotic drug in following 90 days		2		
		Patients with continued antipsychotic therapy in the following 90 days	5	9	1	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	55
		Total prescribers identified	55	54	53	55
		Prescribers successfully notified	53	54	52	55
		Patients with claims for the same antipsychotic within the next 90 days	31	26	31	26
		Patients with claims for a different antipsychotic within the next 90 days	2	2	3	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
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	80	57	66	74
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	56	20	24	26
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	207	169	185	215
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	39	28	26	22
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	3	17	13	25
		Letters Sent To Providers		1		5
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	12	9	13	11
		Letters Sent To Providers	13	7	12	11
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	8	10	12	23
		Letters Sent To Providers	4	8	4	3
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	31	10	10	15
		Letters Sent To Providers	5	1		3
	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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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	10
		Total prescribers identified	15	16	13	10
		Prescribers successfully notified	15	12	12	10
		Patients with paid claims within next 60 days	12	12	8	5
		Patients with denied claim within next 60 days	13	11	7	3

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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	155
		Total prescribers identified	82	91	106	151
		Prescribers successfully notified	61	91	106	148
		Patients with discontinuation of therapy within next 90 days	19	19	25	45
		Patients with new prescription for naloxone within next 90 days	6	9	7	4
		Average number of sedative drugs dispensed within next 90 days	21	25	25	19
		Average number of sedative prescribers writing prescriptions in next 90 days	21	25	25	19
	Oncology Denials	Total patients identified	1	2	2	3
		Total prescribers identified	1	2	2	3
		Prescribers successfully notified	1	2	2	3
		Patients with claims for the same drug within the next 90 days		1	1	2
		Patients with claims for any oncology agent within the next 90 days		1	1	2
	TCAs in Children	TCA Denials in Children	26	21	52	38
		Total patients identified	12	10	19	17
		Total prescribers identified	12	10	19	16
		Prescribers successfully notified	8	6	15	10
		Patients with claims for a TCA within the next 90 days	3	2	2	5

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Buprenorphine: Place in Therapy for Chronic Pain

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Pain management is an important aspect of care for a variety of acute and chronic conditions. Evidence supporting specific non-pharmacologic and pharmaceutical therapy varies depending on the condition, but most guidelines, medical societies, and public health agencies recommend against routinely prescribing opioids for acute or chronic pain conditions due to increasing evidence of short-term adverse events and serious harms reported with long-term use in observational and epidemiologic studies.[1] However, there remains an urgent need to appropriately and effectively manage pain while mitigating risk for potential misuse.

While illicit opioids (such as heroin and non-prescription fentanyl) have been implicated in increased death rates over time, the American Medical Association has reported that nearly half of all heroin users started with an addiction to a prescription opioid medication before switching to heroin due to ease of access.[2] Thus, there is a need for safer options to treat chronic pain. This newsletter will describe available evidence for buprenorphine for chronic pain to evaluate whether it is a safer alternative compared to other opioids.

Buprenorphine for Pain

Unlike other opioids, buprenorphine is a partial mu opioid agonist and a schedule III-controlled substance. Buprenorphine may have potential advantages compared to full or pure opioid agonists (e.g., morphine, fentanyl, oxycodone, hydrocodone, oxymorphone, methadone) or opioids with a mixed mechanism (e.g., tramadol or tapentadol). However, advantages cited in the literature (such as decreased respiratory depression, improved safety in elderly and renal disease, increased efficacy for neuropathic pain, less development of tolerance, and lack of hyperanalgesic effect), are generally based on assumptions about mechanism and pharmacology, and not based on well-designed prospective studies.[3] Additionally, publications which cite these advantages often note manufacturer funding.[3]

Buprenorphine is available in several formulations and doses. Formulations for treatment of OUD usually provide substantially higher doses of buprenorphine than formulations with indications for pain. Formulations that are indicated for treatment of severe pain include buccal films (BELBUCA®; 75-900 mcg/film), transdermal patches (BUTRANS®; 5-20 mcg/hour), and intramuscular or intravenous injections (BUPRENEX®; 300 mcg/mL). Buprenorphine formulations that are FDA-approved for treatment of opioid use disorder (OUD) include subcutaneous injections (e.g., SUBLOCADE®; 200 mg/mL) and sublingual films or tablets with or without naloxone (SUBOXONE®, ZUBSOLV®, SUBUTEX®; 0.7-8 mg/unit). While prescription of buprenorphine for OUD has historically been regulated under the federal DATA-waiver program, recent changes to the program have removed these regulatory requirements.[4] A waiver has never been required to prescribe buprenorphine for pain.

Efficacy of Buprenorphine for Chronic Pain

A systematic review from Agency for Healthcare Research and Quality (AHRQ) published in 2020 and updated in March 2022 evaluated evidence of opioids used to manage chronic pain.[1] The review specifically evaluated evidence of effectiveness based on type of opioid (pure agonist, partial agonist, or opioids with a mixed mechanism). For pain relief, there was moderate quality evidence of no difference in efficacy outcomes between buprenorphine and pure opioid agonists. Direct comparative evidence was limited to 3 randomized controlled trials (RCTs) comparing buprenorphine to tramadol and fentanyl. Placebo-controlled data were also available from 38 trials of pure opioid agonists, 8 trials of buprenorphine (5 evaluated transdermal patch and 2 evaluated buccal formulation), and 16 trials evaluated mixed opioids (tramadol or tapentadol).[1] Subgroup analyses of the placebo-controlled data showed no correlation between type of opioid (full, partial, or mixed) and effects on pain, function, short form (SF)-36 health status, sleep or depression.

Safety of Buprenorphine for Chronic Pain

Short-term studies (with follow-up over 16 months) comparing buprenorphine directly to full opioid agonists found similar harms in people with chronic pain (moderate quality evidence).[1] Compared to placebo, opioids of all types were associated with increased rates of adverse events.[1] Adverse events which were more common than placebo in short-term trials are listed in **Table 1**. Pruritus was the only adverse event which demonstrated a statistical difference based on type of opioid with higher risk associated with pure agonists and mixed mechanism opioids compared to buprenorphine.[1]

Table 1. Adverse event rates associated with opioids in short-term RCTs compared to placebo

Adverse Event (AE)	RR (95% CI)	NNH
Discontinuation for AEs	2.25 (1.86 to 2.73)	10
Somnolence	2.97 (2.44 to 3.66)	11
Nausea	2.46 (2.17 to 2.80)	7
Vomiting	3.57 (2.98 to 4.34)	14
Constipation	3.38 (2.96 to 3.92)	7
Dizziness	2.66 (2.37 to 2.99)	12
Pruritus	3.51 (2.47 to 5.16)	14

*Number needed to harm (NNH) = the number of people who need to be treated in order for one person to experience an adverse event

Because RCTs are not powered or designed to evaluate long-term harms, evidence on serious long-term adverse events is based primarily on observational studies.[1] Most long-term observational studies in patients with chronic pain have not included buprenorphine, but have shown an increased risk of adverse events with opioids compared to matched populations without opioid use. Low quality evidence shows that compared to matched cohorts, opioids are associated with increased risk for:[1]

- abuse, dependence, overdose, addiction
- myocardial infarction, fracture, falls
- endocrine dysfunction (erectile dysfunction, female reproductive dysfunction, androgen deficiency)
- mortality

Risk of overdose increases when opioids are combined with a benzodiazepine (especially with short-term use) or gabapentinoid (particularly at higher gabapentinoid doses).[1] Risk for adverse events also increases with higher opioid doses compared to lower doses, although there is no dose threshold for which there is no risk.[1] In some studies, risk for falls and fractures was highest at the start of therapy and decreased with longer-term use.[1]

Overall, there is insufficient data evaluating long-term safety of buprenorphine for chronic pain and comparing buprenorphine to other opioids for long-term, serious adverse events. One observational study (n=9,500) reported data on buprenorphine compared to other opioids. An increased risk of hip fracture was identified for patients prescribed opioids (age-adjusted incidence 3.47 vs. 1.94 per 100 person-years, hazard ratio [HR] 1.96, 95% CI, 1.27 to 3.02).[1] Risk was not statistically significant for patients prescribed codeine or dihydrocodeine (HR 1.70, 95% CI, 0.89 to 3.26) but was statistically significant for patients prescribed buprenorphine (HR 1.98, 95% CI, 1.33 to 2.95) and other full opioid agonists (HR 2.72, 95% CI, 1.25 to 5.93) compared to no opioid use.[1] There is insufficient evidence to determine if buprenorphine has lower risk of abuse, misuse, or development of OUD compared to other opioids. Pharmacokinetic studies of buprenorphine have documented a plateau effect for respiratory depression, and this may theoretically decrease risk of overdose.[5,6] However, the real-world implications of this effect have not been confirmed in clinical studies. It is currently unknown whether buprenorphine has lower risk of respiratory depression or overdose compared to other opioids.

Guideline Recommendations

Guidelines from the Department of Defense and Department of Veterans Affairs (DOD/VA) and National Institute for Health and Care Excellence (NICE) continue to recommend against initiation of opioids (including buprenorphine) for chronic pain.[2,7,8] Updated guidelines on the use of opioids from the Centers for Disease Control (CDC) recommend initiation of opioids only when:[9]

- alternative therapies including nonpharmacologic and non-opioid pharmacologic therapies are maximized,
- clinician and patient have discussed realistic benefits and risks of treatment and established goals of therapy,
- potential benefits outweigh risks, and
- there is an established plan to reassess therapy and discontinue treatment if benefit is not established.

These recommendations are based on data that opioids generally provided a small improvement in pain and function compared to placebo, but were also associated with short-term harms with evidence of pain attenuation with longer-term use between 3-6 months. No difference in pain or function was found between opioids and non-steroidal anti-inflammatory drugs (NSAIDs) for multiple chronic conditions.[9]

For people who are already established on daily opioid therapy, guidelines recommend careful reassessment of risks and benefits including shared decision making for discontinuation of opioids or risk mitigation for continued therapy.[2,8-10] Withdrawal symptoms have been documented with abrupt discontinuation of opioids (including buprenorphine) during post-marketing studies. The 2022 DOD/VA guideline for the treatment of chronic pain includes a suggestion for use of buprenorphine instead of full agonist opioids for patients prescribed daily opioids for chronic pain (weak recommendation for therapy).[2] The systematic literature review supporting this recommendation found low quality evidence that buprenorphine was equally effective at controlling pain compared to other opioids and insufficient evidence evaluating safety of buprenorphine compared to other opioids. In the absence of any evidence, guideline authors note that the theoretical safety profile of buprenorphine based on the mechanism of action as a partial agonist and status as a schedule III substance may decrease long-term risks compared to full opioid agonists (which are classified as schedule II substances and have known overdose risks).[2] However, potential benefits should be weighed against the lack of evidence for improved safety outcomes compared to other opioids.

Switching to Buprenorphine

Switching between opioid products typically requires careful monitoring for withdrawal symptoms, breakthrough pain, respiratory depression, and overdose. Many protocols describing transition from other opioids to buprenorphine require patients to exhibit mild withdrawal symptoms before initiation of buprenorphine therapy with the goal of avoiding precipitated withdrawal. There are a wide variety of protocols used to switch patients, and uncertainty about buprenorphine dose conversion ratios, variable pharmacokinetics among formulations, and inter-patient variability in opioid potency make standardization of protocols difficult.[11,12] A 2021 systematic review evaluated feasibility, efficacy, and safety of transition to buprenorphine in patients prescribed long-term

opioids for chronic pain.[12] Overall, authors did not identify any studies that evaluated whether switching to buprenorphine impacts important long-term outcomes such as overdose, mortality, and development of OUD. No studies evaluated healthcare utilization, and follow-up periods were generally short (<6 months).[12] In the absence of OUD, it is unclear whether transitioning to buprenorphine is safer than maintenance of current opioid therapy for people with chronic pain. However, many people have chronic pain and concurrent OUD, and switching to sublingual buprenorphine to manage OUD remains one of the first-line treatment option for this population.

Conclusion

Available data indicate that buprenorphine has similar rates of adverse events when compared to other opioids for short-term treatment of chronic pain (moderate quality evidence).[2,9] There is insufficient evidence to determine if buprenorphine is associated with lower risk for long-term safety outcomes of respiratory depression, overdose, and development of OUD compared to other opioids. All formulations of buprenorphine have warnings for abuse, misuse, addiction, respiratory depression, overdose, neonatal opioid withdrawal syndrome, withdrawal symptoms, adrenal insufficiency, and hepatic adverse events in the FDA labeling.

Most chronic pain guidelines do not recommend buprenorphine over other opioids. Instead, alternative therapies should be maximized before initiation of any opioid. Guidelines recommend that patients and providers discuss realistic expectations before initiating opioid treatment. Studies show that opioids generally provide only small improvements in pain and function compared to placebo and they can be associated with significant harms. Before prescribing or increasing the dose of an opioid, providers and patients should have a specific plan in place to assess therapy within 1 to 4 weeks and discontinue the opioid if benefit is not established. In patients already established on opioid treatment, providers and patients should work together to reassess risks and benefits including shared decision making for discontinuation of opioids or risk mitigation for continued therapy. Switching to buprenorphine is an option for providers to consider, but it is currently unknown whether switching therapy will decrease long-term risks of opioid therapy.

Pain Resources for Providers

- Tools for screening, tapering & risk benefit evaluation
- Health and Human Services Guidelines for appropriate dosage reduction
- Pain Education Toolkit for Patients
- Medication Toolkit for Patients

Peer Reviewed By: Roger Chou, M.D., Director of the Pacific Northwest Evidence-based Practice Center and Professor of Medicine at the OHSU School of Medicine and Dara Johnson, PharmD, BCPP, BCACP, Clinical Pharmacy Specialist, Providence Medical Group.

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Update on the Use of SGLT-2 Inhibitors

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The incidence of type 2 diabetes (T2D) continues to rise in adults and children. In Oregon, approximately 287,000 people have diabetes with an estimated total cost to the state of 3 billion dollars annually.[1] In 2017 there were around 220,000 cases of T2D in children, with the highest incidence in ethnic groups such as Blacks and Hispanics.[2] Pharmacotherapy is the cornerstone for management of T2D. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are often used to help lower glucose levels in those with T2D. While they are associated with moderate hemoglobin A1c (HbA1c) reductions, there is also evidence of cardiovascular (CV) and renal benefits.[3] The purpose of this newsletter is to provide updated guideline recommendations for the use of SGLT-2 inhibitors beyond glucose reductions and review evidence for two recently approved therapies, bexagliflozin and sotagliflozin.

Background

Sodium glucose cotransporter-2 inhibitors block the reabsorption of glucose from the renal glomerular filtrate in the renal proximal tubule.[4] This results in reduction in renal absorption of filtered glucose and increased urinary glucose excretion. Additionally, changes in volume status/diuresis may contribute to the mechanism of action conferring CV benefit that has been demonstrated with select SGLT2 inhibitors. Some of the additional benefits beyond glucose lowering demonstrated with SGLT-2 inhibitors include reduction in adverse CV outcomes (e.g., canagliflozin, dapagliflozin, empagliflozin and ertugliflozin*) and improvements in renal outcomes in those with diabetic nephropathy and albuminuria (e.g., canagliflozin) (**Table 1**).[3] There is also evidence of benefit for SGLT2 inhibitors in adults without diabetes for reduction in adverse HF outcomes (e.g., dapagliflozin, empagliflozin) and in people with chronic kidney disease (e.g., dapagliflozin and empagliflozin*[6]). * Not FDA indicated but evidence supports benefit in specific outcome noted.

Table 1. Approved Indications for SGLT2 Inhibitors[3]*

Indications	Drugs	Results for Approved Indications
In People with Type 2 Diabetes		
Improved glycemic control (HbA1c lowering)	Bexagliflozin (Brenzavvy™),	0.37% to 0.79%
	Canagliflozin (Invokana®),	-0.58%
	Dapagliflozin (Farxiga ®) and	-0.43%
	Empagliflozin (Jardiance ®) and	-0.3%
	Ertugliflozin (Steglatro®)	-0.48% to -0.5%
CV risk reduction in patients with T2D and established CV disease	Canagliflozin (Invokana®) and Empagliflozin (Jardiance ®)	3-point MACE: HR 0.86 (95% CI, 0.75 to 0.97) 3-point MACE: HR 0.86 (95% CI, 0.74 to 0.99)
Reduction in risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria >300 mg/day	Canagliflozin (Invokana®)	HR 0.70 (95% CI, 0.59 to 0.82)
HF risk reduction in patients with T2D and established CV disease or multiple CV risk factors	Dapagliflozin (Farxiga ®)	3-point MACE: HR 0.93 (95% CI, 0.84 to 1.03)
In People with or without Type 2 diabetes		
Reduction in risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in patients with CKD at risk of progression	Dapagliflozin (Farxiga ®)	HR 0.61 (95% CI, 0.51 to 0.72)
HF risk reduction in patients with HF	Dapagliflozin (Farxiga ®) Empagliflozin (Jardiance ®)	HR 0.74 (95% CI, 0.65 to 0.85) HR 0.75 (95% CI, 0.65 to 0.86)*/ HR 0.79 (95% CI, 0.69 to 0.90)†
Reductions in risk of CV death, HF hospitalization and urgent HF visits in pts with HF or T2D, CKD, and other CV risk factors	Sotagliflozin (Inpefa™)	HR 0.74 (95% CI, 0.63 to 0.88)

Key: * In patients with reduced ejection fractions; † In patients with preserved ejection fractions
Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MACE = major cardiovascular adverse events; T2D= type 2 diabetes.

Guideline Recommendations

The National Institute for Health and Care Excellence (NICE) updated guidance for the use of dapagliflozin and empagliflozin in 2021 and 2022, respectively, for the management of adults with HF.[7] NICE recommends that adults with chronic HF and ejection fraction less than 40% should be offered SGLT2 inhibitors, if appropriate based on patient specific factors, along with other HF medications.

In 2022, Kidney Disease: Improving Global Outcomes (KDIGO), updated their 2020 recommendations with an emphasis on glucose lowering therapies in patients with chronic kidney disease (CKD), focusing on the use of SGLT-2 inhibitors.[8] First-line drug therapy recommendations include: SGLT2 inhibitors, metformin, renin-angiotensin-system [RAS] inhibitors and moderate- or high-intensity statins. In addition to the composite kidney outcomes (e.g., reduction in end-stage kidney disease, CV death and

hospitalizations for HF), select SGLT2 inhibitors conferred less annual estimated glomerular filtration rate (eGFR) decline and a reduction in albuminuria or decreased progression to severely increased albuminuria.[8]

KDIGO Recommendations for SGLT2 Utilization in CKD[8]:

- SGLT2 inhibitors should be used to treat people with T2D and CKD with an eGFR ≥20 ml/min per 1.73 m^2, with or without hyperglycemia.
- SGLT2 inhibitors with evidence of kidney and CV benefit (e.g., canagliflozin 100 mg, dapagliflozin 10 mg and empagliflozin 10 mg) should be considered as treatment options.
- If a patient has been initiated on a SGLT2 inhibitor, it may be continued even if the eGFR falls below 20 ml/min per 1.73 m^2 unless it is not tolerated or kidney replacement therapy is initiated.

The annual 2023 update from the American Diabetes Association (ADA) on the Standards of Care in Diabetes include recommendations for the use of SGLT2 inhibitors with an updated recommendation based on evidence showing slowed progression of CKD.[9,10] The guidelines strongly recommend the use of SGLT2 inhibitors that have demonstrated CV benefit, irrespective of glucose levels, in those who are high risk or have atherosclerotic CV disease, HF (with preserved or reduced ejection fraction), and/or CKD to reduce cardiorenal risk as part of their glucose lowering regimen (based on high-quality evidence).[9,10]

Bexagliflozin

Bexagliflozin is a SGLT-2 inhibitor approved for use as an adjunct to diet and exercise for controlling glucose levels in adults with T2D.[11] There are 4 published trials demonstrating evidence of efficacy and safety. Bexagliflozin was compared to placebo in 2 trials and compared to active treatment, sitagliptin and glimepiride, in the remaining 2 trials.[12–15] Participants in the trials had T2D with baseline HbA1c levels ranging from 7.98% to 8.3%.[4] The participants were a mean age of 61 years and were predominately White. All of the trials were small (n= 283 - 426). In one trial, the participants had moderate renal impairment.[12] The primary outcome was change in HbA1c for all of the trials. Changes in body mass and the percent of patients obtaining an HbA1c <7% were relevant secondary endpoints.

Bexagliflozin lowered HbA1c in all the trials with difference from placebo ranging from 0.37% to 0.79% in trials lasting up to 96 weeks .[12–14] Bexagliflozin was found to be non-inferior to both sitagliptin and glimepiride, as add-on therapy to metformin. Bexagliflozin demonstrated reductions in body mass in both placebo and active treatment comparison trials ranging from -2.0 kg to -3.75 kg. Mean number of patients obtaining a HbA1c <7% was 34% with bexagliflozin vs. 21.5% for placebo.[12]

The most common adverse reactions with bexagliflozin are female genital mycotic infections, urinary tract infections and increased urination.[8] Bexagliflozin should not be used in people with a GFR less than 30 mL/min/1.73 m^2 and is contraindicated in people on dialysis. There is no data to evaluate how bexagliflozin compares to other SGLT2 inhibitors and evidence to evaluate the impact on long-term cardiovascular or renal outcomes are not currently published.

Sotagliflozin

Sotagliflozin is a SGLT2 inhibitor indicated to reduce the risk of CV death, hospitalization for HF and urgent HF visits in adults with HF or T2D, CKD and other CV risk factors.[16] Sotagliflozin inhibits both SGLT2 and SGLT1.

Sotagliflozin has been studied for HF, CKD, and type 1 diabetes (T1D); however, it is only approved to reduce CV risk in patients with and without diabetes.[16] Sotagliflozin was approved in Europe as an adjunct to insulin therapy to improve glucose control in people with T1D and later withdrawn due to commercial reasons.[17] The FDA did not approve sotagliflozin for glucose lowering in patients with T1D due to increased incidence of diabetic ketoacidosis (DKA) compared to placebo.[18]

The SOLOIST and SCORED trials were used for FDA approval of sotagliflozin (**Table 2**).[19,20] The CV benefits demonstrated in the SCORED trial were driven by reductions in HF hospitalizations (HR 0.67 (95% CI, 0.55 to 0.82; P<0.001). There were no statistical differences in the incidence of CV death between sotagliflozin and placebo in both the SOLOIST and SCORED trials. Additional glucose lowering studies in patients with stage 3 CKD demonstrated slight HbA1c reductions with 400 mg sotagliflozin (mean difference from placebo -0.24%; 95% CI, -0.39 to 0.09; P=0.002) and no statistical difference in HbA1c lowering between sotagliflozin and placebo in those with severe renal impairment (eGFR 15 to 30 ml/min/1.73 m^2).[21,22] In overweight patients, sotagliflozin was associated with weight loss of -1.0 kg to -3.45 kg in studies lasting up to 52 weeks.

Table 2. Trials Demonstrating Sotagliflozin Efficacy

Trial	Participants	Composite of total CV deaths, hospitalizations for HF, and urgent visits for HF
SCORED Trial[20]	Adults with T2D and CKD	1.Sotagliflozin: 5.6 events per 100 patient-years 2. Placebo: 7.5 events per 100 patient-years HR 0.74 (95% CI, 0.63 to 0.88); P<0.001
SOLOIST Trial[19]	Adults with T2D and worsening HF	1. Sotagliflozin: 245 events (51.0%) 2. Placebo: 355 events (76.3%) HR 0.67 (95% CI, 0.52 to 0.85); P<0.001

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HR = hazard ratio; T2D = type 2 diabetes.

Common sotagliflozin adverse events occurring in placebo controlled trials in 5% or more of patients include the following: urinary tract infection, volume depletion, diarrhea, and hypoglycemia.[16] Sotagliflozin carries a warning of increased risk of DKA. There is insufficient comparative evidence to support the use of sotagliflozin over other SGLT2 inhibitors.

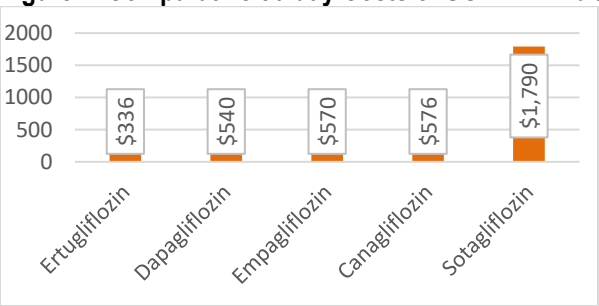
Pediatric Indication

In June of 2023 empagliflozin and empagliflozin/metformin (Jardiance® and Synjardy®), respectively, were approved for use in children and adolescents, 10 years and older with T2D, to improve blood sugar control as an adjunct to diet and exercise.[23] Evidence for efficacy was demonstrated in a 26-week, placebo-controlled, randomized, double-blind study which evaluated HbA1c reductions with the use of empagliflozin and linagliptin.[24] Empagliflozin is the only oral T2D therapy, besides metformin, indicated for use in pediatric patients.

Comparative Pricing

The cost for a thirty-day supply of a SGLT2 inhibitor is displayed in Figure 1. The costs are considered high compared to other oral therapies to treat T2D, such as metformin and sulfonylureas. There is no direct comparative evidence suggesting superior efficacy to support the use of the highest cost therapy, sotagliflozin. There is currently no cost data available for the new agent bexagliflozin.

Figure 1. Comparative 30-day Costs of SGLT2 Inhibitors[25,26]



Oregon Fee-For-Service Policy for SGLT2 Inhibitors:

- Preferred therapies are: canagliflozin, dapagliflozin, and empagliflozin
- Non-preferred therapies are: ertugliflozin, bexagliflozin and sotagliflozin

Conclusion

An increasing body of evidence has demonstrated benefits of SGLT2 inhibitors in people with and without diabetes. While cardiovascular and renal benefits appear to be a class effect, current guidelines recommend that therapies with demonstrated evidence be preferentially utilized (**Table 1**). Adverse events associated with SGLT2 inhibitors should be weighed against the benefits of moderate glucose reductions and reduced risk of adverse CV and renal outcomes. As with all pharmacotherapy, patient specific characteristics and comorbidities should be considered when determining the optimal treatment regimen.

Peer reviewed by: Robert Hughes, DO, Family Medicine, Samaritan Health Services

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2023 Global Initiative for Chronic Obstructive Lung Disease Report: Focus on Revised Recommendations for Inhaler Products

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Chronic Obstructive Pulmonary Disease (COPD) is a common respiratory condition, with incident rates around 10 percent worldwide in individuals aged 40 years or older.[1] It is characterized by cough, dyspnea, and airflow limitation.[1] Common risk factors include smoking, fume and dust exposure, and pulmonary or systemic infections.[1] People with COPD can have frequent office visits, hospitalization from exacerbations, and require chronic therapy, which results in high utilization of available healthcare resources.[1]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report committee published updated guidance with recommendations for the diagnosis, management, and prevention of COPD in early 2023.[2] The GOLD report is updated based on new evidence identified during a standard review process that occurs twice a year.[2] Based on recent evidence, the GOLD Science Committee revised its recommendations on initial pharmacological treatment and follow-up pharmacological treatment for people with COPD.[3] In particular, their position on the role of Long-Acting Beta Agonist (LABA) plus Long-Acting Muscarinic Antagonist (LAMA) and LABA plus Inhaled Corticosteroids (ICS) in managing COPD has been revised.[3]

The purpose of this newsletter is to review new evidence presented in the 2023 GOLD Report recommendations to enhance management of COPD and to describe updated COPD assessment tools. In addition, this newsletter will compare costs of recommended inhaler therapy and summarize the Oregon Health Plan (OHP) Fee-For-Service (FFS) policy for inhalers used to manage COPD.

COPD Classifications

Therapy for COPD is guided by an assessment of airflow obstruction severity, consideration of the patient's quality of life, and their risk for future events (e.g. exacerbations and hospital admissions).[4] One common clinical tool used for assessing COPD disease severity is the modified Medical Research Council dyspnea questionnaire (mMRC).[1] This tool assesses the level of activity that causes patients to experience shortness of breath graded on a scale from 0 (dyspnea only with strenuous exercise) to 4 (too dyspneic to leave the house).[1] A second clinical tool is the COPD Assessment Test (CAT).[1] This questionnaire measures the patient's assessment of the impact of COPD on their daily life and how it changes over time.[1] It utilizes eight questions that have a value ranging from 0 (never having symptoms) to 5 (always having symptoms) which adds to a total score.[1] A higher score indicates increased disease severity with a minimum clinically important difference defined as a change of 2 points.[1,5] Lastly, Forced Expiratory Volume in 1 second (FEV1) as a percentage of predicted value can also be used by clinicians to measure disease severity and progression.[4] In 2023, GOLD provided updated recommendations for how to categorize people based on COPD severity. GOLD guidelines continue to recommend that number of exacerbations, mMRC and CAT scores be used to define disease severity, but they group people into 3 levels of severity instead of 4 groups (See **Figure 1**). Members with 2 or more moderate exacerbations or at least 1 exacerbation leading to hospitalization now fall into the highest disease severity category (Group E) regardless of mMRC or CAT score; this new group is a combination of Groups C and D from previous guidelines.[4]

Figure 1. GOLD 2023 Guidance for Initial COPD Pharmacological Treatment Options[4]

≥ 2 moderate exacerbations or ≥1 leading to hospitalization	Group E: LABA + LAMA (consider LABA+LAMA+ICS if blood eosinophils ≥ 300	
0 or 1 moderate exacerbations (not leading to hospital admission)	Group A: bronchodilator (SABA)	Group B: LABA+LAMA
	mMRC 0-1, CAT < 10	**mMRC ≥ 2, CAT ≥ 10**

GOLD Group Classifications

For patients with a FEV1/Forced Vital Capacity (FVC) ratio less 0.7, an assessment of airflow limitation severity is based on a post-bronchodilator value of FEV1 percentage of reference value.[4] Patients would be categorized as GOLD 1 (mild) with a FEV1 ≥ 80 percent, GOLD 2 (moderate) with a FEV1 between 50 and 79 percent, GOLD 3 (severe) with a FEV1 between 30 and 49 percent, and GOLD 4 (very severe) with a FEV1 < 30 percent.[4]

2023 GOLD Report Recommendations

The 2023 GOLD report updated previous recommendations of LAMA for patients in group B based on new evidence from a high-quality meta-analysis and randomized controlled trials (RCTs). Data from the EMAX trial provide high quality evidence that umeclidinium plus vilanterol was superior to umeclidinium monotherapy for the outcome of FEV1 at 24

weeks for patients at low exacerbation risk.[4,6] The change from baseline in trough FEV1 at 24 weeks was 66 mL greater with umeclidinium plus vilanterol compared to umeclidinium alone (95% CI: 43 to 81, p<0.001) and 141 mL greater with umeclidinium plus vilanterol compared to salmeterol alone (95% CI: 118 to 164, p<0.001).[6] However, it is difficult to access the clinical meaningfulness of these results as a precise minimal clinically important difference for FEV1 has not been established.[7] Umeclidinium plus vilanterol also demonstrated improvements in the Transition Dyspnea Index versus umeclidinium and salmeterol monotherapies at 24 weeks (versus umeclidinium: 0.37 points; 95% CI: 0.06 to 0.68; p=0.018 and versus salmeterol: 0.45 points; 95% CI: 0.15 to 0.76; p=0.004).[6] This index measures changes in dyspnea severity from baseline and has a minimally important difference of greater than or equal to 1 unit.[8] When compared to both salmeterol and umeclidinium monotherapy, umeclidinium plus vilanterol did show a statistically significant difference, but did not achieve thresholds for clinical meaningfullness.[6]

Mortality Benefit

Current evidence supports a reduction in mortality with pharmacotherapy and non-pharmacotherapy in COPD patients. Two RCTs, IMPACT and ETHOS, compared single inhaler triple therapy to dual long-acting bronchodilator therapy.[4] For patients with symptoms and a history of frequent and/or severe exacerbations, both trials reported reduced mortality with triple therapy compared to dual therapy.[4] Several RCTs have also shown reduced mortality with non-pharmacological therapy including smoking cessation, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation, and lung volume reduction surgery.[4]

Additional Treatment Strategies

Most of the evidence supporting recommendations for bronchodilators in stable COPD is based on high-quality evidence from RCTs (Evidence A) or moderate quality evidence from RCTs with some limitations (Evidence B).[4] When selecting a specific agent for a patient, considerations should be given to availability and affordability, as there are no preferred active ingredients within therapeutic classes.[4] The recommendations for bronchodilators are listed in **Figure 2.**

Figure 2. Bronchodilators in COPD[4]

Key Points for Bronchodilators

- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea
- When initiating treatment with long-acting bronchodilators, LABAs plus LAMAs are preferred. Patients with persistent dyspnea on a single agent should be escalated to two

The evidence supporting the recommendations for anti-inflammatory agents, specifically for ICS, is equally robust.[4] Almost all of the recommendations are supported by publications graded as Evidence A. Important highlights for the use of anti-inflammatory agents are listed below in **Figure 3.**

Figure. 3 Considerations for Treatment Selection of Anti-Inflammatory Agents[4]

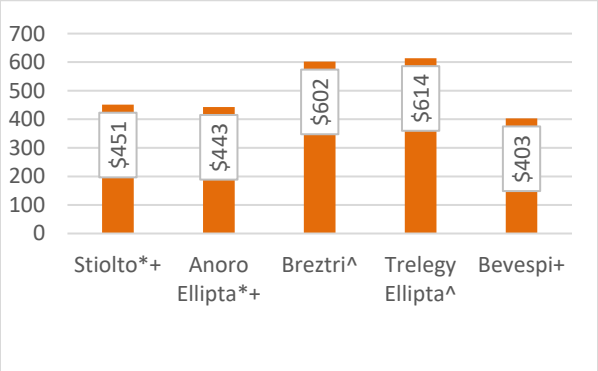
Key Points for Anti-Inflammatory Agents

- Long-term monotherapy with ICS is not recommended
- LABA plus LAMA plus ICS is preferred over LABA plus ICS therapy
- If patients with COPD have features of asthma, treatment should always contain an ICS
- If patients have a blood eosinophil count greater than or equal to 300 cells per microliter, treatment may include an ICS

Comparative Costs

Based on the 2023 GOLD report, most COPD patients should be initiated on LABA plus LAMA therapy.[4] In addition, patients who were initiated on LABA or LAMA monotherapy and are experiencing dyspnea or exacerbations should be transitioned to combination therapy.[4] Based on the average actual acquisition costs, dual therapy inhalers cost more than single agent products; however, the cost is lower than two separate monotherapy inhalers. The average acquisition costs for long-acting agents are listed in **Figure 4**. Also, combination inhalers may also improve adherence as non-adherence rates to COPD medication are estimated to be between 22 and 93 percent (depending on the definition of adherence used).[9] Overall, therapy selection should be patient specific, considering several factors including disease burden, patient lifestyle, and comparative costs.

Figure 4. Comparative Monthly Cost of Long-Acting Agents Combination inhalers



* OHP FFS Preferred Agent
+LABA/LAMA dual therapy inhaler
^LABA/LAMA/ICS triple therapy inhaler
**Prices based on 1 inhaler from Myers and Stauffer. Accessed July 24, 2023.

OHP FFS Policy Guidance

Preferred therapies for FFS members are based on effectiveness, safety and cost considerations (**Figure 5).**

Figure 5. Preferred Treatment Options for Inhaled COPD Treatment

OHP FFS Preferred COPD Inhalers

- SAMA: Atrovent or Combivent,
- LABA: Serevent
- LAMA: Spiriva or Incruse Ellipta
- LABA + LAMA: Stiolto or Anoro Ellipta

Conclusion

The 2023 Gold report provides updated recommendations for initial therapy options in patients with COPD.[10] These recommendations support the use of LABA plus LAMA combination therapy over monotherapy,.[10] The updated recommendations provide a simplified treatment algorithm that will hopefully benefit providers and patients.[10]

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Prior Authorization Update: Bempedoic Acid

Date of Review: December 2023
Generic Name: bempedoic acid; bempedoic acid and ezetimibe
PDL Class: Other Dyslipidemia Drugs

End Date of Literature Search: 08/16/2023
Brand Name (Manufacturer): Nexletol; Nexlizet (Esperion Therapeutics)
Dossier Received: No

Purpose for Drug Evaluation:

- Evaluate new evidence for the effectiveness and safety of bempedoic acid for the prevention of cardiovascular (CV) mortality and CV events in patients with established atherosclerotic cardiovascular disease (ASCVD) and high-risk CV patients to evaluate if there is a need for a prior authorization (PA) update.

Plain Language Summary:

- This review looks at new evidence for using medications to treat high cholesterol, also called dyslipidemia. Dyslipidemia can lead to an increased risk of heart attack or stroke.
- Statin medications lower the cholesterol levels in the blood and prevent heart attacks in people with dyslipidemia. If a statin alone cannot lower their cholesterol levels to an acceptable range, then a second medication is often added.
- One cholesterol lowering medication that has been approved for use in combination with statin medication is bempedoic acid. This medication works to help your body eliminate cholesterol from the bloodstream and can lower cholesterol levels. However, previous studies have not studied if it prevents heart attacks, stroke, or death.
- In a recently published study, in patients who could not tolerate first line statin medications, bempedoic acid decreased heart attacks and surgeries to restore blood flow to the heart.
- Statins are considered first line therapy for patients at risk for heart attacks, strokes and death from high levels of cholesterol. However, bempedoic acid is an option in patients who have tried multiple statin medications and cannot take them due to side effects.
- Based on previous studies, the Oregon Health Authority has adopted a policy that requires patients to have a history of cardiovascular disease and be on statin therapy for Medicaid to pay for bempedoic acid. This is called prior authorization.

Research Questions:

1. Is there new evidence for bempedoic acid and bempedoic acid/ezetimibe in reducing CV outcomes in patients treated for the primary or secondary prevention of CV disease?
2. Is there new evidence for long-term safety of bempedoic acid and bempedoic acid/ezetimibe?
3. Are there specific subpopulations for which bempedoic acid may be specifically indicated, more effective, or associated with less harm?

Author:

Conclusions:

- There is moderate-quality evidence that bempedoic acid lowers risk of a composite of death from CV causes, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization compared to placebo [11.7% versus 13.3%; absolute risk reduction (ARR) 1.6% / number needed to treat (NNT) 63; p = 0.004] in patients with a history of CV event or at high-risk for a CV event who cannot tolerate more than a low dose of a statin.[1] This was primarily driven by reductions in non-fatal CV events and coronary revascularization.[1]
- There is moderate-quality evidence that bempedoic acid does not decrease CV death or all-cause mortality in statin intolerant patients compared to placebo.
- There is low-quality evidence based on a prespecified subgroup analysis that bempedoic acid lowers risk of a composite outcome of death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization compared to placebo (5.3% vs. 7.6%; ARR 2.3%; NNT 43) in patients at high-risk for a CV event.[2]
- There is insufficient evidence evaluating clinical CV outcomes in patients on maximally tolerated statin therapy and limited data in low-risk individuals on therapy for primary prevention of CVD.
- There is insufficient evidence evaluating bempedoic acid in reducing CV outcomes in patients from racial and ethnic minority populations.

Recommendations:

- Continue to prioritize statin optimization in patients with clinical atherosclerotic cardiovascular disease (ASCVD) and those at high risk for CV disease. Bempedoic acid should not be considered an alternative to statin therapy.
- Update prior authorization criteria to include coverage for bempedoic acid for high-risk primary prevention in patients with documented statin intolerance already on ezetimibe.
- Evaluate costs in executive session.

Summary of Prior Reviews

- There is moderate-quality evidence that bempedoic acid modestly lowers low-density lipoprotein cholesterol (LDL-C) compared to placebo (17% to 18% placebo-adjusted treatment difference from baseline at week 12) in patients with established CVD on maximally tolerated statin therapy who require additional LDL-C lowering (i.e. LDL ≥ 70 mg/dL).
- There is low-quality evidence that the combination of bempedoic acid and ezetimibe lowers LDL-C compared to placebo, bempedoic acid monotherapy and ezetimibe monotherapy (treatment difference of -38.2%, -18.9% and -13.5%, respectively).
- There is insufficient evidence to determine the long-term effectiveness of bempedoic acid or combination bempedoic acid and ezetimibe on clinically meaningful outcomes, including CV mortality and major adverse cardiovascular events (MACE).
- There are several concerning safety signals seen in 52-week trials of bempedoic acid including tendon rupture, gout, nephrolithiasis, and new-onset benign prostatic hypertrophy (BPH). More data are needed to better quantify the risks associated with therapy. Additionally, bempedoic acid resulted in multiple changes to lab parameters during treatment, including increases in serum creatinine, liver transaminases, creatinine kinase and decreases in white blood cell (WBC) count, neutrophils and hemoglobin.

Background:

Based on high-quality and consistent evidence demonstrating ASCVD risk reduction, statins are recommended as first line pharmacological agents for primary and secondary prevention of cardiovascular disease (CVD).[3] The 2018 American College of Cardiology (ACC) guidelines recommend non-statin therapy in specific settings.[3] In high-risk CVD, the guideline recommends adding non-statins when LDL-C remains above 70 mg/dL despite maximally tolerated statin therapy.[3] Among the potential non-statin therapies, the ACC guidelines recommend adding ezetimibe first, followed by a PCSK9 inhibitor if LDL-C levels remain above

70mg/dL.[3] This recommendation is supported by evidence of CV risk reduction with ezetimibe and PCSK9 inhibitors when used in combination with statin therapy.[3] There is a lack of data demonstrating CV risk reduction with other lipid lowering therapies, including fibrates and omega-3 fatty acids.[3]

Bempedoic acid was approved by the Food and Drug Administration (FDA) as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL-C.[4] Approval was based on the results from the CLEAR – Harmony and CLEAR – Wisdom trials.[4] Both trials resulted in a significant reduction in LDL-C from baseline at week 12 compared to placebo (treatment difference -18.1%; 95% CI -20 to -16.1% in CLEAR Harmony and -17.4%; 95% CI -21 to -13.9% in CLEAR Wisdom).[5,6] Significant reductions in non-HDL cholesterol, total cholesterol, apolipoprotein B and high-sensitivity C-reactive protein were also observed.[5,6] Since its approval, an additional study (CLEAR Outcomes) evaluated the impact of bempedoic acid on CV outcomes in patients who are unwilling or unable to take statin medications.[1]

Prior to the reporting of the CLEAR – Outcomes trial, the ACC released an expert opinion on the use of non-statin therapies for the lowering of LDL-C.[7] In the report, they recommend the addition of bempedoic acid if additional LDL-C lowering is indicated despite triple therapy with a maximally tolerated statin, ezetimibe, and PCSK9 inhibitor.[7] For patients with statin intolerance, the report recommends PCSK9 inhibitors for lipid lowering. If patients with statin intolerance are unwilling to take an injectable medication, then bempedoic acid may be considered.

The National Lipid Association defines statin intolerance as one or more adverse effects associated with statin therapy that improves with dose reduction or discontinuation and a trial of at least 2 statin medications at the lowest approved daily dose.[8] In addition, they define partial intolerance as an inability to tolerate the recommended dose while possibly being able to tolerate lower statin doses, a different statin, or alternative regimen.[8] While up to 25% of patients who start on statin therapy discontinue due to adverse effects, a randomized controlled trial has shown that most symptoms caused by statin are nocebo.[9] The author of this study recommend that clinicians do not interpret symptom intensity or timing as statin causation because the pattern is identical for placebo.[9]

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 1,** which includes dates, search terms and limits used. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.

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

Systematic Reviews:
After review, 5 systematic reviews were excluded due to a surrogate outcome (i.e., LDL-C)[10-12] or poor quality (i.e., AMSTAR II assessment).[13,14]

New Guidelines:
Two new guidelines have been published since 2021. Both were excluded for not including bempedoic acid or awaiting results from ongoing clinical trials.[15,16] One expert opinion was identified but was excluded since it was not a high-quality clinical practice guideline.[7]

New Formulations or Indications:
No new formulations or indications identified.

New FDA Safety Alerts:
No new FDA Safety Alerts identified.

Randomized Controlled Trials:
A total of 8 citations were manually reviewed from the initial literature search. After further review, 7 citations were excluded because of wrong study design (i.e. simulation model, rationale and design of a trial)[17,18] , drug (i.e. alirocumab)[19] , or outcome studied (i.e. LDL-C, patient characteristics, glycemic changes from baseline).[20-23] The single trial which evaluated bempedoic acid is summarized below in **Table 1**.

Table 1. Randomized Controlled Trial Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. CLEAR – Outcomes [1] DB, PC, RCT	1. 180 mg bempedoic acid once daily 2. Placebo Duration: 24 months	Demographics: Mean age 65 y/o 91% white 70% had ASCVD 23% on statins 12% on ezetimibe Mean LDL 139 mg/dL Key Inclusion Criteria: • 18-85 years • ASCVD or high CV risk • Statin intolerant • LDL-C ≥100 mg/dL Key Exclusion Criteria: • eGFR < 30 ml/min • recent ACS • Implantable device • NYHA Class IV heart failure • Uncontrolled HTN • HbA1c ≥10% • Liver disease	ITT: 1. 6992 2. 6978 Attrition: 1. 295 2. 358	Primary Endpoint: Composite of death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization 1. 819 (11.7%) 2. 927 (13.3%) HR: 0.87 (95% CI 0.79 to 0.96) p = 0.004 Secondary Endpoint: Composite of death from CV causes, nonfatal MI, or nonfatal stroke 1. 575 (8.2%) 2. 663 (9.5%) HR: 0.85 (95% CI 0.76 to 0.96) p = 0.006 Fatal or nonfatal MI 1. 231 (3.7%) 2. 334 (4.8%) HR: 0.77 (95% CI 0.66 to 0.91) p = 0.002 Coronary revascularization 1. 435 (6.2%) 2. 529 (7.6%) HR: 0.81 (95% CI 0.72 to 0.92) p = 0.001	1.6%/63 1.3%/77 1.1%/91 1.4%/72	Adverse event leading to discontinuation of trial regimen 1. 759 (10.8%) 2. 722 (10.4%) Hyperuricemia 1. 763 (10.9%) 2. 393 (5.6%) Gout 1. 215 (3.1%) 2. 143 (2.1%)	NA NA NA P values and CI NR	**Risk of Bias (low/high/unclear)**: Selection Bias: low; patients were randomized 1:1 via interactive web response system Performance Bias: low; double-blinded study Detection Bias: low; objective outcomes and outcome assessors were blinded Attrition Bias: low; less than 10% attrition and efficacy analyses were performed on ITT population Reporting Bias: low; outcomes reported as prespecified Other Bias: high; funded by Esperion Therapeutics **Applicability**: Patient: A majority (70%) of patients were considered secondary prevention, however the trial did include patients at high-risk for a CV event; data is only in for statin intolerant patients Intervention: dose selection based on phase 2 data Comparator: placebo is an appropriate comparator with background lipid lowering therapy Outcomes: data on CV outcomes Setting: multicenter study across 1200 sites in 32 countries (22 European countries, 3 North American countries, 4 South American countries, Australia, India, New Zealand, and South Africa)

				Death from CV causes 1. 269 (3.8%) 2. 257 (3.7%) HR: 1.04 (95% CI 0.88-1.24)	NS			
Abbreviations: ACS = acute coronary syndrome; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; CV = cardiovascular event; DB = double blind; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HR = hazard ratio; HTN = hypertension; ITT = intention to treat; LDL-C = low density lipoprotein cholesterol; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; NYHA = New York Heart Association; PC = placebo-controlled; PCSK9 = proprotein convertase subtilsin-kexin type 9; RCT = randomized controlled-trial; ULN = upper limit normal									

Clinical Efficacy:

The CLEAR–Outcomes trial was the first clinical trial designed to evaluate the effects of bempedoic acid on CV outcomes. [1] This trial was double-blind, placebo-controlled study with statin-intolerant patients randomized to receive either bempedoic acid 180 mg or placebo once daily.[1] Investigators defined statin intolerance as patient-reported intolerance due to an adverse event that started or increased during statin therapy or improved when statin therapy was discontinued, resulting in an inability to tolerate 2 or more statins at any dose or 1 statin at any dose and an unwellness or inability to attempt a second statin medication. [1] Also, patients were allowed to continue statin therapy if the dose they currently received was defined as very low dose statin therapy. [1] The primary endpoint was a composite of death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization. [1]

Overall risk of bias of the study was low. However, extensive exclusion criteria limits applicability to complex patients seen in clinical practice. While this trial included both primary and secondary prevention patients, 70% had ASCVD, limiting generalizability to patients on therapy for primary prevention. Almost all participants were white (91%) and it is difficult to apply results to other high-risk subgroups, including Black patients which included only 3% of the population. Furthermore, the study included a 4-week run-in period with single-blind placebo. Patients who were unable to tolerate therapy due to adverse effects or with adherence less than 80 percent were not eligible for randomization.[1] Of the 22084 patients who were screened, 7187 were excluded prior to randomization, leading to a 32.5% of screening failures.[1] This limits the study population to individuals less likely to experience side effects. Lastly, this study used a definition of statin intolerance that does not match the definition employed in clinical practice. This difference creates a concern for clinical applicability.

Participants in the bempedoic acid arm had a significant reduction in the primary CV outcome (11.7% versus 13.3%; ARR = 1.6%; NNT = 63; p = 0.004) over a median of 3.4 years. [1] This was primarily driven by a reduction in fatal or nonfatal MI (3.7% versus 4.8%; ARR = 1.1%; NNT = 91; p = 0.002) and coronary revascularization (6.2% versus 4.8%; ARR = 1.42%; NNT= 72; p = 0.001).[1] There was no significant reduction in CV death or all-cause mortality. In addition, participants experienced significant reductions in LDL at 6 months (-21.1 versus -0.8).[1] Of note, 22.9% of participants were on a baseline statin, 11.5% were on ezetimibe, 0.7% were on bile acid sequestrants, 5.3% were on fibrates, 0.5% were on PCSK9 inhibitors, and 0.5% were on a niacin derivative.[1]

This study focused on patients who were intolerant to statin medications. There is insufficient evidence evaluating CV benefit in patients with ASCVD on maximally tolerated statin therapy and in a broader low risk primary prevention population. In CLEAR-Outcomes, 30% of participants enrolled in the study did not have a history of a CV event and were included in the high-risk primary prevention cohort (n=4206).[2] To meet high-risk criteria, participants had to have an LDL-C of 100 mg/dl higher with a Reynolds Risk score > 30% or a SCORE Risk score > 7.5% over 10 years, or coronary artery calcium score > 400 Agatston units, or presence of type 1 or type 2 DM in women older than 65 years or men older than 60 years.[2] The Reynolds Risk score is a risk assessment used in the United States (US).[24] It differs from ASCVD assessments in that it excludes individuals with diabetes but does include high-sensitivity C-reactive protein.[24] The SCORE Risk assessment is a common tool used in European countries to predict 10-year risk of cardiovascular death.[24] A published subgroup analysis of primary prevention

participants found a significant reduction in the CV composite endpoint with bempedoic acid compared to placebo (5.3% vs. 7.6%; HR 0.70; 95% CI 0.55-0.89; NNT 43).[2] There was also a reduction seen in MI (1.4% vs. 2.2%; HR 0.61; 95% CI 0.39-0.98), CV death (81.8% vs. 3.1%; HR 0.61; 95% CI 0.39 to 0.98), and all-cause mortality (3.6% vs. 5.2%; HR 0.73; 95% CI 0.54 to 0.98).[2] However, these findings of a subgroup analysis should not be used to make strong conclusion due to the increased risk of false-positive results. In the primary prevention subgroup, 66% of participant had diabetes and 42% met the high-risk clinical score enrollment criteria.[2]

Clinical Safety:

There were not significantly more discontinuations due to adverse events in the bempedoic acid group compared to placebo (10.8% vs. 10.4%).[1] Higher discontinuation rates were seen in previous clinical trials (10.9% versus 7.5%), however the CLEAR Harmony trial did not have a run-in period unlike the CLEAR-Outcomes trial.[1,5,6] The presence or lack of a run-in period could be a potential reason for differences in discontinuations due to adverse events. Similar to previous trials, more patients on bempedoic acid experienced hyperuricemia (10.9% vs. 5.6%), gout (3.1% vs. 2.1%), increased alanine aminotransferase (1.2% vs. 0.8%), and increased aspartate aminotransferase (1.1% vs. 0.6%) compared to placebo.[1] Adverse events occurring at rates greater than 2 percent and at higher rates compared to placebo are included in **Table 2**. [1]

Table 2. Adverse Events Occurring in More than 2% of Patients and at Higher Rates than Placebo

	Bempedoic Acid (N=7001)	Placebo (N=6964)
Hypoglycemia	304 (4.3%)	267 (3.8%)
Elevated hepatic enzyme level	317 (4.5%)	209 (3.0%)
Renal Impairment	802 (11.5%)	599 (8.6%)
Hyperuricemia	763 (10.9%)	393 (5.6%)
Gout	215 (3.1%)	143 (2.1%)
Cholelithiasis	152 (2.2%)	81 (1.2%)

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24. 1. Quispe R FR, Cainzos-Achirica M, et al. Risk assessment for cardiovascular disease prevention: Comparing the American and European approaches. American College of Cardiology. November 21, 2019. Accessed September 15, 2023. https://www.acc.org/Latest-in-Cardiology/Articles/2019/11/21/07/26/Risk-Assessment-for-Cardiovascular-Disease-Prevention. .

Appendix 1: Medline Search Strategy

OVID Medline

1. bempedoic acid.af. 307
2. (coronary disease or coronary artery disease or dyslipidemia or dyslipidemias or myocardial infarction or stroke or cardiovascular disease or cardiovascular diseases).af. 1162143
3. 1 and 2 204
4. limit 3 to (english language and humans and yr="2021 -Current" and (clinical trial, all or controlled clinical trial or meta-analysis or randomized controlled trial or "systematic review") 13

Appendix 2: Key Inclusion Criteria

Population	Individuals with cardiovascular disease or at high-risk for cardiovascular disease
Intervention	Bempedoic acid or bempedoic acid/ezetimibe
Comparator	Placebo or active control
Outcomes	Cardiovascular events, all-cause mortality, cardiovascular mortality
Timing	At least 12 weeks
Setting	Outpatient or inpatient after acute coronary syndrome

Bempedoic Acid

Goal(s):
- Promote use of bempedoic acid that is consistent with medical evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- Bempedoic Acid (Nexletol™)
- Bempedoic acid and ezetimibe (Nexlizet™)

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code; go to #2	
2. Does the patient have clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of one or more ASCVD events (see below) **OR** a diagnosis of homozygous or heterozygous familial hypercholesterolemia (HeFH or HoFH) OR at high risk for CVD, including those with: • Diabetes mellitus OR • 10-year ASCVD risk of 10% or greater? Major ASCVD events • Recent ACS (within past 12 months) • History of MI (other than recent ACS from above) • History of ischemic stroke • Symptomatic peripheral artery disease • Coronary artery disease	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria		
3. Has the patient taken a daily high-intensity statin (see table below) for at least 3 months with a LDL-C still ≥ 70 mg/dl with ASCVD or ≥ 100 mg/dl with HeFH or HoFH or high-risk CVD? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin 2) Baseline LDL-C (untreated) 3) Recent LDL-C	**Yes:** Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: Baseline LDL-C _____ Date:_____ Recent LDL-C _____ Date:_____	**No:** Go to #4
4. Does the patient have a history of: • rhabdomyolysis caused by a statin, OR • a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin, OR • statin intolerance, defined as one or more adverse effects associated with statin therapy that improves with dose reduction or discontinuation and a trial of at least 2 statin medications at the lowest approved daily dose? Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	**Yes:** Confirm chart documentation of diagnosis or labs and go to #5 1. Statin #1: Dose: Date Initiated: 2. Statin #2 Dose: Date Initiated: Recent LDL-C _____ mg/dL Date: _____	**No:** Pass to RPh; deny for medical appropriateness
5. Has the patient taken ezetimibe 10 mg daily for at least 3 months and still requires additional LDL-C lowering (LDL-C still ≥ 70 mg/dl with ASCVD or ≥ 100 mg/dl with HeFH or HoFH or high-risk CVD), **OR** have a contraindication to ezetimibe?	**Yes:** Go to #6	**No:** Pass to RPH; deny for medical appropriateness

Approval Criteria		
6. Is the patient adherent with a high-intensity statin and/or ezetimibe?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	**No:** Pass to RPh; deny for medical appropriateness

High- and Moderate-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)	**Moderate-intensity Statins** (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40-80 mg	Pitavastatin 1-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

P&T / DUR Review: *12/23 (MH), 08/20 (MH)*
Implementation: *TBD; 9/1/20*

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

Policy Proposal: Over-the-Counter (OTC) Drugs

Plain Language Summary:

- Over-the-counter (OTC) medicines are products that people can buy without needing a prescription from a doctor. These medicines are usually available in places like pharmacies, grocery stores, and convenience stores. OTC drugs are generally considered safe when used as directed.
- Oregon Medicaid will only pay for OTC medicines when prescribed by a provider. Some pharmacists can write prescriptions for OTC products as a provider.
- We recommend maintaining a list of classes that include OTC medicines and propose a general policy for new OTC medicines. Under this policy, Medicaid can pay for OTCs that are in an existing class. Medicaid will not pay for other OTCs until they are reviewed by the Pharmacy and Therapeutics Committee and added to the OTC list.

Purpose for the Proposal:
The purpose of the prior authorization (PA) proposal is to clarify types of over-the-counter (OTC) drugs that are covered under the Oregon Health Plan and propose a method to maintain this list of drug classes.

Background:
Over-the-counter medications can be approved by the FDA through a variety of pathways. New molecular entities can be submitted as non-prescription drugs to the FDA using a new drug application without first receiving approval as a prescription drug (referred to as direct-to-OTC). Manufacturers can also request a currently approved prescription drug receive marketing status as a non-prescription drug (referred to as an Rx-to-OTC switch).[1] Prescription-to-nonprescription switches are categorized as a full switch, in which all drug products are switched to nonprescription status, or a partial switch, in which some conditions of use (e.g., indications) are switched to nonprescription status, but others retain their prescription-only status.[2] **Table 1** lists examples of recent prescription to non-prescription switches approved by the FDA in recent years.

Table 1. Recent OTC products approved by the FDA.[3]

Generic Name (Brand)	Approval Date	Indication/Purpose	Type of Approval
Norgestrel (OPILL)	July 2023	Prevention of pregnancy	Full Rx-to-OTC switch
Naloxone (NARCAN)	March 2023	Treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression	Full Rx-to-OTC switch
Momentasone furoate (NASONEX)	March 2022	Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: nasal congestion; runny nose; sneezing; itchy nose	Partial Rx-to-OTC switch
Alacafadine (LASTACAFT)	December 2021	Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair and dander	Full Rx-to-OTC switch
Azelastine (ASTEPRO)	June 2021	Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: nasal congestion; runny nose; sneezing; itchy nose	Partial Rx-to-OTC switch

Policies for coverage of over-the-counter (OTC) medications under Medicaid plans differ from coverage of prescription products in several ways.

- Coverage of OTCs is an optional benefit for Medicaid. States can opt to cover certain classes or categories of non-prescription drugs based on information listed in their state plan. Historically, Oregon Medicaid has covered certain classes of OTC medications. Examples include cough and cold medications, analgesics, and drugs for gastrointestinal symptoms. Recently, the state plan was updated to allow more flexibility when determining coverage of OTCs. Instead of having a static list of OTC drug classes, the state plan was updated to rely on recommendations from the P&T committee for coverage of OTC medications. Classes which currently include covered OTC drugs are listed in **Appendix 1**.
- When Medicaid elects to cover OTC drugs, anyone who is dual eligible for both Medicare and Medicaid is entitled to receive equitable coverage for the OTC drug under Medicaid. In these circumstances, because many Medicare plans do not cover OTC drugs, Medicaid becomes the primary payer of covered OTC products for dual eligible members.
- In order for prescription drugs to be covered by Medicaid, manufacturers generally have to participate in the Medicaid rebate program. However, unlike prescription products, the state has more flexibility to cover non-rebatable OTC medications. Many OTC products are rebate eligible, and while use of rebatable OTC products is encouraged, the state can make exceptions to cover non-rebatable OTCs. Products which have historically been added to the rebate exception list are generally preferred in a PDL class and have no comparable, rebatable, and marketed alternatives. Examples include select laxatives for chronic constipation, nicotine replacement, and melatonin for children.

When applicable, additional utilization controls and benefit plan coding continue to apply to OTC products. Some drugs may have coverage criteria, and requirements vary depending on the class. Like prescription drugs, all OTC products must still be prescribed by a licensed practitioner (which can include a pharmacist within their scope of practice). This proposal outlines a basic framework to update and maintain the list of covered OTC classes when new drugs are approved by the Food and Drug Administration (**Appendix 2**).

Proposal and Methods:

Proposed coverage rules and process for new OTC formulations:

1. For new OTC formulations that fall within an existing PDL class previously reviewed by the P&T Committee, the product will be added to the FFS benefit and the OTC list will be updated at a subsequent Pharmacy & Therapeutics Meeting as needed. Exceptions to the standard rebate process will be determined by the Oregon Health Authority on a case-by-case basis based on access, availability, and affordability. Existing utilization controls will be applied and PDL status will be designated according to the current policy for line extensions and new formulations outlined below:
    a. When a new strength or formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply until the new strength or formulation is presented to the P&T Committee for review.
    b. If a new strength or formulation becomes available for an existing preferred drug and the new product significantly differs from the existing medication in clinical uses or cost, the drug will not be preferred until the drug is reviewed by the P&T Committee.
2. For new OTC formulations that are not in an existing PDL class or are not in a drug category currently on the OTC list, the product will be designated as not covered until reviewed by the P&T Committee.

Recommendation:

- Update operating procedures to clarify policy and process to maintain a list of PDL classes that include covered OTC medications.
- Update the OTC list to include new daily contraceptives.

Abbreviated Drug Review

OPILL (norgestrel tablet)	**Indications:** Prevention of pregnancy

Dose: 0.075 mg tablet taken at the same time every day. Use a condom or barrier method for the first 2 days, for 2 days after a missed dose, or if taking a dose more than 3 hours late

- 0.075 mg tablet taken at the same time every day. Use a condom or barrier method for the first 2 days, for 2 days after a missed dose, or if taking a dose more than 3 hours late

Background

Norgestrel was first approved by the Food and Drug Administration (FDA) in 1973 and marketing was discontinued in 2005. In 2023, norgestrel was re-approved as the first over-the-counter (OTC) daily, progestin-only contraceptive. Historically, OTC emergency contraception (e.g., levonorgestrel) has been covered for members with Oregon Medicaid. Pharmacists in Oregon can also prescribe legend contraceptives. However, barriers to access still exist, and about half of pregnancies in the US are unintended. Rates of unintended pregnancy are particularly high in adolescents and people with lower incomes.

Efficacy

The FDA review of efficacy and safety was primarily based on original studies for norgestrel conducted for approval of the prescription product in 1973. Efficacy of contraceptives is typically evaluated using the Pearl Index or the number of contraceptive failures per 100 person-years. In original studies of norgestrel, the estimated Pearl index was 2.3 pregnancies per 100 person-years of exposure (2.3%). Evidence from published literature indicates that real-world use after non-prescription approval would have a higher Pearl Index, around 7% or higher. FDA labeling classifies norgestrel in the same category as other daily oral contraceptives with Pearl Indices of 4 to 7%. Other non-prescription contraceptive products such as male and female condoms and spermicides have Pearl Indices between 14% and 28%.

Safety

- Many safety concerns associated with daily oral contraceptives are related to inclusion of estrogen. Compared to combined oral contraceptives (COCs), progestin-only contraceptives have lower risk for thromboembolic events, cardiovascular events, and hypertension. They are the preferred option over COCs in high-risk subpopulations such as those over age 35 years with migraine headaches or who smoke.
- Labeling for norgestrel includes warnings for use in progestin-sensitive cancers and for people with history of breast cancer. In self-selection studies of this product (n=206), 95% (95% CI 91-97) of people with current or past breast cancer correctly identified that they should not take norgestrel. Additionally, progestin-sensitive cancers are uncommon in people under 40 years of age which will be the primary population using this birth control method. Thus, FDA reviewers noted that risk for recurrence or worsening of progestin-sensitive cancers was low in the population likely to use norgestrel.
- The most common adverse event associated with norgestrel was vaginal bleeding (21% in primary studies used for initial approval). With approval as a non-prescription product, there is risk that the patient may attribute vaginal bleeding to norgestrel and not recognize the need to seek evaluation for a separate condition that may cause vaginal bleeding. However, serious conditions that cause uterine bleeding such as endometrial cancer are typically rare in the population expected to use norgestrel for birth control. The estimated rate for endometrial cancer is less than 0.04% in people under 50 years of age.
- There is also potential for reduced bone mineral density and increased fracture risk with very long-term use. Other progestin-only contraceptives like depot medroxyprogesterone acetate can decrease bone mineral density because they strongly suppress estrogen. However, similar effects have not been documented with norgestrel in short-term studies or post-marking experience. Prescription labeling for progestin-only oral contraceptives does not currently recommend monitoring for bone mineral density.
- Norgestrel does not protect against human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or other sexually transmitted infections (STIs) and should not be used as an emergency contraceptive. FDA reviewers note risk for increased STI transmission if condom use declines with approval of a nonprescription contraceptive, but felt that overall risks for negative public health impacts were likely outweighed by positive public health impacts for prevention of unintended pregnancies.
- Norgestrel is not recommended in people who are pregnant or in combination with another hormonal birth control or intra-uterine device. Drug interactions with certain antiepileptics, HIV drugs, pulmonary hypertension medications, and St John's Wort may decrease contraceptive efficacy.

Recommendation

Recommend coverage of daily OTC contraceptives for members with Oregon Fee-for-Service Medicaid.

References

Murry, KM. Decisional Memorandum New Drug Application 17031 Supplement 41 Application for Full Prescription-to-Nonprescription Switch of Norgestrel Tablets 0.075 mg. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/017031Orig1s041SumR.pdf. Accessed November 1, 2023.

References:

1. Food and Drug Administration. Drug Application Process for for Nonprescription Drugs. https://www.fda.gov/drugs/types-applications/drug-application-process-nonprescription-drugs. Updated June 28, 2022. Accessed November 1, 2023.
2. Food and Drug Administration. Prescription-to-Nonprescription (Rx-to-OTC) Switches. https://www.fda.gov/drugs/drug-application-process-nonprescription-drugs/prescription-nonprescription-rx-otc-switches. Updated June 28, 2022. Accessed November 1, 2023.
3. Food and Drug Administration. Prescription to Over-the-Counter (OTC) Switch List. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/prescription-over-counter-otc-switch-list. Updated July 7, 2023. Accessed November 1, 2023.

Appendix 1. Over-the-counter Drug List

Oregon Fee-for-service (FFS) Over-the-counter (OTC) Drug List
Effective: July 1, 2023

The following drug classes include over-the-counter (OTC) products determined to be cost-effective and clinically appropriate by the Oregon Pharmacy and Therapeutics (P&T) Committee. Select OTC products in these classes are included as a covered pharmacy benefit for Oregon Health Plan clients who are not enrolled in a Coordinated Care Organization (CCO). Coverage is generally limited to products manufactured by companies who have signed a federal rebate agreement, and they must be prescribed by a licensed practitioner. Example OTC products are listed below. Some drugs may have coverage criteria, and requirements vary depending on the class. For more comprehensive coverage requirements visit https://www.oregon.gov/oha/HSD/OHP/Pages/Policy-Pharmacy.aspx to review the current fee-for-service (FFS) Preferred Drug List (PDL) and prior authorization criteria.

Class	Examples of commonly covered products
Analgesics	ibuprofen naproxen sodium acetaminophen
Antacid, H2 Antagonists	famotidine ranitidine HCl
Antacid, Proton Pump Inhibitors	omeprazole
Antibiotics, Topical	bacitracin neomycin/bacitracin/polymyxinB
Antidiarrheals	bismuth subsalicylate loperamide HCl
Antiemetics, Conventional	dimenhydrinate meclizine HCl
Antifungals, Topical	terbinafine HCl
Antifungals, Vaginal	miconazole nitrate
Antihistamines, First Generation	chlorpheniramine maleate diphenhydramine HCl
Antihistamines, Second Generation	cetirizine HCl loratadine
Antiparasitics, Topical	permethrin
B-vitamins, Oral	cyanocobalamin (vitamin B-12) folic acid

	pyridoxine HCl (vitamin B6)
Calcium/Vit D Replacement, Oral	calcium carbonate cholecalciferol (vitamin D3)
Contraceptives	levonorgestrel norgestrel
Cough and Cold	guaifenesin pseudoephedrine HCl
Diabetes, Insulins	insulin NPH hum/reg insulin hm insulin NPH human isophane insulin regular, human
Iron Replacement, Oral	ferrous gluconate ferrous sulfate
Laxatives, Chronic Constipation	calcium polycarbophil docusate sodium magnesium hydroxide sennosides
Magnesium Replacement, Oral	magnesium oxide
Miscellaneous	fluoride for children
Multivitamins, Oral	various
Nasal Allergy Inhalers	budesonide triamcinolone acetonide
Opioid Reversal Agents	nalmefene naloxone
Pain Medications, Topical	lidocaine HCl
Platelet Inhibitors	aspirin
Prenatal Vitamins	various
Sedatives	diphenhydramine HCl doxylamine succinate melatonin for children
Steroids, Topical	hydrocortisone
Tobacco Smoking Cessation	nicotine replacement

OREGON HEALTH AUTHORITY
DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES
Updated: June 2023

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

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

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the OHA for drugs to be included on the preferred drug list (PDL).
    a. The P&T Committee may direct a Subcommittee to prepare these reviews.

2. Advise the OHA on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.

3. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs, as well as the ability of Oregonians to access prescriptions that are appropriate for their clinical conditions.

4. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs. Meeting materials including written public comments, recordings, documents, and minutes remain publicly available online after the meeting. Comments are subject to Oregon public records law and should not disclose identifiable, personal health information.

5. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.

6. Consider input from Mental Health Clinical Advisory Group (MHCAG) on topics involving mental health. The Mental Health Clinical Advisory Group can make recommendations to both the Oregon Health Authority and the Pharmacy and Therapeutics Committee for:

a. Implementation of evidence-based algorithms.
b. Any changes needed to any preferred drug list used by the authority.
c. Practice guidelines for the treatment of mental health disorders with mental health drugs.
d. Coordinating the work of the group with an entity that offers a psychiatric advice hotline.

7. Guide and approve meeting agendas.

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

AD HOC SUBJECT MATTER EXPERT INVOLVEMENT:

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

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

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

CONDUCT OF MEETINGS:

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

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

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

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

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

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

7. Agenda items for which there are no recommended changes based on the clinical evidence may be included in a consent agenda.
    a. Items listed under the consent agenda will be approved by a single motion without separate discussion. If separate discussion is desired, that item will be removed from the consent agenda and placed on the regular business agenda.
    b. Consent agenda items may include (but are not limited to) meeting minutes, drug class literature scans, and abbreviated drug reviews for unfunded conditions.

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

CONFLICT OF INTEREST POLICY:

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

1. All potential initial committee members, staff members and consultants, future applicants, expert or peer reviewers, and ad-hoc subject matter experts selected for individual P&T Committee meetings are subject to the Conflict of Interest disclosure requirements in ORS Chapter 244 and

are required to submit a completed disclosure form as part of the appointment process and annually during their appointment. Any changes in status must be updated promptly.

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

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

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

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

PUBLIC COMMENT:

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

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

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

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

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

    c. Please address written testimony related to final posted documents to the P&T Committee. Interested parties may submit written testimony on agenda items being considered by the P&T committee through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management).

Written testimony that includes clinical information should be submitted at least 2 weeks prior to the scheduled meeting to allow staff and Committee members time to review the information.

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

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

3. Written public comment is welcome from all interested parties on draft documents posted prior to the meeting.
   a. Written public comments submitted during the draft comment period are only considered by staff in order to prepare final documents. Only written public comment submitted based on final documents will be submitted to the P&T Committee for consideration.
   b. Interested parties may submit written testimony on posted draft documents through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management).

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

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

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

DRUG AND DRUG CLASS REVIEWS:

1. Drug Class Reviews and New Drug Evaluations:

   a. The P&T Committee will review drugs and drug classes that have not been previously reviewed for PDL inclusion or for clinical PA criteria and will be prioritized based on:
      i. Potential benefit or risk

ii. Use or potential use in covered population
iii. Potential for inappropriate use
iv. Alternatives available
v. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.

b. The P&T Committee will make a reasonable effort to perform a timely review of new FDA-approved drug products following their market release, when they are a new molecular entity and are candidates for coverage under the pharmacy benefit.
   i. Until new drugs are reviewed by the P&T Committee, drugs meeting the following criteria will be reviewed to ensure they are used appropriately for an FDA-approved or compendia-supported indication, with FDA-approved dosing, and that the indication is funded by the OHP:
      a. A new drug in a drug class with clinical prior authorization criteria.
      b. A new drug used for a non-funded condition on the HERC Prioritized List of Health Services.
      c. A new drug not in a PDL class with existing PA criteria identified by the reviewing pharmacist during the weekly claim processing drug file load costing more than $5,000 per claim or $5,000 per month.

c. Line Extension and Combination Product Policy Policy for existing drugs or active ingredients
   i. Line extensions include new strengths or new formulations of an existing drug.
      1. When a new strength or formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply until the new strength or formulation is presented to the P&T Committee for review.
      2. If a new strength or formulation becomes available for an existing preferred drug and the new product significantly differs from the existing medication in clinical uses or cost, the drug will not be preferred until the drug is reviewed by the P&T Committee.
   ii. When a new combination product becomes available that is a formulation of one or more drugs that have been reviewed for the PDL, the product will be designated a non-preferred drug until the P&T Committee reviews the combination product.
   iii. When a product becomes available that is a biosimilar for one or more drugs that have been reviewed for the PDL, where applicable, the product will be designated a non-preferred drug until the P&T Committee reviews the product. A complete list of biological products and biosimilar products can be accessed at the FDA's Purple Book website.
   iv. Over-the-counter (OTC) formulations:
      1. When a product becomes available that is an over-the-counter formulation, the product will be added to the fee-for-service (FFS) benefit if it falls within an existing PDL class previously reviewed by P&T. The policy outlined above for line extensions will apply. Exceptions to the standard rebate process will be determined by the Oregon Health Authority on a case-by-case basis based on access, availability, and affordability.
      ~~1.~~2. If OTC formulations that are not in an existing PDL class or are not in a drug category currently on the OTC list, then the product will be designated as not covered until the P&T Committee reviews the product.

2. Drug Class Literature Scans and Abbreviated Drug Reviews:

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

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Drug Class Review: Topical Moisturizers

Date of Review: December 2023 **End Date of Literature Search:** 10/04/2023

Plain Language Summary:

- People commonly apply skin moisturizers to prevent dry, scaly, itchy, or flaky skin. Dryness can cause the skin to break down which can lead to infections. Atopic dermatitis and ichthyosis are two types of skin disease that commonly have dry, scaly, itchy, or flaky skin.
- Evidence shows that moisturizers reduce disease severity in people with atopic dermatitis. The National Institute for Health and Care Excellence recommends emollients for children with atopic dermatitis.
- The National Institute for Health and Care Excellence also recommends topical products to prevent skin damage for people who have high risk for skin ulcers. Risk for skin damage is increased for people with swollen limbs, dry inflamed skin, who use of diapers, or who are unable to move. People at high risk for skin damage usually have more than one of these conditions.
- Evidence shows that moisturizers do not prevent development of atopic dermatitis in otherwise healthy infants unless there is a strong family history indicating increased risk for disease. Use of moisturizers in infants with healthy skin may increase risk for skin infections.
- There is no evidence that shows one moisturizer is better than another.
- The Oregon Health Authority (OHA) does not currently pay for moisturizers for people with Medicaid. We recommend that OHA begin to pay for moisturizers for people with severe skin disease. Before OHA will pay for a moisturizer, the provider should document disease severity.

Purpose for Class Review:
To evaluate whether skin emollients, protectants, or moisturizers should be added as covered medications to the fee-for service (FFS) benefit for funded conditions.

Research Questions:
1. What is the evidence for clinical efficacy for skin moisturizers, emollients, or protectants for treatment or prevention of skin conditions (e.g., dermatitis/eczema, ichthyosis)?
2. What is the evidence for harms of skin moisturizers, emollients or protectants in people with skin conditions?
3. Is there comparative evidence to demonstrate meaningful differences in effectiveness or harms in certain subpopulations based on patient or disease characteristics (e.g., age, diagnoses, symptom severity)?

Conclusions:
- Six systematic reviews evaluated efficacy of emollients for primary prevention of skin conditions and associated complications.
    - There was moderate quality evidence that skin care interventions in infants did not prevent development of eczema or atopic dermatitis compared to usual care at 1 to 3 years of age.[1-3] In studies of infants at high risk for development of AD based on family history, use of emollients decreased

risk compared to usual care (relative risk [RR] 0.75, 95% confidence interval [CI] 0.62 to 0.91, moderate-quality evidence) at 6 to 24 months, but use of emollients was also associated with increased risk of infection (67 vs. 50 per 1000; RR 1.33, 95% CI 1.01 to 1.75; moderate-quality evidence).[1,3]
    - Use of topical emollients or moisturizers in preterm infants may increase risk of infection (insufficient evidence), but likely has no impact on short-term mortality (over 2-4 weeks).[4]
    - There is insufficient evidence to assess whether moisturizers can help prevent occupational dermatitis of the hands.[5]
    - There is insufficient evidence to assess whether moisturizers can help maintain skin integrity and prevent skin damage in older people.[6]
- Compared to placebo or no treatment, moisturizers improved the following outcomes in people with atopic dermatitis or eczema:[7]
    - patient reported eczema severity (78% vs. 37%; RR 2.46, 95% CI 1.16 to 5.23; low-quality evidence),
    - provider reported disease severity (standardized mean difference [SMD] -0.65; 95% CI -0.89 to -0.41; high-quality evidence); and
    - people who experienced a flare (13% vs. 48%; RR 0.33, 95% CI 0.17 to 0.62; moderate-quality evidence).
- When moisturizers were added to active topical therapy, there were small improvements in provider reported disease severity that did not meet thresholds for clinically important differences (SMD -0.87, 95% CI -1.17 to -0.57; moderate-quality evidence).[7] There was low-quality evidence that combination use of moisturizer and active treatment reduced flares compared to just active treatment alone (31% vs. 13%; RR 0.43, 95% CI 0.20 to 0.93).[7] Guidance from the National Institute for Health and Care Excellence (NICE) recommends emollients for children with eczema or atopic dermatitis even when symptoms are controlled.[8]
- Guidance from NICE suggests use of a barrier preparation to prevent skin damage in adults at high risk of developing a moisture lesion or incontinence-associated dermatitis and infants or children who are incontinent. People at high risk for lesions usually have multiple risk factors (such as those with incontinence, limited mobility, nutritional deficiency, edema, dry or inflamed skin).[9] There was insufficient evidence to support one product or type of moisturizer over another for atopic dermatitis or dermatitis associated with incontinence.[7,10]
- There was insufficient evidence to evaluate efficacy or safety of moisturizers for chronic pruritus of unknown origin or infantile seborrheic dermatitis.[11,12]
- No high quality systematic reviews were identified that evaluated emollients for ichthyosis. European guidelines from 2019 recommend emollients for all forms of congenital ichthyosis based on low-quality evidence.[13]

Recommendation:
- Add coverage for select topical moisturizers with prior authorization (PA) to limit coverage to funded conditions.
- Update benefit plan exclusion criteria to reflect coverage for moisturizers and review process for exceptions.
- There are no PDL recommendations for specific products based on the clinical evidence. Determine coverage based on anticipated availability of products and evaluation of costs in executive session.
- Consider whether implementation of a PA would cost more than open access for preferred products.

Background:
A variety of conditions cause dry, scaly, itchy or flaky skin. Common conditions include atopic dermatitis or eczema, psoriasis, xerosis, and contact dermatitis. The Health Evidence Review Commission (HERC) has recommended funding for only severe inflammatory skin conditions on the prioritized list of health services. Severe disease is defined based on functional impairment and involvement of hands, feet, face, mucus membranes, or at least 10% of the body surface area.[14]

Treatments for skin disease vary based on condition, but typically include a variety of topical options such as corticosteroids, calcineurin inhibitors, and retinoids. Systemic therapy may be recommended for severe symptoms and may include retinoids, immunosuppressants, or targeted immune modulators. These prescription medications are covered by fee-for-service (FFS). In some cases, PA criteria limits use to funded conditions based on disease severity.

Skin moisturizers are also commonly recommended to treat symptoms of dry, itchy, or flaky skin. Moisturizers can contain hydrophilic components, to help skin hydration, or lipophilic components, to prevent evaporation of water from the skin and assist skin barrier recovery.[7] Examples of common components include humectants to retain water (e.g., urea, glycerol, lactic acid), occlusives which form a layer on the skin and prevent water loss (e.g., petrolatum, dimethicone, and mineral oil), and emollients to soften the skin (e.g., lanolin, glycerol or glyceryl stearate, soy sterols).[7] While there are some prescription emollients available, the vast majority of products are available as only over-the-counter formulations. State Medicaid programs have more flexibility for coverage of over-the-counter medicines, and can elect to cover or exclude these drugs from their Medicaid drug program. Because mild and moderate skin disease are unfunded, skin moisturizers, with the exception of zinc oxide, have historically not been covered in FFS Medicaid. Beginning in January 2024, the Health Evidence Review Commission has modified the prioritized list to add congenital (or inherited) ichthyosis associated with severe symptoms to a funded line. This prompted re-evaluation of coverage for topical moisturizers.

Ichthyosis is characterized by hyperkeratoic, scaling skin.[15] It can be inherited or acquired. Acquired ichthyosis is more likely to present in adults. It can arise from a variety of circumstances including drugs, autoimmune or inflammatory conditions, infections, or endocrine and metabolic diseases. Acquired ichthyosis typically improves once the triggering conditions are resolved. Management of acquired ichthyosis is focused on treating the underlying cause.[15]

Inherited ichthyosis is caused by genetic mutations in proteins and lipids that maintain skin integrity.[15] It typically presents in infancy or early childhood. The most common type of inherited ichthyosis, ichthyosis vulgaris, is typically associated with light scaling and thickening of the skin on the palms and soles of the feet (called hyperlinear palmoplantar markings).[15] Other less common genetic defects can be associated with blistering, skin erosion, other organ involvement, or delayed development. Rare forms of ichthyosis, such as harlequin ichthyosis, are associated with restrictive, adherent scaling that limits mobility. Diagnosis is typically based on clinical presentation, family history, and/or skin biopsy.[15] Genetic testing may help confirm some of the more severe forms of the disease. Prognosis varies depending on severity of symptoms and type of ichthyosis. Common complications of the disease include heat intolerance from inability to sweat and complications of the ears and eyes.[15] Desquamated skin in the outer ear canal can lead to pain and impaired hearing, and ectropion, a condition where the lower eyelid turns outward, is common in people with ichthyosis.[15] Skin infections, growth delay, nutritional deficiency, decreased range of motion, and psychological symptoms are associated with more severe disease.[15]

The goal of treatment for inherited ichthyosis is symptom management to reduce complications of the disease. There is limited evidence for most treatments and many recommendations are based on expert opinion.[13] Non-pharmacologic treatment recommendations include regular bathing to soak the skin, mechanical desquamation of scales with a cloth or sponge, and multidisciplinary support from psychologists, dermatologists, otolaryngologists, and ophthalmologists.[13,15] Pharmacologic treatments include use of topical emollients and keratolytics, topical retinoids, or systemic retinoids for more severe symptoms that are unresponsive to topical therapy.[15] European guidelines from 2019 for the management of congenital ichthyosis recommend topical moisturizers for all ichthyoses.[13] Common options include petrolatum or petroleum jelly, urea, propylene glycol, lactic acid, and salicylic acid. There is insufficient information to support use of any specific product over another.[13,15,16] Moisturizers are applied *at least* twice daily after bathing, and therefore, patient preferences and tolerability can be a major factor contributing to therapy compliance.[13] There is mixed evidence for use of immunosuppressants for symptom improvement in patients with inherited ichthyosis. Topical steroids and topical calcineurin inhibitors may be considered for short-term flares, but caution is recommended with long-term use due to risks of systemic absorption and skin atrophy.[15] Systemic interleukin inhibitors have been studied for inherited ichthyosis, with limited results. A small randomized controlled trial (RCT) of secukinumab in adults with inherited ichthyosis demonstrated no improvement in symptoms or disease severity.[17]

There are over 150 unique types and combinations of topical moisturizers currently reported by First Databank, the company that Oregon Medicaid uses to supply drug information. In FFS, analysis of denied claims indicates that the most commonly prescribed moisturizers include zinc oxide, lanolin

alcohol/mo/w.pet/ceres (MINERIN), ammonium lactate, mixed zinc oxide formulations (zinc oxide/menthol, zinc oxide/cod liver oil), dimethicone, and mineral oil/petrolatum.

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

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines.

Systematic Reviews:
Emollients for Primary Prevention
Three high-quality systematic reviews evaluated emollients for prevention of atopic dermatitis (AD) in infants.[1-3] One of these reviews, a 2022 Cochrane systematic review, identified 33 studies (n=25,827) evaluating skin interventions in infants of which 11 evaluated outcomes of interest for eczema, food allergy and adverse events.[1] Included studies were primarily conducted in infants who were classified as having high risk for atopic dermatitis based on family history.[1] The primary comparison for most studies was skin care interventions (including use of emollients) compared to standard infant skin care (such as bathing without a specific intervention).[1] The specific emollient used varied between studies, and follow-up for studies ranged from 24 hours to 3 years.[1] There was moderate-quality evidence from 7 RCTs that skin care interventions (including use of emollients) did not prevent development of eczema compared to usual care at 1 to 3 years of age.[1] Use of skin care interventions also had no impact on time to onset of eczema compared to usual care based on moderate-quality evidence from 9 RCTs.[1] There was moderate-quality evidence that use of a skin care regimen increased risk for skin infection compared to usual care (67 vs. 50 per 1000; RR 1.33, 95% CI 1.01 to 1.75; 6 RCTs; n=2728).[1] Evidence for allergy-related outcomes was mixed and graded as low quality indicating uncertainty in treatment effects.[1]

The second systematic review evaluated emollients specifically for prevention of atopic dermatitis in infants less than 6 weeks of age. This review included many of the same studies as the Cochrane review, and found no difference in risk of development of AD compared to usual care (RR 0.84; 95% CI 0.64 to 1.10; I^2=60%; 10 RCTs; low quality evidence).[3] However, authors noted subgroup differences based on baseline risk for development of AD. In studies of infants at high risk for development of AD based on family history, authors noted that use of emollients decreased risk compared to usual care (RR 0.75, 95% CI 0.62 to 0.91, n=1033; 8 RCTs; I^2 = 10%; moderate-quality evidence) at 6 to 24 months.[3] There was no difference in development of food sensitization or allergy with use of emollients compared to standard care (RR 0.85; 95% CI 0.65 to 1.11; 5 RCTs; n=1455; moderate-quality evidence). An increased risk of skin infection with use of emollients was noted when compared to usual care (RR 1.34, 95% CI 1.03 to 1.75, 3 RCTs; I^2 = 100%).[3]

The third systematic review evaluating emollients for prevention of AD in infants found similar results. The authors concluded that emollients may not prevent AD in healthy infants, but may decrease risk for those at increased risk of development for AD.[2] All 3 of these systematic reviews noted substantial heterogeneity among studies including definitions for infants at risk for AD, criteria and timing of AD diagnosis, type of intervention and emollient used.[1-3] Included studies also had notable limitations including variable adherence to treatment, risk for attrition, lack of blinding and risk of reporting bias which contributed to uncertainty in results.[1-3]

A 2016 Cochrane review evaluated whether use of topical emollients or moisturizers decreased risk of infection or mortality in preterm infants. Infection is a major cause of morbidity and mortality in preterm infants.[4] The review identified 18 RCTs (n=3089) which assessed topical ointments, creams, and oils. All trials had risk for performance and detection bias as they were unblinded. About half of trials had unclear risk for selection bias because of inadequate methodologic reporting. Trials were generally of short duration and outcomes were typically assessed upon discharge from the hospital. There was low-quality evidence from 8 RCTs (n=2086) that topical ointments or creams did not decrease risk for invasive infection (RR 1.13, 95% CI 0.97 to 1.31) or mortality (RR 0.87, 95% CI 0.75 to 1.03) in preterm infants compared to routine skin care.[4] In a subgroup analysis of studies to high-income countries, there was risk of infection with use of ointments or creams compared to usual care (RR 1.25, 95% CI 1.04 to 1.50; NNH 17, 95% CI 9 to 100; 2 trials, 1210 infants).[4] There was no difference in invasive infection (low-quality evidence) or mortality (moderate-quality evidence) with use of plant or vegetable oils compared to usual care.[4] Trials had significant heterogeneity that was not explained by subgroup analyses evaluating participants based on gestational age at birth or study location.[4]

A 2018 Cochrane review evaluated moisturizers and barrier creams for prevention of occupational dermatitis of the hands.[5] While emollients are commonly used to prevent and improve skin symptoms, authors found insufficient evidence to confidently assess effectiveness of moisturizers and barrier creams.[5] Nine RCTs (n=2888) were included in the review and the primary outcome was development of irritant hand dermatitis.[5] Evidence was significantly limited by unclear risk for selection performance and reporting bias in included studies.[5] There was high heterogeneity related to how dermatitis was assessed, products used, occupations for involved participants, and duration of treatment. Participants included metal workers exposed to cutting fluids, dye and print factory workers, cleaners and kitchen workers, healthcare workers, hairdressers, and gut cleaners in swine slaughterhouses.[5] Study durations ranged from one month to 3 years.[5] Differences between groups were small, often below what would be considered a clinically important difference, and results were imprecise for all outcomes.[5] All outcomes were graded as low or very low quality indicating substantial uncertainty in the true treatment effect.[5]

A 2020 Cochrane review evaluated emollients to help maintain skin integrity in older people who were living in residential care settings.[6] Six RCTs were included in the review and evaluated a range of interventions including use of moisturizing soap, soaking with water, oil or lotion and application of leave-on moisturizers.[6] In most studies, average age of included participants was over 80 years.[6] In 2 RCTs, participants had dry skin and other trials recruited people who had otherwise normal skin.[6] Duration of trials ranged from 5 days to 6 months. Studies were generally small and had high risk for attrition, performance, and detection bias.[6] The primary outcome was frequency of skin damage which was reported in only one trial.[6] Overall, authors concluded that evidence was insufficient to determine whether use of moisturizers or regular skin hygiene regimens prevents skin damage or improves symptoms of dryness in older adults.[6]

<u>Emollients for Treatment</u>

A 2017 Cochrane review included 77 RCTs (n=6603) evaluating efficacy of moisturizers for treatment of atopic dermatitis or eczema.[7] About half of the included studies were single center studies, and RCTs were generally small (most included between 20 and 60 participants).[7] Most included participants had mild to moderate disease and very few studies evaluated similar types of moisturizers. Compared to placebo, vehicle or no treatment, moisturizers improved the number of patients who reported improved eczema severity (78% vs.37%; RR 2.46, 95% CI 1.16 to 5.23; I^2= 95%; number needed to treat [NNT] = 2; low-quality evidence), provider reported disease severity (SMD of -0.65; 95% CI -0.89 to -0.41; P< 0.00001; I^2 = 75%; high-quality evidence); and people who experienced a flare (13% vs. 48%; RR 0.33, 95% CI 0.17 to 0.62; P = 0.0006; I^2 = 73%; NNT = 4, 95% CI 3 to 5; moderate-quality evidence).[7] There was no difference in health-related quality of life or adverse events with moisturizers compared to placebo, vehicle or no treatment (low-quality evidence).[7] Moisturizers were directly compared in 22 RCTs with no strong evidence that any type of product improved flares, disease severity or quality of life more than another.[7] Six RCTs (n=648) evaluated whether addition of a moisturizer to other topical treatment (e.g., steroids or calcineurin inhibitors) improved symptoms over 2 to 4 weeks.[7] Patient reported disease severity was not assessed. Changes in provider-reported disease severity were statistically improved with combination treatment compared to

topical steroids alone, but did not meet thresholds for minimum clinically important differences (SMD -0.87, 95% CI -1.17 to -0.57; moderate-quality evidence).[7] One study small evaluating flares, documented that combination use of moisturizer and active treatment reduced flares compared to just active treatment alone (31% vs 13%; RR 0.43, 95% CI 0.20 to 0.93; NNT = 6, 95% CI 3 to 57; low-quality evidence).[7]

A 2016 Cochrane review included 13 RCTs (n=1295) evaluating efficacy of topical treatments for prevention and treatment of dermatitis associated with urinary or fecal incontinence in adults.[10] All trials were conducted in nursing homes or hospitals and 9 RCTs were single center studies.[10] Most RCTs had high or unclear risk of selection bias, were unblinded, and more than half had high or unclear risk for attrition bias.[10] Average age for enrolled participants was between 59 and 89 years of age, and 6 RCTs evaluated prevention of dermatitis, enrolling participants who did not yet have any symptoms of redness or skin erosion.[10] Interventions were grouped into 2 categories: skin cleansers and products intended to be left on the skin such as moisturizers and protectants.[10] There were direct comparisons for various topical leave-on products compared in 8 RCTs. Products included various zinc oxide formulations, dimethicone, petrolatum, Desitin (combination zinc oxide/lanolin/petrolatum/cod liver oil), Calmoseptine (combination zinc oxide/menthol/chlorothymol/ glucerine/lanolin/sodium bicarbonate/phenol/thymol).[10] There was no difference in incidence of dermatitis when comparing various products. Evidence was limited to a single trial for each comparison. Incidence of bacterial or fungal infections were rarely reported (2.8% of participants in one RCT). There was evidence from 2 trials that soap and water may be less effective than a skin cleanser (RR 0.39, 95% CI 0.17 to 0.87; 1 RCT; n=65; low-quality evidence) or washcloth with cleansing, moisturizing and protecting properties (RR 0.31, 95% CI 0.12 to 0.79; 1 RCT; n=121 moderate-quality evidence) for prevention and treatment of dermatitis associated with incontinence.[10]

A 2020 Cochrane review did not identify any eligible RCTs that evaluated emollients or cooling lotions for treatment of chronic pruritus of unknown origin.[11] Notably, this review excluded studies in which pruritus was caused by a known dermatological or systemic condition.[11] A 2019 Cochrane review evaluating efficacy of interventions for infantile seborrheic dermatitis found insufficient information to evaluate efficacy of emollients or moisturizers based on results from 2 small RCTs.[12]

After review, 10 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

Guidelines from NICE make the following recommendations for use of moisturizers and emollients for prevention and treatment of skin conditions:

- For adults who are at high risk of developing a moisture lesion or incontinence-associated dermatitis (such as those with incontinence, edema, dry or inflamed skin), consider using a barrier preparation to prevent skin damage.[9] Risk is evaluated based on predisposing risk factors and skin assessment. People at high risk for pressure ulcers will usually have multiple risk factors (such as limited mobility, history of pressure ulcers, nutritional deficiency, or cognitive impairment). Skin assessment evaluates pain or discomfort, skin integrity, discoloration, and variations in heat, firmness or moisture.[9]
- For neonates, infants, children and young people who are incontinent, use barrier preparations to help prevent skin damage and moisture lesions.[9]
- For children with eczema or atopic dermatitis, emollients are the basis of management and should always be used, even when atopic eczema is clear.[8] Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other active treatments (e.g., topical steroids, calcineurin inhibitors, phototherapy, or systemic therapy).[8] For prevention of secondary bacterial infections caused by eczema, recommendations are made to manage underlying disease and flares with treatments such as emollients and topical corticosteroids, whether antibiotics are offered or not.[18]

European guidelines for congenital ichthyosis were published in 2019.[13,19] A systematic literature search was conducted to evaluate current literature. However, very few RCTs or controlled trials were identified. Most articles identified were case reports or small series. Recommendations were categorized according to the level of evidence outlined in **Table 1.** Because of limited evidence, many recommendations are based on expert opinion.

Table 1. Evidence grades for guideline recommendations

Grade of Recommendation	Correlating level of evidence
A	At least one high quality systematic review or RCT (level 1 evidence) with low risk of bias and directly applicable to the target population
B	High quality systematic reviews of case-control or cohort studies (level 2 evidence), directly applicable to the target population and demonstrating consistent results OR evidence extrapolated from low quality systematic review or RCTs (level 1 evidence)
C	Well conducted case-control or cohort studies (level 2 evidence) with low risk of bias, directly applicable to the target population and demonstrating consistent results
D	Non-analytical studies like case reports or case series (level 3 evidence) or expert opinion (level 4 evidence)

Recommendations for use of topical products are outlined below:[13]

- Emollients should be used in all types of ichthyosis (level 1 evidence; Grade B).
- Emollients should be applied several times a day and ideally after bathing (level 3 evidence; Grade D).
- Occlusive moisturizers are unsuitable for hot climates because of risk for overheating (level 4 evidence; Grade D).
- Emollients containing urea are unsuitable for inflamed or eroded skin or on flexural areas (such as armpits, knees, elbows, or groin) (level 3 evidence; Grade D).
- Topical agents (such as keratolytics or retinoids) are recommended for thickened/hyperkeratotic skin (level 1 evidence; Grade B).
- Keratolytics should be avoided in people with inflamed or eroded skin, on the flexures and face (level 1 evidence; Grade B). Caution is recommended for infants due to risk of systemic absorption (level 3 evidence; Grade D). Topical retinoids are contraindicated in pregnancy (level 1 evidence; Grade B).

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18. National Institute for Health and Care Excellence. Secondary bacterial infection of eczema and other common skin conditions: antimicrobial prescribing. NICE guideline [NG190]. March 2021. https://www.nice.org.uk/guidance/ng190. Accessed October 4, 2023.
19. Mazereeuw-Hautier J, Hernandez-Martin A, O'Toole EA, et al. Management of congenital ichthyoses: European guidelines of care, part two. *The British journal of dermatology.* 2019;180(3):484-495.

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to October 04, 2023

1	emollient.mp.	1098
2	exp Emollients/	5707
3	1 or 2	6304
4	limit 3 to "systematic review"	78

Appendix 3: Key Inclusion Criteria

Population	People with severe skin inflammatory skin disease or ichthyosis
Intervention	Emollients, protectants, or moisturizers
Comparator	Placebo
Outcomes	Symptoms, disease severity, function, quality of life, skin infection

Setting	Outpatient

Appendix 4: Proposed Prior Authorization Criteria

Moisturizers, topical

Goal(s):
- Limit use to funded conditions. Allow case-by-case review for members covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program.

Length of Authorization:
- 12 months

Requires PA:
- All topical emollients, protectants, or moisturizers

Covered Alternatives:
- Covered products include: TBD
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the request for treatment of severe skin disease? Severe disease is defined by the prioritized list as: • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: 1. At least 10% body surface area involved OR 2. Hand, foot, face, or mucous membrane involvement	**Yes:** Go to #4	**No: For age ≥ 21 years:** Pass to RPh; deny, not funded by the OHP **For age < 21 years:** Go to #3

Approval Criteria		
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity
4. Is the request for a preferred product?	**Yes:** Approve for 12 months	**No:** Go to #5
5. Has the patient failed to have benefit with (or have contraindications to) at least 2 preferred products?	**Yes**: Approve for 12 months	**No**: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *12/23 (SS)*
Implementation: *TBD*

Exclusion List

- Deny payment for drugs that are only FDA-approved for indications that are not covered by the Oregon Health Plan (OHP).
- Allow case-by-case review for members covered under the EPSDT program.
- Other exclusionary criteria are in rules at: https://www.oregon.gov/oha/HSD/OHP/Pages/Policy-Pharmacy.aspx

A full list of exclusions and limitations is listed in OAR 410-121-0147 Exclusions and Limitations (DMAP Pharmaceutical Services Program): https://secure.sos.state.or.us/oard/displayChapterRules.action?selectedChapter=87

Examples of drugs which are not covered include (but may not be limited to):

- Expired drug products;
- Drug products from non-rebatable manufacturers, with the exception of selected oral nutritionals, vitamins, and vaccines;
- Active Pharmaceutical Ingredients (APIs) and Excipients as described by Centers for Medicare and Medicaid (CMS);
- Drug products that are not assigned a National Drug Code (NDC) number;
- Drug products that are not approved by the Food and Drug Administration (FDA);
- Non-emergency drug products dispensed for Citizenship Waived Medical client benefit type;
- Drug Efficacy Study Implementation (DESI) drugs;
- Medicare Part D covered drugs or classes of drugs for fully dual eligible clients

NOTE: Returns as "70 – NDC NOT COVERED"

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. For what reason is it being rejected?		
3. "70" NDC Not Covered (Transaction line states "Bill Medicare"	**Yes:** Go to the Medicare B initiative in these criteria.	**No:** Go to #4
4. "70" NDC Not Covered (Transaction line states "Bill Medicare or Bill Medicare D"	**Yes:** Informational PA to bill specific agency	**No:** Go to #5
5. "70" NDC Not Covered (due to expired or invalid NDC number)	**Yes:** Informational PA with message "The drug requested does not have a valid National Drug Code number and is not covered by Medicaid. Please bill with correct NDC number."	**No:** Go to #6
6. "70" NDC Not Covered (due to DME items, excluding diabetic supplies) (Error code M5 –requires manual claim)	**Yes:** Informational PA (Need to billed via DME billing rules) 1-800-336-6016	**No:** Go to #7
7. "70" NDC Not Covered (Transaction line states "DESI Drug")	**Yes:** Pass to RPh. Deny (DESI Drug) with message, "The drug requested is listed as a "Less-Than-Effective Drug" by the FDA and not covered by Medicaid."	**No:** Go to #8
8. Is the request for a patient ≥21 years of age?	**Yes**: Go to #9	**No**: Go to EPSDT assessment Message: Requests for non-covered services can be considered with individual review under EPSDT.

Approval Criteria		
9. "70" NDC Not Covered (Transaction line states "Non-Rebatable Drugs")	**Yes:** Go to #10	**No:** Go to #12
10. Is the request for an over-the-counter (OTC) product? See types of OTC products currently covered by OHP here: www.orpdl.org	**Yes**: Go to #11	**No:** Pass to RPh. Deny (Non-Rebatable Drug) with message "The drug requested is made by company that does not participate in Medicaid Drug Rebate Program and is therefore not covered"
11. Is there documentation that covered alternatives are not medically appropriate or are unavailable? Note: many OTC products have rebatable or legend alternatives that are covered.	**Yes:** Pass to RPh; Deny and refer non-rebatable products to DMAP for consideration of a rebate-exception. Document reason (e.g., drug shortage, lack of covered alternatives, intolerance/contraindication to alternatives, etc)	**No:** Pass to RPh. Deny (Non-Rebatable Drug) with message "The drug requested is made by company that does not participate in Medicaid Drug Rebate Program and is therefore not covered. Consider switching treatment to a covered alternative."

Approval Criteria		
12. RPh only: "70" NDC Not Covered (Drugs on the Exclusion List) All indications need to be evaluated to see if they are covered and whether they are above the line or below the line.	**Above:** Deny with yesterday's date (Medically Appropriateness) and use clinical judgment to APPROVE for 1 month starting today to allow time for appeal. Message: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	**Below:** Pass to RPh; Deny. Not covered Message: "The treatment for your condition is not a covered service on the Oregon Health Plan."
13.		
14.		

EPSDT Assessment		
1. Is the request for a member ≥21 years of age?	**Yes:** Go to Approval Criteria	**No:** Go to #2
2. Is the request for a cosmetic indication, impotency, erectile dysfunction or infertility? These conditions are not covered under the OHP. See state plan full coverage list.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not covered Message: "The treatment for your condition is not a covered service on the Oregon Health Plan."
3. Is the request for a funded condition?	**Yes:** Go to #5	**No:** Go to #4

EPSDT Assessment		
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 #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is the request for an FDA approved indication?	**Yes:** Go to #7	**No:** Go to #6
6. Is there documentation that the requested treatment is supported by guidelines and compendia?	**Yes:** Go to #7 Document guideline, compendia, and/or literature referenced by the provider.	**No:** Pass to RPh. Deny; medical appropriateness. Off-label requests must include supporting literature.
7. Is there documentation that alternative therapies (including covered pharmacologic and non-pharmacologic therapies) provide inadequate treatment, are not medically appropriate, are unavailable, or are inaccessible?	**Yes:** Pass to RPh; Deny; non-covered service and refer to DMAP for secondary evaluation. Message: The requested treatment cannot be approved without secondary evaluation by DMAP. The request has been referred for evaluation under EPSDT.	**No:** Pass to RPh. Deny; medical appropriateness. Document therapies that have been previously tried. Consider switching to a covered alternative if appropriate.

If the DMAP call center notes a drug is often requested for a covered indication, notify Lead Pharmacist so that policy changes can be considered for valid covered diagnoses.

Table 1. Drug categories commonly used for non-covered conditions

Exclusion List		
Drug Code	**Description**	**DMAP Policy**
DCC = 1	Drugs To Treat Impotency/ Erectile Dysfunction	Impotency Not Covered on OHP List, BPH is covered
DCC = B	Fertility Agents	Fertility Treatment Not Covered on OHP List

DCC= F	Weight Loss Drugs	Obesity is a covered condition, but weight loss drugs are not a covered drug class. Case-by-case review for members covered under the EPSDT program allowed.
HIC3= L1C	Hypertrichotic Agents, Systemic/Including Combinations	Cosmetic Indications Not Covered
HIC3= Q6F	Contact Lens Preparations	Cosmetic Indications Not Covered
HIC3=L5B	Sunscreens	Cosmetic Indications Not Covered
HIC3=L5C	Abrasives	Cosmetic Indications Not Covered
HIC3=L7A	Shampoos	Cosmetic Indications Not Covered
HIC3=L8A	Deodorants	Cosmetic Indications Not Covered
HIC3=L8B	Antiperspirants	Cosmetic Indications Not Covered
HIC3=L9A	Topical Agents, Misc	Cosmetic Indications Not Covered
HIC3=L9C	Antimelanin Agents	Cosmetic Indications Not Covered
HIC3=L9D	Topical Hyperpigmentation Agent	Cosmetic Indications Not Covered
HIC3=L9F	Topical Skin Coloring Dye Agent	Cosmetic Indications Not Covered
HIC3=L9I	Topical Cosmetic Agent; Vit A	Cosmetic Indications Not Covered
HIC3=L9J	Hair Growth Reduction Agents	Cosmetic Indications Not Covered
HIC3=Q5C	Topical Hypertrichotic Agents	Cosmetic Indications Not Covered

Table 2. Drugs requiring alternative billing

Exclusion List		
Drug Code	**Description**	**DMAP Policy**
DCC = D	Diagnostics	DME Billing Required
DCC= Y	Ostomy Supplies	DME Billing Required
HIC3= B0P	Inert Gases	DME Billing Required

Table 3. Drugs commonly used for unfunded conditions or OTC drugs that have not been reviewed for coverage under the Oregon Health Plan

Exclusion List		
Drug Code	**Description**	**DMAP Policy**
HIC3=D6C	Alosetron Hcl	IBS Not Funded on OHP List
HIC3=D6E	Tegaserod	IBS Not Funded on OHP List

HIC3=L3P	Topical Antipruritic Agents	Not Covered OTC
HIC3=L4A	Astringents	Not Covered OTC
HIC3=L5A; Except HSN= 002466 (Podophyllin Resin), 006081 (podofilox), 002470 (benzoyl peroxide)	Keratolytics	Not Covered OTC; Warts, Corns/Calluses; Seborrhea Are Not Funded on OHP List
HIC3=L5B	Sunscreens	Not Covered OTC
HIC3=L5C	Abrasives	Not Covered OTC; Acne, Warts, Corns/Callouses; Diaper Rash, Seborrhea Are Not Funded on OHP List
HIC3=L5E	Anti Seborrheic Agents	Seborrhea Not Funded on OHP List
HIC3=L5G	Rosacea Agents, Topical	Rosacea Not Funded on OHP list, some acne severities are Funded
HIC3=L6A; Except HSN = 002577 (coal tar) 002576 002574 036916 002572 (Capsaicin)	Irritants	Not Covered OTC; Seborrhea, Sprains Not Funded on OHP List
HIC3=L7A	Shampoos	Not Covered OTC; Seborrhea, Not Funded on OHP List
HIC3=L9A	Topical Agents, Misc	Not Covered OTC; Warts, Corns/Callouses; Diaper Rash, Seborrhea, are Not Funded on OHP List
HIC3=Q6R, Q6U, Q6D	Antihistamine-Decongestant, Vasoconstrictor and Mast Cell Eye Drops	Allergic Conjunctivitis Not Funded on OHP List

HIC3= U5A, U5B, U5F & S2H plus HSN= 014173	Herbal Supplements " Natural Anti-Inflammatory Supplements" - Not Including Nutritional Supplements such as: Ensure, Boost, Etc.	Not Covered OTC
HSN=003344	Sulfacetamide Sodium/Sulfur Topical	Seborrhea Not Funded on OHP list
HSN=025510	Rosacea	Rosacea Not Funded on OHP List, some acne severities are funded
TC=93; Except select products TBD	Emollients/Protectants	Not Covered OTC

P&T Review: *3/18; 2/23/06*
Implementation: *4/16/18; 5/1/16; 9/1/06; 1/1/12*

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Salem, Oregon 97301-1079
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Drug Class Literature Scan: Erythropoiesis Stimulating Agents

Date of Review: December 2023

Date of Last Review: January 2019
Literature Search: 10/23/2018 – 8/14/2023

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

Purpose: Evaluate new evidence published since the last review in 2019 and assess utilization of prior authorization (PA) criteria.

Plain Language Summary:

- Erythropoietin is a hormone produced in the kidneys that causes the body to make red blood cells in the bone marrow. Medicines that increase erythropoietin production are called erythropoiesis-stimulating agents. These medicines must be injected by a health care provider either under the skin (subcutaneously) or into a vein (intravenously). Some people can self-administer these medicines at home after they learn how to prepare and use the injection.
- Erythropoietin-stimulating agents treat people who do not make enough red blood cells (a condition called anemia). Red blood cells carry oxygen from the lungs to the rest of the body. Anemia can make people feel tired or out of breath and may increase the need for a blood transfusion. The Food and Drug Administration has approved erythropoietin-stimulating agents for anemia associated with kidney disease, cancer treatment, and human immunodeficiency virus (HIV) infection. Providers also prescribe them for certain patients having surgery to reduce the need for a blood transfusion.
- Administration of these medicines can increase the risk of blood clots, stroke, heart attack, and death. To reduce the risk of side effects, people getting these medicines must be closely monitored by their provider. Blood tests are frequently obtained to check how well the medicine is working and to decide the best dosing schedule.
- Providers must explain to the Oregon Health Plan (OHP) why someone needs epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta before the OHP fee-for-service program will pay for it when the prescription is picked up at the pharmacy. This process is called prior authorization.

Conclusions:

- Since the previous 2019 Pharmacy and Therapeutics (P & T) Committee review of the class of erythropoiesis-stimulating agents (ESAs), 2 systematic reviews[1,2] and one guideline[3] have been updated.
- A 2023 Cochrane review evaluated recent evidence for the use of ESAs to manage anemia in adults with chronic kidney disease (CKD).[1] This review concluded epoetin alfa and darbepoetin alfa may be superior to placebo for the prevention of blood transfusion based on moderate- to very low-quality evidence, but increased the odds of hypertension compared to placebo (moderate-quality evidence).[1] Effects on death (any cause), were generally uncertain

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between any ESA formulation and placebo or other ESA product (low-quality evidence).[1] The other potential benefits of ESAs, such as reduction in fatigue and breathlessness, remain uncertain due to sparse data.[1]

- A 2020 Cochrane review evaluated the efficacy of preoperative epoetin therapy administered with iron in reducing the need for red blood cell (RBC) transfusions in preoperatively anemic adults undergoing non-cardiac surgery.[2] Moderate-quality evidence suggests that preoperative epoetin administered with iron therapy to anemic adults prior to non-cardiac surgery reduces the need for RBC transfusion and, when given at higher doses, increases the hemoglobin (Hb) concentration preoperatively compared to control treatment (placebo, no treatment, or standard of care with or without iron).[2] The administration of epoetin and iron treatment did not decrease the mean number of units of RBC transfused per patient (moderate-quality evidence) compared with control treatment.[2] There were no important differences in the risk of adverse events or mortality within 30 days (moderate-quality evidence), nor in length of hospital stay between those who received epoetin with iron and those who did not (low-quality evidence) compared with control treatment.[2]
- In 2019, the American Society of Clinical Oncology and American Society of Hematology (ASCO/ASH) updated clinical practice guidelines recommendations for use of ESA therapy in patients with chemotherapy-induced anemia.[3] Providers should offer an ESA to patients receiving cancer treatment that is not curative in intent and presenting with Hb less than 10 g/dL (High quality of evidence [QoE]; Strong recommendation).[3] ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (High QoE: Strength of recommendation: strong).[3]
- Most ESA claims are processed as physician administered claims (PAD), there is very little point of sale (POS) processing.

Recommendations:

- Based on review of recent evidence, no changes to the Preferred Drug List (PDL) are recommended.
- Retire ESA PA criteria due to limited POS utilization.
- Review drug costs in executive session.

Summary of Prior Reviews and Current Policy

- Epoetin alfa is Food and Drug Administration (FDA) approved for the treatment of anemia due to CKD in children and adults, anemia due to zidovudine therapy in HIV-infected adults, and anemia due to the effects of concomitantly administered myelosuppressive chemotherapy in patients aged 5 years and older with nonmyeloid malignancies receiving chemotherapy.[4] It is also indicated to reduce the need for allogeneic blood transfusions in adults electing noncardiac, nonvascular surgery.[4] Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being.[4] Epoetin alfa is not indicated for use under the following conditions:
    - cancer patients receiving hormonal therapy, therapeutic biologic products, or radiation therapy unless also receiving concurrent myelosuppressive chemotherapy;
    - cancer patients receiving myelosuppressive chemotherapy when the expected outcome is curative;
    - cancer patients receiving myelosuppressive chemotherapy when anemia can be managed by transfusion;
    - surgery patients who are willing to donate autologous blood;
    - surgery patients undergoing cardiac or vascular surgery; or
    - as a substitute for RBC transfusion in patients requiring immediate correction of anemia.[4]

  The manufacturer has issued a black boxed warning for epoetin alfa due to the increased risk for death, serious adverse cardiovascular reactions, and stroke in patients with CKD when epoetin is administered to a target hemoglobin (Hb) level greater than 11 g/dL.[4] In patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers, epoetin is associated with increased risk of tumor progression or recurrence.[4] In addition, due to the increased risk

of deep vein thrombosis (DVT) in perisurgical patients, DVT prophylaxis is recommended with administration of epoetin alfa.[4] The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) anemia workgroup published guidance that recommends balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension) when initiating and maintaining ESA therapy.[5] For adult CKD, non-dialysis patients, ESA therapy should not be initiated when Hb concentrations are greater than or equal to 10 g/dL.[5]

- Darbepoetin alfa and methoxy polyethylene glycol-epoetin beta have the similar limitations of use and an identical black box warning as epoetin alfa.[6,7] Darbepoetin is FDA-approved for treatment of anemia due to CKD in children and adults and anemia due to chemotherapy in adults with cancer.[6] Methoxy polyethylene glycol-epoetin beta is only FDA-approved for management of anemia due to CKD in people aged 5 years and older.[7]
- Prior DURM reviews have demonstrated a lack of difference in safety and efficacy for darbepoetin alfa and epoetin alfa and determined that preference can be established based on cost.[8-10] Darbepoetin alfa (ARANESP) is the current preferred agent. Epoetin alfa (PROCRIT and EPOGEN), epoetin alfa-epbx (RETACRIT), and methoxy peg-epoetin beta (MIRCERA) are currently non-preferred agents (see **Appendix 1**). Current policy requires prior authorization (PA) for all agents (see **Appendix 5**). The PA ensures that erythropoiesis-stimulating agents (ESAs) are covered according to Oregon Health Plan guidelines and current medical literature. The Health Evidence Review Commission (HERC) has a Guideline Note in the Prioritized List (Guideline Note 7) regarding ESA use in indications of anemia induced by cancer chemotherapy, anemia associated with HIV/AIDS, and anemia associated with chronic renal failure.[11] The guidance describes which Hb levels are required and when reassessment should occur.[11]
- In the second quarter of 2023 (April 1 through June 30) there were no POS claims processed for ESAs, all the claims were processed as PAD claims, mostly for patients with end stage renal disease.

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

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

New Systematic Reviews:

Cochrane: Erythropoiesis-Stimulating Agents for Anemia in Adults with Chronic Kidney Disease

A 2023 Cochrane review evaluated recent evidence for the use of ESAs to manage anemia in adults with CKD.[1] This was an update to a 2014 publication on the same topic. The objective was to compare the efficacy and safety of epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and biosimilar ESAs against each other or versus placebo in adults with CKD. The review included people requiring dialysis, not needing dialysis, and those who received a renal transplant.[1] Epoetin beta is not FDA-approved in the United States (US), so evidence for its safety and efficacy is not included in the summary of this systematic review. Literature was searched through April 2022 for eligible RCTs.[1] Sixty-two new studies (n=9,237) were included in the 2023 update, for an overall total of 117 studies with 25,237 participants.[1] The prespecified outcomes included need for blood transfusion, incidence of hypertension and fatigue related to

anemia, and mortality rates. The recently published RCTs did not evaluate changes in fatigue as an outcome.[1] This review primarily included participants with kidney failure dependent on dialysis or those with moderate-to-advanced CKD [estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m²].[1] Data on the use of ESAs in kidney transplant recipients were relatively sparse, and the findings of this review may not be directly applicable to this clinical setting.[1]

Many studies included in this review were at high or unclear risk of bias in most methodological domains.[1] Only 2 studies were at low risk of bias for allocation concealment, blinding of outcome assessment and attrition from follow-up.[1] Allocation concealment was reported using low-risk methods in 17 studies (15%), and blinding of outcome assessment was reported in seven studies (6%).[1] There was complete outcome data in only 25 studies (22%), with 40 studies (34%) reporting incomplete outcome data, and missing data were unclearly documented in 51 studies (44%).[1] Overall, results remain similar in this update compared to the previous 2014 review.[1] Due to a lack of direct of comparative evidence, the authors completed a network meta-analysis. For the purposes of this review, only results from meta-analyses using direct comparative evidence are summarized.

Epoetin alfa and darbepoetin alfa were compared to placebo to assess prevention of blood transfusions in 6 RCTs.[1] For preventing blood transfusion, epoetin alfa may be superior to placebo (odds ration [OR] 0.15, 95% confidence interval [CI] 0.04 to 0.58, 5 RCTs, n=385; I^2 = 81%; low-quality evidence) and darbepoetin alfa was probably superior to placebo (OR 0.53, 95% CI 0.46 to 0.63; 1 RCT, n=4038; moderate-quality evidence).[1] No study evaluated the impact of methoxy polyethylene glycol-epoetin beta on reducing blood transfusions compared to placebo.[1]

When ESAs were compared with each other, epoetin alfa probably increased the odds of blood transfusion compared to darbepoetin alfa (OR 2.31, 95% CI 1.34 to 3.97; 3 RCTs, n=1191; I^2 = 0%; moderate-quality evidence).[1] There was no difference on the odds of blood transfusion with epoetin alfa compared to a biosimilar epoetin (OR 0.90, 95% CI 0.57 to 1.44, 7 RCTs, n=2335; I^2 = 0%; low-quality evidence) or biosimilar darbepoetin alfa (OR 0.68, 95% CI 0.34 to 1.34, 1 RCT, n=752; low-quality evidence).[1] Darbepoetin alfa had no difference on the odds of blood transfusion compared to methoxy polyethylene glycol-epoetin beta (OR 1.36, 95% CI 0.64 to 2.89; 4 RCTs, n=1191; I^2 = 46%; very low-quality evidence), a biosimilar epoetin (OR 0.31, 95% CI 0.01 to 7.79, 1 RCT, n=74; low-quality evidence), or a biosimilar darbepoetin alfa (OR 1.05, 95% CI 0.07 to 16.88, 1 RCT, n=385; low-quality evidence), but confidence in these results remains uncertain.[1]

Three agents (epoetin alfa, darbepoetin alfa and biosimilar epoetin) were compared with placebo to evaluate risk of death for any cause in 8 RCTs.[1] Compared to placebo, effects on risk of death were uncertain for epoetin alfa (OR 0.57, 95% CI 0.15 to 2.26, 5 RCTs, n=455; I^2 = 0%; low-quality evidence), darbepoetin alfa (OR 1.00, 95% CI 0.84 to 1.19, 2 RCTs, n=4,854; I^2 = 31%; low-quality evidence), and biosimilar epoetin (no events, 1 RCT, n=40; low-quality evidence).[1] No study evaluated the impact of methoxy polyethylene glycol-epoetin beta on mortality compared to placebo.[1]

When ESAs were compared to each other, the odds of death from any cause with epoetin alfa were uncertain when compared to darbepoetin alfa (OR 0.78, 95% CI 0.50 to 1.22, 9 RCTs, n=1913; I^2 = 0%; low-quality evidence) or biosimilar epoetin (OR 1.01, 95% CI 0.69 to 1.47; 13 RCTs, n=4154; I^2 = 22%; low-quality evidence).[1] The odds of death with darbepoetin alfa were uncertain when compared to methoxy polyethylene glycol-epoetin beta (OR 1.07, 95% CI 0.68 to 1.68, 5 RCTs, n=1498; I^2 = 0%; low-quality evidence) or a biosimilar darbepoetin alfa (OR 0.61, 95% CI 0.19 to 1.91, 3 RCTs, n=335; I^2 = 0%; low-quality evidence).[1]

To evaluate risk of hypertension, epoetin alfa and darbepoetin alfa were assessed against placebo in 3 RCTs.[1] The odds of hypertension were probably increased with epoetin alfa (OR 4.10, 95% CI 2.16 to 7.76, 2 RCTs, n=251; I^2 = 0%; moderate-quality evidence) and darbepoetin alfa (OR 1.14, 95% CI 0.99 to 1.32, 1 RCT, n=4038; moderate-quality evidence) when compared to placebo.[1] No study evaluated the risk of hypertension for methoxy polyethylene glycol-epoetin beta versus placebo.[1]

When ESAs were compared to each other, the odds of hypertension were uncertain for epoetin alfa compared to darbepoetin alfa (OR 0.93, 95% CI 0.68 to 1.25, 6 RCTs, n=2090; I^2 = 32%; low-quality evidence), a biosimilar epoetin (OR 1.21, 95% CI 0.76 to 1.93, 7 RCTs, n=1940; I^2 = 27%; low-quality evidence), or a biosimilar darbepoetin alfa (OR 0.72, 95% CI 0.15 to 3.44, 1 RCT, n=747; low-quality evidence).[1] The odds of hypertension were uncertain for darbepoetin alfa compared to methoxy polyethylene glycol-epoetin beta (OR 0.91, 95% CI 0.62 to 1.33, 6 RCTs, n=1568; I^2 = 27%; low-quality evidence) or a biosimilar darbepoetin alfa (OR 0.93, 95% CI 0.51 to 1.70, 3 RCTs, n=609; I^2 = 3%; low certainty evidence).[1]

Despite the inclusion of 61 studies since the previous version of this review in 2014, few studies were adequately powered to detect differences in patient-level outcomes.[1] There was important clinical diversity in studies based on the age of the participants, stage of CKD and duration of treatment.[1] This review concluded epoetin alfa and darbepoetin alfa may be superior to placebo for the prevention of blood transfusion based on moderate- to very low-quality evidence, but increased the odds of hypertension compared to placebo (moderate-quality evidence).[1] Effects on death (any cause), were generally uncertain between any ESA formulation and placebo or other ESA product (low-quality evidence).[1] The other potential benefits of ESAs, such as reduction in fatigue and breathlessness, remain uncertain due to sparse data.[1] In summary, current data from RCTs are insufficient to evaluate comparative efficacy and safety of different ESA formulations.[1]

Cochrane: Erythropoietin Plus Iron versus Control Treatment Including Placebo or Iron for Preoperative Anemic Adults Undergoing Non-Cardiac Surgery

A 2020 Cochrane review evaluated the efficacy of preoperative epoetin therapy (subcutaneous or parenteral) with iron (enteral or parenteral) in reducing the need for allogeneic RBC transfusions in preoperatively anemic adults undergoing non-cardiac surgery.[2] This was an update to a 2016 publication on this topic. Literature was searched through August 2019.[2] Twelve RCTs (n=1880) which compared preoperative epoetin and iron therapy to control treatment (placebo, no treatment, or standard of care with or without iron) met inclusion critera.[2] The surgery types included hip joint arthroplasty or hip or knee replacement (5 trials), colorectal cancer surgery (4 trials), hysterectomy (2 trials), and gastrointestinal surgery (1 trial) and included participants with mild and moderate preoperative anemia (Hb from 10 to 12 g/dL).[2] The duration of preoperative treatment varied across the trials, ranging from once a week to daily or a 5-to-10-day period, and in one trial preoperative epoetin was given on the morning of surgery and for five days postoperatively.[2] Intravenous iron was administered in 4 RCTs and oral iron was used in 8 RCTs.[2] The primary outcome was need for RBC transfusion. Secondary outcomes included Hb concentration directly before surgery, number of RBC units transfused, mortality within 30 days of surgery, adverse events, and length of hospital stay.[2] The overall risk of bias for selection bias, performance bias, and attrition bias was low in more than 50% of the included studies.[2] For allocation concealment, detection bias, and other bias, the risk of bias to was low for about 20% of the included studies.[2] Risk of reporting bias was low for only 10% of the included studies.[2]

Compared to control treatment, preoperative epoetin and iron given to anemic adults reduced the need for RBC transfusion (risk ratio [RR] 0.55, 95% CI 0.38 to 0.80, n=1880; 12 RCTs; I^2 = 84%; moderate-quality evidence).[2] Preoperative high-dose epoetin (500 to 600 IU/kg body weight) and iron increased the Hb concentration (mean difference [MD] 1.87 g/dL, 95% CI 1.26 to 2.49; n=852; studies = 3; I^2 = 89%; low-quality evidence) but not low-dose epoetin (150 to 300 IU/kg body weight) and iron (MD 0.11 g/dL, 95% CI −0.46 to 0.69, n=334, 4 RCTs; I^2 = 69%; low-quality evidence) when compared to control treatment.[2]

For people who needed a RBC transfusion, there was probably little or no difference in the number of RBC units transfused when epoetin and iron were given preoperatively (MD −0.09, 95% CI −0.23 to 0.05, n=1420, 6 RCTs; I^2 = 2%; moderate-quality evidence) compared to control treatment.[2] There was probably little or no difference in the risk of mortality within 30 days of surgery (RR 1.19, 95% CI 0.39 to 3.63, n=230, 2 RCTs; I^2 = 0%; moderate-quality evidence) or of adverse events including local rash, fever, constipation, or transient hypertension (RR 0.93, 95% CI 0.68 to 1.28, n=1722; 10 RCTs; I^2 = 0%; moderate-quality evidence).[2] The administration of epoetin with iron before non-cardiac surgery did not clearly reduce the length of hospital stay of preoperative anemic adults (MD −1.07, 95% CI −4.12 to 1.98, n=293, 3 RCTs; I^2 = 87%; low-quality evidence) compared to control treatment.[2]

In summary, moderate-quality evidence suggests that preoperative epoetin and iron therapy administered to anemic adults prior to non-cardiac surgery reduces the need for RBC transfusion and, when given at higher doses, increases the Hb concentration preoperatively.[2] The administration of epoetin and iron treatment did not decrease the mean number of units of RBC transfused per patient (moderate-quality evidence).[2] There were no important differences in the risk of adverse events or mortality within 30 days (moderate-quality evidence), nor in length of hospital stay between those who received epoetin with iron (low-quality evidence) and those who did not.[2]

After review, 20 systematic reviews were excluded due to poor quality,[12-16] wrong study design of included trials (e.g., observational),[17,18] comparator (e.g., no control or placebo-controlled),[19-30] or outcome studied.[31-33]

New Guidelines:

American Society of Clinical Oncology and American Society of Hematology: Management of Cancer-Associated Anemia with Erythropoiesis-Stimulating Agents

A 2019 clinical guideline from ASCO/ASH updated previous recommendations for the use of ESAs in patients with anemia due to cancer chemotherapy.[3] The guideline is based on evidence from 15 meta-analyses and 2 RCTs published through 2018.[3] A growing body of evidence suggests that adding iron to treatment with an ESA may improve hematopoietic response and reduce the likelihood of RBC transfusion.[3] The biosimilar literature review suggests that biosimilars of epoetin alfa have similar efficacy and safety to reference products, although evidence in cancer remains limited.[3] Erythropoiesis-stimulating agents (including biosimilars) may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose Hb has declined to less than 10 g/dL.[3] Red blood cell transfusion is also an option in these patients.[3] With the exception of selected patients with myelodysplastic syndromes, ESAs should not be offered to most patients with nonchemotherapy-associated anemia.[3] During ESA treatment, Hb may be increased to the lowest concentration needed to avoid transfusions.[3] Iron replacement may be used to improve Hb response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency.[3]

Strength of recommendations based quality of evidence include:

- Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose Hb has declined to less than 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (High QoE: Strength of recommendation: strong).[3]
- ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent (Moderate QoE: Strength of recommendation: strong).[3]
- ESAs may be offered to patients with lower risk myelodysplastic syndromes and a serum erythropoietin level ≤ 500 IU/L (Moderate QoE; Strength of recommendation: moderate).[3]
- ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (High QoE: Strength of recommendation: strong).[3]
- Iron replacement may be used to improve Hb response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Moderate QoE: Strength of recommendation: weak).[3]
- The authors of the guideline arrived at informal consensus that epoetin alfa, darbepoetin, and biosimilar epoetin alfa are equivalent with respect to effectiveness and safety based on low- to moderate-quality evidence.[3]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
darbepoetin alfa in polysorbat	ARANESP	INJECTION	SYRINGE	Y
darbepoetin alfa in polysorbat	ARANESP	INJECTION	VIAL	Y
epoetin alfa	EPOGEN	INJECTION	VIAL	N
epoetin alfa	PROCRIT	INJECTION	VIAL	N
epoetin alfa-epbx	RETACRIT	INJECTION	VIAL	N
methoxy peg-epoetin beta	MIRCERA	INJECTION	SYRINGE	N

Appendix 2: New Comparative Clinical Trials

A total of 339 citations were manually reviewed from the initial literature search. After further review, 338 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstracts is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Locatelli, et al.[34] MC, OL, NI RCT N= 2825 Duration: ~8.5 years	1.Methoxy polyethylene glycol-beta dosed per protocol n = 1412 2. ESAs (Epoetin alfa, epoetin beta, and darbepoetin dosed per approved label) n=1413	Adult CKD patients with anemia. Anemia defined as Hb < 11 g/dL.	Composite endpoint: incidence of death, nonfatal MI, or nonfatal stroke. Prespecified NI margin of 1.2 for the HR	Incidence of death, MI or stroke 1. 45.4% (n=640) 2. 45.7% (n=644) HR 1.03 95% CI 0.93 to 1.15 P=0.004 for NI In patients with anemia of CKD, once-monthly methoxy polyethylene glycol-epoetin beta was noninferior to conventional, shorter-acting ESAs with respect to rates of major adverse cardiovascular events or all-cause mortality.	-OL, NI study is less robust than blinded superiority RCT -Funded by manufacturer of methoxy polyethylene glycol-beta
Abbreviations: CKD = chronic kidney disease; CI = confidence interval; CV = cardiovascular; dL = deciliter; ESAs = erythropoiesis stimulating agents; g = grams; Hb = hemoglobin; HR = hazard ratio; MC = multi-center; MI = myocardial infarction; OL = open-label; NI = noninferiority; RCT = randomized controlled trial					

Appendix 3: Abstracts of Comparative Clinical Trials

Cardiovascular Safety and All-Cause Mortality of Methoxy Polyethylene Glycol-Epoetin Beta and Other Erythropoiesis-Stimulating Agents in Anemia of CKD: A Randomized Noninferiority Trial[34]

Background and objectives: Erythropoiesis-stimulating agents correct anemia of CKD but may increase cardiovascular risk. We compared cardiovascular outcomes and all-cause mortality associated with monthly methoxy polyethylene glycol-epoetin beta with those of the shorter-acting agents epoetin alfa/beta and darbepoetin alfa in patients with anemia of CKD.

Design, setting, participants, & measurements: We conducted a multicenter, open-label, noninferiority trial in which patients were randomized to receive methoxy polyethylene glycol-epoetin beta or reference erythropoiesis-stimulating agents, stratified by maintenance or correction treatment status and C-reactive protein level. The trial had a prespecified noninferiority margin of 1.20 for the hazard ratio (HR) for the primary end point (a composite of all-cause mortality, nonfatal myocardial infarction or stroke, adjudicated by an independent blinded committee). This trial is registered with ClinicalTrials.gov, number NCT00773513.

Results: In total, 2818 patients underwent randomization, received methoxy polyethylene glycol-epoetin beta or a reference agent, and were followed for a median of 3.4 years (maximum, 8.4 years). In the modified intention-to-treat analysis, a primary end point event occurred in 640 (45.4%) patients in the methoxy polyethylene glycol-epoetin beta arm, and 644 (45.7%) in the reference arm (HR 1.03; 95% confidence interval [95% CI], 0.93 to 1.15, *P*=0.004 for noninferiority). All-cause mortality was not different between treatment groups (HR 1.06; 95% CI, 0.94 to 1.19). Results in patient subgroups on dialysis or treated in the correction or maintenance settings were comparable to the primary analysis.

Conclusions: In patients with anemia of CKD, once-monthly methoxy polyethylene glycol-epoetin beta was noninferior to conventional, shorter-acting erythropoiesis-stimulating agents with respect to rates of major adverse cardiovascular events or all-cause mortality.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to July Week 5 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to August 14, 2023

1	Darbepoetin alfa/	1126
2	Epoetin Alfa/	1595
3	Epoetin alfa-epbx.mp.	6
4	Erythropoietin/ or methoxy peg-epoetin beta.mp.	16284
5	1 or 2 or 3 or 4	16529
6	limit 5 to (english language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or 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"))	339

Erythropoiesis Stimulating Agents (ESAs)

Goal(s):

- Cover ESAs according to OHP guidelines and current medical literature.
- Cover preferred products when feasible.

Length of Authorization:

- 12 weeks initially, then up to 12 months
- Quantity limit of 30 day per dispense

Requires PA:

- All ESAs require PA for clinical appropriateness.

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 continuation of therapy previously approved by the FFS program?	**Yes:** Go to #14	**No:** Go to #3
3. Is this an OHP covered diagnosis?	**Yes:** Go to #4	**No:** Current age ≥21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #12
4. Is the requested product preferred?	**Yes:** Go to #6	**No:** Go to #5

Approval Criteria		
5. Will the prescriber change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Is the diagnosis anemia due to chronic renal failure[1,2] or chemotherapy[3]?	**Yes:** Go to #7	**No:** Go to #8
7. Is Hb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% and/or ferritin >100 ng/mL?	**Yes:** Approve for 12 weeks with additional approval based upon adequate response.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the diagnosis anemia due to HIV[4]?	**Yes:** Go to #9	**No:** Go to #10
9. Is the Hb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% **AND** Endogenous erythropoietin <500 IU/L **AND** If on zidovudine, is dose <4200 mg/week?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the diagnosis anemia due to ribavirin treatment[5]?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the Hb <10 g/dL or Hct <30% **AND** Is the transferrin saturation >20% and/or ferritin >100 ng/mL **AND** Has the dose of ribavirin been reduced by 200 mg/day and anemia persisted >2 weeks?	**Yes:** Approve up to the length of ribavirin treatment.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is the request for: 1) an FDA approved indication AND 2) is the request for a preferred product or has the patient failed to have benefit with, or have contraindications or intolerance to the preferred products?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. 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:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical necessity.
14. Has the patient responded to initial therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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P&T Review: *12/23 (DM); 1/19 (JP); 7/16; 5/14; 11/12; 6/12; 2/12, 9/10*
Implementation: *TBD; 3/19; 10/13/16; 1/1/13; 9/24/12; 5/14/12*

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New Drug Evaluation: Jesduvroq (daprodustat) oral tablets

Date of Review: December 2023
Generic Name: daprodustat

End Date of Literature Search: 09/13/23
Brand Name (Manufacturer): JESDUVROQ (GlaxoSmithKline)

Dossier Received: yes

Plain Language Summary:

- The United States (US) Food and Drug Administration (FDA) approved a new medicine called daprodustat for anemia in adults with chronic kidney disease (CKD) who have been on dialysis for at least 4 months. It should not be prescribed for people who are not on dialysis and should not be used as a substitute when someone needs a blood transfusion to urgently correct an anemia. It is taken by mouth.
- Chronic kidney disease happens when the kidneys do not filter the blood as well as they should, and the ability of the kidneys to filter blood is not likely to improve. When chronic kidney disease is severe a person may need dialysis. Dialysis is a treatment to clean the body's blood when the kidneys are not able to. It helps remove waste and extra fluid from the blood. Most people with chronic kidney disease have anemia.
- Anemia due to chronic kidney disease is a condition where the body does not have enough red blood cells to carry oxygen throughout the body. Red blood cells carry oxygen from the lungs to the rest of the body. Anemia can make people feel tired or out of breath and may increase the need for a blood transfusion. This type of anemia is very common in people on dialysis.
- Medicines called erythropoiesis stimulating agents have been used for this type of anemia for decades. These drugs must be injected, and they can increase the risk of blood clots, stroke, heart attack, and death.
- Evidence shows that daprodustat increased hemoglobin (Hb), a type of measurement of red blood cells, in patients with anemia and chronic kidney disease who are on dialysis. It did not improve anemia more than erythropoiesis stimulating agents.
- Daprodustat has a similar number of severe side effects as erythropoiesis stimulating agents in patients on dialysis. Evidence does not show that daprodustat is safer than erythropoiesis stimulating agents and has similar warnings for blood clots, stroke, heart attack, and death
- We recommend that daprodustat be non-preferred, and that providers explain why someone needs daprodustat before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What are the comparative benefits and harms of daprodustat in patients with chronic kidney disease (CKD)?
2. Are there subgroups of patients for which daprodustat is more effective or cause more harm than other available options (e.g. erythropoiesis stimulating agents [ESA])?

Author: Sara Fletcher, PharmD, MPH, BCPS

Conclusions:

- The efficacy and safety of daprodustat was evaluated in 5 global clinical studies[1-5], 3 of which included dialysis patients. The phase 3, open-label, ESA-controlled ASCEND-D study was the primary trial used by the FDA to support approval.[1]
- When daprodustat was compared to ESAs (intravenous [IV] epoetin alfa or subcutaneous [SC] darbepoetin alfa), both therapies had similar improvements in hemoglobin (Hb) over 28 to 52 weeks in patients with anemia of CKD on dialysis based on moderate quality evidence (ASCEND-D: daprodustat 0.28±0.02 g/dL vs. ESA 0.10±0.02 g/dL; mean adjusted difference, 0.18; 95% confidence interval [CI] 0.12 to 0.24; P<0.001 for noninferiority).[1]
- There is moderate quality evidence of no difference in first major adverse cardiac event (MACE) after randomization between daprodustat and ESAs (ASCEND-D: daprodustat 25.2% vs. ESA 26.7%; hazard ratio [HR] 0.93; 95% CI 0.81 to 1.07, p<0.001 for noninferiority).[1]
- Daprodustat has a box warning similar to ESA medications regarding the increased risk for death, serious adverse cardiovascular reactions, and stroke in patients with CKD on dialysis when the medication is administered to a target Hb level greater than 11 g/d.[6]
- There is insufficient long-term evidence for the use of daprodustat. Most results are applicable to White patients, though Black patients were well represented in the US cohort of the ASCEND-D trial.[1] Patients not on dialysis have more risk of harm compared to ESAs, and should not use daprodustat.[7,8]

Recommendations:

- Maintain daprodustat as non-preferred on the preferred drug list (PDL).
- Implement proposed PA criteria to ensure appropriate and safe use.
- Evaluate costs in executive session.

Background:

Anemia of chronic disease is a common complication of chronic kidney disease (CKD). Prevalence of CKD is 15% of the US population, and 17 million people have stage 3 to 5 disease.[8] Anemia affects 90% of those on dialysis (stage 5).[8] Patients often require blood transfusions and suffer from anemia related symptoms such as fatigue. The current standard of care are ESAs (e.g., epoetin alfa, darbepoetin alfa, epoetin beta) which stimulate red blood cell (RBC) production in the bone marrow and are approved for both dialysis dependent (DD) and non-dialysis dependent (NDD) anemia. Most patients have a concomitant absolute or functional iron deficiency and receive concomitant iron replacement. All ESA products are injectable (IV or SC).[8] ESA use in CKD has been found to increase major adverse cardiovascular events (MACE) and this is exacerbated by higher Hb targets.[8] While there is no identified target value, the Kidney Disease Improving Global Outcomes Clinical Practice Guidelines (KDIGO) guidelines advise against maintaining Hb above 11.5 g/dL and does not recommend starting ESA treatment in NDD patients with Hb at or greater than 10 g/dL.[8] These agents have a boxed warning for cardiovascular events with increased risk of death, myocardial infarction (MI), stroke, venous thromboembolism.[7,8] Additionally, for patients with certain types of cancer, there are boxed warnings for risk of tumor progression and recurrence. If used before surgery, there are risks for deep vein thrombosis (DVT), and DVT prophylaxis is recommended.[7]

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

Clinical Efficacy:

Daprodustat (JESDUVROQ) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI).[6] Daprodustat was submitted to the FDA with the applicant-proposed indication of "treatment of anemia due to CKD in adult patients on dialysis and not on dialysis", but after review, the FDA approved daprodustat for "treatment of anemia due to CKD in adults who have been receiving dialysis for at least 4 months" with a maximum daily dose of 24 mg.[8] Daprodustat is the first oral dosage form in the US for treatment of anemia; current ESAs are only available as injectable drugs. Product labeling limitations state daprodustat has not been shown to improve quality of life, fatigue, or patient well-being, and that it is not indicated as a substitute for transfusion in patients requiring immediate correction of anemia or in patients who are not on dialysis.[6]

Five global phase III studies[1-5] (**Table 3**) with different patient populations (e.g. dialysis dependent [DD] and non-dialysis dependent [NDD]), comparators, and dosing intervals (e.g. thrice weekly) were assessed by the FDA for approval.[8] Daprodustat was studied in hemodialysis, peritoneal dialysis, and non-dialysis patients in additional non-global studies conducted in Japan.[9-12] Those enrolling a study population of more than 100 patients are summarized in **Table 4**.[9,10] It was determined that both DD and NDD populations showed efficacy with daprodustat in increased Hb similar to ESAs, however differing safety findings between the 2 groups led to the more restrictive labeling than requested by the manufacturer.[8] Daprodustat is the first marketed HIF PHI. Two HIF PHI products (roxadustat and vadadustat) have been issued complete response letters (i.e., denials of approval) due to thrombosis and thromboembolic risk above the ESA standard of care and safety issues including liver injury (vadadustat).[8] Daprodustat is approved in Japan and roxadustat is approved in both Japan and the European Union.[13]

The Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Dialysis (ASCEND-D) study was used as the primary basis for approval in the DD population (**Table 2**).[1,8] This randomized, open-label, phase III trial compared treatment with daprodustat versus an ESA.[1] Adult patients with CKD and on dialysis for at least 90 days and an ESA for at least 6 weeks, with a baseline Hb of 8.0 to 11.5 g/dL were screened into a 4-week placebo plus ESA run-in period.[1] People with compliance between 80% and 120% with placebo during the run-in were randomized to open-label treatment with daprodustat or continuation of ESA. Daprodustat dosing was based on previous ESA dose and adjusted using an algorithm based on Hb level.[1] A rescue algorithm for IV iron, red blood cell (RBC) transfusion, and iron management was also provided.[1]

Block style 1:1 randomization with stratification occurred in 2964 patients.[1] The groups were well balanced with a median age of 58-59 years and median body mass index (BMI) of 26.8 kg/m^2. Of enrolled participants, 57.3% were male, 67% were White, 15.6% were Black (39.0% Black in US cohort), 44.9% had preexisting CV disease, and 17.4% had a preexisting thromboembolic event.[1] Malignancy within the previous 2 years (or basal cell cancer within 4 weeks) was an exclusion criteria and 4.9% of patients had coexisting cancer.[1] New or recurrent cancer (except localized squamous cell or basal cell carcinoma of the skin) was a prespecified reason to discontinue randomized treatment.[1] Eight percent of each group withdrew from the study, while 53% prematurely discontinued the study drug in each group but were followed to study completion or death.[8] Drug discontinuation reasons were similar between groups and included adverse event (16%), protocol-defined cessation criteria (e.g. cancer, pregnancy, rescue therapy, liver abnormalities, prohibited medication use) (15-16%), kidney transplant (9%), and death while on treatment (8%).[8]

The primary efficacy endpoint of mean change in Hb level from baseline to weeks 28 through 52 met noninferiority criteria (noninferiority margin -0.75 g/dL) with change in daprodustat 0.28±0.02 g/dL and ESA 0.10±0.02 g/dL (mean adjusted difference, 0.18; 95% CI 0.12 to 0.24; P<0.001).[1] Missing values were imputed using multiple imputation on the assumption that data were missing at random.[1]

This open-label trial introduced potential performance bias, though endpoints were objective or adjudicated by a blinded independent assessment committee. While few patients withdrew from the study, more than half discontinued the study medications for various reasons. Attrition was similar between groups but magnitude of drug effects may be reduced. This medication was appropriately studied versus the current standard of care.

Clinical Safety:
The primary noninferiority safety outcome was first occurrence of an adjudicated MACE after randomization as a composite of death from any cause, nonfatal MI, or nonfatal stroke.[1] The noninferiority margin was changed from 1.20 to 1.25 to speed trial closeout during the coronavirus disease 2019 pandemic.[1] Daprodustat was found non-inferior to ESA for first MACE (25.2% vs 26.7%; HR 0.93; 95% CI 0.81 to 1.07, p<0.001).[1] Adverse events occurring in more than 5% of daprodustat patients compared to ESAs were hypertension (24% for both), abdominal pain (11% vs. 8%), dizziness (7% vs. 6%), and hypersensitivity (7% for both).[6] Worsening of hypertension occurred in 19.8% of patient taking daprodustat and 20.5% of patients taking ESAs.[1]

The FDA assessment of safety findings between the DD and NDD patients led to the more restrictive labeling than requested by the manufacturer. Adjudicated cardiovascular (CV) endpoints in NDD patients showed elevated risks for stroke, thromboembolic disease, vascular access thrombosis, and MI relative to ESAs, and these risks were further increased in the US population.[8] There was also a possible increased risk of acute kidney injury in the NDD population and the oral route could lead to reduced healthcare encounters (with decreased monitoring) which may potentiate these effects if Hb increase is excessive or rapid.[8]

Daprodustat has a boxed warning for increased risk of death, MI, stroke, venous thromboembolism, and thrombosis of vascular access. This increased risk of thrombotic vascular events, including MACE, is further increased by targeting Hb greater than 11 g/dL.[6] No trial has identified an optimal Hb target level and the lowest dose sufficient to reduce the need for RBC infusions should be used.[6]

Contraindications include use with strong cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) and uncontrolled hypertension, as well as warnings for risk of heart failure hospitalization in those with history of heart failure, hypertension, gastrointestinal erosion, malignancy, and use in NDD CKD patients where it is not indicated.[6]

The open-label study design may introduce bias when identifying and reporting of adverse events. The short duration and high drug discontinuation rate in both groups may make assessment of certain events, such as malignancy and MACE, incomplete.

Look-alike / Sound-alike Error Risk Potential: none

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Hematologic response as assessed by Hb levels
2) Need for transfusions due to anemia
3) Symptoms of anemia (e.g., fatigue)
4) Quality of life
5) Serious adverse events (e.g., mortality, MACE)
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Mean Hb change from baseline

Table 1. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Reversible inhibitor of HIF-PH1, PH2, and PH3, resulting in stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes (including erythropoietin).
Oral Bioavailability	65%; not affected by high fat/high calorie meal compared to fasted state
Distribution and Protein Binding	Steady-state volume of distribution 14.2 L Plasma protein binding >99%
Elimination	18.9 L/h plasma clearance, 15 L/h blood clearance, hepatic extraction 18% 74% feces, 21% urine
Half-Life	1 - 4 hours
Metabolism	60% metabolites when radiolabeled daprodustat given to healthy adults

Abbreviations: HIF = hypoxia-inducible factor; h = hours; PHI = prolyl hydroxylase inhibitors; L = liters

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Singh AK et al.[1,8,13] ASCEND-D NCT02879305 Phase 3, RCT, OL	1. Dapro oral starting between 4 and 12 mg daily 2. ESA: IV EPO if HD or SC DARB if PD Initial doses based on previous ESA dose. -4w placebo run-in period. Previous ESA therapy continued during screening and run-in period, People were randomized if were adherent to	Demographics: Dapro; ESA -Median age 58y; 59y -White 66.9%; 66.5% -Black 15.3%; 15.8% -Asian 11.8%; 12.3% -HD 88.5%; 88.6% -Median BMI 26.8 -Time since dialysis started 0-2 y 30.5%; 30.5% 2 to <5y 36.0%; 35.8% >/= 5y 33.6%; 33.6% -ESA hyporesponsiveness 12.3%; 12.2% -CV disease 44.8%; 45.0% -Thromboembolic event 18.4%; 16.4%	ITT: Dapro: 1487 ESA: 1477 Attrition: Withdrawn Dapro: 117 (8%) ESA: 111 (8%) Drug discontinuation for reason other than death: Dapro: 45.1% ESA: 44.8% Died while taking study treatment: Dapro: 8%	Primary Endpoints (non-inferiority): Mean change (±SE) in Hb level from baseline to average during primary evaluation period (28-52w) Non-inferiority margin -0.75 mg/dL 1. 0.25±0.02 g/dL 2. 0.10±0.02 g/dL Mean adjusted difference 0.08 95% CI 0.12 to 0.24 p-value<0.001 Secondary Endpoint (Superiority assessment):	NA NA	Outcome: Primary Safety Endpoint (non-inferiority): First occurrence of adjudicated MACE, composite of death from any cause, nonfatal MI, Nonfatal stroke Non-inferiority margin 1.20 then amended to 1.25 to speed trial closeout due to coronavirus pandemic. 1. 374 (25.2%) 2. 394 (26.7%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) 1:1 block randomization with stratification. Baseline characteristics appeared balanced. Performance Bias: (High) OL design (investigators and patients knew assignment, sponsor and steering committee unaware of aggregate treatment assignments throughout the trial.) Detection Bias: (Low) OL design with objective primary efficacy outcome (investigators and patients knew assignment, sponsor and steering committee unaware of aggregate treatment assignments throughout the trial.) MACE adjudication conducted by a blinded independent committee led by the Duke Clinical Research Institute. Attrition Bias: (High) High drug discontinuation but balanced between groups. Missing data handled appropriately

	placebo and Hb 8.0-11.5 g/dL -Treatment-evaluated every 4w for 1y then every 12w until study target number of adjudicated first MACE events (945 events changed to 664 events with protocol update in July 2020) -1:1 block randomization stratified by type of dialysis, geographic region, and participation in ambulatory substudy monitoring blood pressure.	-Hb median 10.4 g/dL; 10.5 g/dL -median ferritin 589 ng/mL; 604 ng/dL <u>Key Inclusion Criteria</u>: -Age 18-99y -CKD with dialysis for ≥ 90d -ESA ≥ 6w -Hb 8.0-12.0 g/dL -serum ferritin >100 mg/mL -Transferrin saturation >20% -Compliance with run-in placebo <u>Key Exclusion Criteria</u>: -Anemia unrelated to CKD -Recent CV event -Current or recent ca -Planned kidney transplant -Liver disease	ESA: 8%	-Average monthly dose of IV iron from baseline to week 52 1. 90.8±3.3 mg 2. 99.9±3.3 mg Mean difference -9.1 mg 95% CI -18.4 to 0.2	NA	HR 0.93 95% CI 0.81 to 1.07 p-value<0.001 AE leading to study withdrawal: 1. 1 (<1%), nonfatal 2. 0 (0%) Death: 1. 244 (16.4%) 2. 233 (15.8%)		with multiple imputation using missing at random assumption used to handle missing Hb values. Tipping point analysis used as a sensitivity analysis to evaluate a missing not at random approach. <u>Reporting Bias</u>: (Low) Protocol and supplemental data available. <u>Other Bias:</u> (Unclear) Study sponsor and an academic steering committee designed and oversaw the trial conduct and analysis. Placebo run-in with compliance requirements before randomization. **Applicability**: <u>Patient</u>: Primarily studied in White participants but some racial diversity was included. Run in period may screen for certain patient types. <u>Intervention</u>: Appropriate based on earlier trial phase dose testing. <u>Comparator</u>: Compared to ESA standard of care. Most commonly used ESA was epoetin alfa. <u>Outcomes</u>: Appropriate clinical markers for safety and efficacy. QoL changes not assessed. <u>Setting</u>: 431 centers in 35 countries

<u>Abbreviations</u>: ARR = absolute risk reduction; BMI = body mass index; ca = cancer; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; d= day; Dapro = daprodustat; DARB = darbepoetin alfa; dL = deciliter; EPO = epoetin alfa; ESA = erythropoiesis stimulating agent; g/= gram; Hb = hemoglobin; HD = hemodialysis; ITT = intention to treat; IV = intravenous; MACE = major adverse cardiovascular event; mg = milligram; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; ng = nanogram; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PD = peritoneal dialysis; PP = per protocol; QoL = quality of life; R = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SE = standard error; tx = treatment; w = week; y = year.

Table 3: Summary of ASCEND Studies[8]

	Non-Dialysis Studies		Dialysis Studies		
	ASCEND-ND[5]	**ASCEND-NHQ[4]**	**ASCEND-D[1]**	**ASCEND-TD[2]**	**ASCEND-ID[3]**
Population	NDD Baseline ESA use or no baseline ESA use	NDD No recent ESA use	HD or PD Baseline ESA use	HD Baseline ESA use	ID No baseline ESA use
Daprodustat Dosing	Once Daily	Once Daily	Once Daily	Three Times a Week	Once Daily
Control	SC DARB	Oral placebo	IV EPO or SC DARB	IV EPO	SC or IV DARB

# of participants*	4500	600	3000	402	300
Blinding	OL (sponsor blind)	DB	OL (sponsor blind)	DB, DD	OL (sponsor blind)
Randomization	1:1	1:1	1:1	2:1	1:1
Stratification	• Region • Current ESA use • Participation in ABPM substudy	• Region	• Dialysis type (HD or PD) • Region • Participation in ABPM substudy	• Region	• Dialysis type (HD or PD) • Dialysis start planned or unplanned
Evaluation Period	Weeks 28-52	Weeks 24-28	Weeks 28-52	Weeks 28-52	Weeks 28-52
Hb target range	10-11 g/dL	11-12 g/dL	10-11 g/dL	10-11 g/dL	10-11 g/dL
Primary Outcome (efficacy)	Change in Hb from baseline NI margin -0.75 g/dL	Change in Hb from baseline Superiority 1-sided α 0.025	Change in Hb from baseline NI margin -0.75 g/dL	Change in Hb from baseline NI margin -0.75 g/dL	Change in Hb from baseline NI margin -0.75 g/dL
Primary Outcome Result	Mean ± SE Dapro: 0.66 ± 0.02 g/dL DARB: 0.74 ± 0.02 g/dL 0.08 g/dL difference 95% CI 0.03 to 0.13	Dapro: 1.58 g/dL PB: 0.19 g/dL AMD 1.40 g/dL 95% CI 1.23 to 1.56	Mean ± SE Dapro: 0.25 ± 0.02 g/dL ESA: 0.10 ± 0.02 g/dL AMD 0.08 95% CI 0.12 to 0.24	Adjusted mean ± SE Dapro: -0.04 ± 0.045 g/dL EPO: 0.02 ± 0.066 g/dL model-adjusted treatment difference -0.05 g/dL 95% CI -0.21 to 0.10	Adjusted mean ± SE Dapro: 1.02 ± 0.09 g/dL DARB: 1.12 ± 0.09 g/dL AMD -0.10 g/dL 95% CI -0.34 to 0.14
Primary Outcome (safety)	First MACE NI margin 1.25	NA	First MACE NI margin 1.25	NA	NA
First MACE	Dapro: 378/1937 (19.5%) DARB: 371/1935 (19.2%) HR 1.03 95% CI 0.89 to 1.19 NI margin 1.25	NA	Dapro: 374/1487 (25.2%) ESA: 394/1477 (26.7%) HR 0.93 95% CI 0.81 to 1.07 NI margin 1.25	NA	NA

Abbreviations: ABPM = ambulatory blood pressure monitoring; AMD = adjusted mean treatment difference; CI = confidence interval; Dapro = daprodustat; DARB = darbepoetin alfa; DB = double-blind; DD = double-dummy; dL = deciliter; EPO = epoetin alfa; ESA = erythropoiesis stimulating agent; g = grams; Hb = hemoglobin; HD = hemodialysis; HR = hazard ratio; ID = incident dialysis; IV = intravenous; MACE = major adverse cardiovascular event; NA = not applicable; NDD = non-dialysis dependent; NI = noninferiority; OL = open-label; PB = placebo; PD = peritoneal dialysis; SC = subcutaneous; SE = standard error.
*rounded

Table 4. Summary of Non-Global, Japan based Studies[9,10]

	Nangaku et al[9]	**Akizawa et al[10]**
Population	NDD Baseline or no baseline ESA use	HD Baseline ESA use
Daprodustat Dosing	Once Daily	Once Daily
Control	Epoetin beta pegol (route not stated)	IV DARB

# of participants*	299 (Baseline ESA naïve participants [n=82] enrolled before protocol amendment to lower daprodustat starting dose in ESA naïve patients were excluded from ITT primary efficacy analysis.)	271
Blinding	OL	DB, DD
Randomization	1:1	1:1
Stratification	• Current ESA use • Hb level	NA
Evaluation Period	Weeks 40-52	Weeks 40-52
Hb target range	11-13 g/dL	10-12 g/dL
Primary Outcome	Mean Hb NI margin -1.0 g/dL	Mean Hb NI margin -1.0 g/dL
Primary Outcome Result	Dapro: 12.0 g/dL 95% CI 11.8 to 12.1 Epoetin beta: 11.9 g/dL 95% CI 11.7 to 12.0 Difference 0.1 g/dL 95% CI -0.1 to 0.3	Dapro: 10.9 g/dL 95% CI 10.8 to 11.0 DARB: 10.8 g/dL 95% CI 10.8 to 11.0 Difference 0.1 g/dL 95% CI -0.1 to 0.2
Abbreviations: CI = confidence interval; Dapro = daprodustat; DARB = darbepoetin alfa; DB = double-blind; DD = double-dummy; dL = deciliter; ESA = erythropoiesis stimulating agent; g = grams; Hb = hemoglobin; HD = hemodialysis; ITT = intention to treat; IV = intravenous; NA = not applicable; NDD = non-dialysis dependent; NI = noninferiority; OL = open-label.		

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Appendix 1: Prescribing Information Highlights

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

JESDUVROQ (daprodustat) tablets, for oral use
Initial U.S. Approval: 2023

WARNING: INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, and THROMBOSIS OF VASCULAR ACCESS.
See full prescribing information for complete boxed warning.

- **JESDUVROQ increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE). (5.1)**
- **Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial venous thrombotic events, as occurs with erythropoietin stimulating agents (ESAs), which also increase erythropoietin levels. (5.1)**
- **No trial has identified a hemoglobin target level, dose of JESDUVROQ, or dosing strategy that does not increase these risks. (2.4)**
- **Use the lowest dose of JESDUVROQ sufficient to reduce the need for red blood cell transfusions. (2.4)**

----------INDICATIONS AND USAGE----------
JESDUVROQ is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months. (1)
Limitations of Use
Not shown to improve quality of life, fatigue, or patient well-being.
Not indicated for use:

- As a substitute for transfusion in patients requiring immediate correction of anemia.
- In patients not on dialysis.

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

- Administer orally once daily, with or without food. (2.2, 2.3)
- See Full Prescribing Information for starting dosage based on hemoglobin level, liver function and concomitant medications, and for dose titration and monitoring recommendations. (2.3, 2.4, 2.5, 2.6)

---------- DOSAGE FORMS AND STRENGTHS----------
Tablets: 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg. (3)

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

- Strong cytochrome P450 2C8 (CYP2C8) inhibitors such as gemfibrozil. (4)
- Uncontrolled hypertension. (4)

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

- Risk of Hospitalization for Heart Failure: Increased in patients with a history of heart failure. (5.2)
- Hypertension: Worsening hypertension, including hypertensive crisis may occur. Monitor blood pressure. Adjust anti-hypertensive therapy as needed. (5.3)
- Gastrointestinal Erosion: Gastric or esophageal erosions and gastrointestinal bleeding have been reported. (5.4)
- Not indicated for treatment of anemia of CKD in patients who are not dialysis-dependent (5.5)
- Malignancy: May have unfavorable effects on cancer growth. Not recommended if active malignancy. (5.6)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥10%) are hypertension, thrombotic vascular events, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Moderate CYP2C8 Inhibitors: Reduce starting dose. (7.1)
- CYP2C8 Inducers: Monitor hemoglobin and adjust the dose of JESDUVROQ as appropriate. (7.2)

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

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Breastfeeding not recommended until one week after the final dose. (8.2)
- Hepatic Impairment: Reduce the starting dose in patients with moderate hepatic impairment (Child-Pugh Class B). JESDUVROQ not recommended in severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2023

Daprodustat (JESDUVROQ)

Goal(s):
- To limit utilization to FDA-approved indications and in populations with proven safety

Length of Authorization:
- Up to 12 months

Requires PA:
- Pharmacy and physician administered claims

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this for anemia of chronic disease due to chronic kidney disease in an adult (18 years or older)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient been on dialysis for at least 4 months?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have a documented contraindication or intolerance to an erythropoiesis stimulating agent (ESA) (e.g., epoetin or darbepoetin)?	**Yes:** Go to #6	**No:** Go to #5
5. Does the patient have documented a lack of response to an ESA after at least 4 months of therapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is there documentation of active malignancy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is there documentation that the patient has uncontrolled hypertension (≥140mmHg/≥90mmHg)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the patient taking a strong cytochrome P450 2C8 inhibitor (example: gemfibrozil)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months (max 24 mg daily)

P&T/DUR Review: 12/23 (SF)
Implementation: TBD

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Drug Class Update with New Drug Evaluation: Antidepressants

Date of Review: December 2023

Date of Last Review: February 2023
Dates of Literature Search: 12/01/2022 - 09/15/2023
Brand Name (Manufacturer): Zurzuvae (Biogen Inc)
Dossier Received: no

Generic Name: zuranolone

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the use of antidepressants and review the evidence for zuranolone, a newly approved drug for postpartum depression (PPD).

Plain Language Summary:
- This review looks at new research for medicines used to treat depression, called antidepressants. Certain antidepressants are also used for other conditions, such as helping people to stop smoking and to reduce pain. There is also a new drug recently approved by the Food and Drug Administration (FDA) for depression that occurs in the post-partum period (4 weeks or less after having a baby) called zuranolone.
- The antidepressant called bupropion was shown to be more helpful at helping people quit smoking compared to a sugar pill (placebo) or no treatment.
- The antidepressant called duloxetine has shown benefit in reducing pain intensity when compared to placebo.
- The National Institute for Health and Care Excellence (NICE) looked at the studies for the antidepressant esketamine in people that have depression that has not resolved with treatment with at least 2 other antidepressants, but they could not find enough information to routinely recommend esketamine for these people.
- The American College of Physicians (ACP) recommends antidepressants to be tried as a first treatment option in people with depression. Behavioral counseling is also recommended as initial therapy.
- The Food and Drug Administration approved the antidepressant zuranolone for treating people with post-partum depression. Zuranolone helped improve symptoms of depression more than placebo in people who had recently given birth that had a diagnosis of severe depression.
- Based on this information, no changes to the antidepressant preferred drug list for the Oregon Health Plan fee-for-service program is recommended. Members may not use zuranolone for more than 14 days as recommended by the FDA.

Research Questions:
1. Is there new comparative evidence related to efficacy of antidepressants for important outcomes (e.g., symptom reduction and remission)?

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2. Is there new comparative evidence for harms for antidepressants?
3. Are there specific populations based on demographic characteristics, such as age, race, ethnicity, pregnancy status, or people with certain comorbidities, for which certain antidepressants are better tolerated or more effective than other antidepressants in improving symptoms and remission of depression?
4. What is the comparative evidence for efficacy and harms for zuranolone?

Conclusions:

- Two new systematic reviews with meta-analyses, 2 new clinical guidelines and one new drug approval were identified for this review.
- A Cochrane review evaluated antidepressants for long-term smoking cessation and found high quality evidence that bupropion had higher smoking cessation rates compared to placebo or no treatment (relative risk [RR] 1.60; 95% confidence interval [CI], 1.49 to 1.72).[1] Serious adverse events were not found to differ between groups. Evidence for other antidepressants for efficacy in smoking cessation was insufficient.
- A Cochrane review evaluated the use of antidepressants for managing chronic pain in adult patients.[2] Duloxetine 60 mg daily was found to provide substantial pain relief (50% or more reduction in pain intensity from baseline) compared to placebo, which was clinically and statistically significant (RR 1.91; 95% CI, 1.69 to 2.17). The review found insufficient evidence to assess safety outcomes, such as adverse events and withdrawals.
- Guidance from NICE on the use of esketamine in treatment-resistant depression found a reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) score for patients treated with esketamine versus placebo (-19.8 vs. -15.8, respectively).[3] The difference seen with esketamine was clinically significant but the NICE was uncertain of the evidence. Current guidance does not support esketamine for individuals with treatment-resistant depression.
- The American College of Physicians (ACP) strongly recommend treatment with a second-generation antidepressant (e.g., selective serotonin reuptake inhibitors [SSRI] or serotonin-norepinephrine reuptake inhibitor [SNRI]) in adults in the acute phase of major depressive disorder based on moderate quality evidence.[4]
- In August 2023, zuranolone received FDA- approval for treatment of postpartum depression (PPD). Efficacy from two phase 3 trials demonstrated a reduction in the 17-point Hamilton Depression Rating Scale (HAMD-17) by 4.0 and 4.2 points more than placebo in patients that had severe PPD, which was statistically and clinically significant.[5,6] The most common adverse events associated with zuranolone were somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infections.
- There is insufficient evidence to determine the most effective therapies for treatment-resistant depression in any identified populations based on age, race ethnicity, or people with certain co-morbidities.

Recommendations:

- No changes to the Oregon Health Plan fee-for-service preferred drug list (PDL) are recommended.
- Implement safety edit for zuranolone to ensure product use is limited to populations with established safety and efficacy.
- Evaluate costs in the executive session.

Summary of Prior Reviews and Current Policy

- Antidepressants are designated preferred or part of the voluntary PDL.
- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics, adverse effects and cost.
- At the February 2023 meeting, no PDL changes were recommended based on review of recently published evidence. The PA criteria for tricyclic antidepressants, esketamine and brexanolone were updated.

Background:
Antidepressant medications are categorized based on mechanism of action and chemical structure. They are classified as first-generation (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (SSRIs, serotonin and norepinephrine reuptake inhibitors [SNRIs], and newer antidepressants). They are used for a wide variety of psychiatric conditions including depression, post-traumatic stress disorder (PTSD), bipolar disorder, obsessive compulsive disorder, anxiety disorders and bulimia.[7] Specific antidepressants have Food and Drug Administration (FDA) labeled indications for other conditions including fibromyalgia (not a funded diagnosis by the Health Evidence Review Commission), diabetic peripheral neuropathy, PPD, premenstrual dysphoric disorder, and smoking cessation.[7] This review highlights antidepressant therapies with new evidence for the treatment of PPD, smoking cessation and chronic pain.

Postpartum depression is a common medical condition in females, with an incidence of 13.2% in new female parents.[1] Postpartum depression is defined as depressive symptoms that occur within 4 weeks after giving birth. Untreated PPD can result in maternal suicide as wells as negative effects to infant and child development.[1] The pathophysiology of PPD is thought to be due to neuroactive steroids and gamma-aminobutyric acid (GABA) changes.[2] Currently there are 2 approved therapies for PPD, oral zuranolone and brexanolone (given as a continuous intravenous [IV] infusion over 60 hours). Antidepressant medications are also used as adjunctive therapy for smoking cessation, in which bupropion has the most evidence for improving quit rates.[3] There is evidence for the use of antidepressants to assist in the management of chronic pain. Chronic pain is defined as pain lasting 3 or more months with estimated incidence rates of one in 5 adults worldwide.[1] Depression is found to be more common in individuals with chronic pain. Guidance from NICE in 2022 recommends the use of duloxetine, amitriptyline, fluoxetine, paroxetine, citalopram and sertraline for the management of chronic pain.[4]

The choice of antidepressant is typically dependent on patient preference and adverse effect profile, as current evidence demonstrates little difference in efficacy between agents. Second-generation antidepressants are recommended as first-line agents due to improved tolerability, decreased risk of adverse events, and less risk for overdose, compared to first-generation antidepressants. For the treatment of moderate to severe depression in adults, guidelines from both NICE and the American Psychiatric Association (APA) recommend combination antidepressant and psychotherapy.[4,8] SSRIs are recommended by NICE as a first-line option, though individual drug choice can vary depending on adverse effects. APA guidelines support SSRIs, SNRIs, mirtazapine, or bupropion as reasonable first-line treatment options.

It is not uncommon for first-line treatments to fail to manage depressive symptoms. It is estimated that for major depressive disorder, about two-thirds of patients have an inadequate response to initial therapy and about one-third of patients have treatment-resistant depression.[3] There is no consistent definition in the literature for treatment-resistant depression; however, it is often described as failure to 2 or more antidepressants given at adequate doses.[9] There is little evidence to guide next steps in therapy after an initial treatment failure.[3] Common treatment options used in clinical practice include trial of a different first-line antidepressant, use of an antidepressant from a different class, and augmentation of current therapy with a second agent. All antidepressants for major depressive disorder (MDD) have an FDA black box warning for suicide risk in young adults and can be associated a discontinuation syndrome when agents are abruptly stopped. Other notable adverse events include risk for serotonin syndrome, which increases when used in combination with other serotonergic medications, and anticholinergic adverse events.

Goals of treatment for antidepressants typically include symptom and function improvement, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. There is some evidence that measurement-based care (MBC), via depression rating scale improves outcomes. However, the recommendation from the Veterans Administration (VA)/ Department of Defense (DoD) for use of these scales was weak due to lack of high-quality supporting evidence.[7] Some of the most

commonly used rating-scales and thresholds include the MADRS and HAM-D. The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[11] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52) with scores of 10-13 indicating mild depression, 14-17 indicating mild to moderate depression and 17 and greater indicating moderate to severe depression.[11] The FDA has stated that this tool is valuable in the study of depressive symptoms but may be associated with a higher representation of evaluation of somatic symptoms (e.g., insomnia and somatic anxiety) compared to other tools. Remission is defined as the person being free from depressive symptoms for several months after two or more depressive episodes and typically a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[11] A 2-point improvement on the MADRS may be associated with a minimum clinically important improvement and HAM-D scores of 3 to 7 points may be clinically significant.[11]

In Oregon, mental health drug classes, including antidepressants, are carved out from the coordinated care organizations (CCOs) and paid for by fee-for-service. Non-preferred products do not automatically require prior authorization, but safety criteria are in place for esketamine, brexanolone, and TCAs in children. In the second quarter of 2023 there were over 373,000 antidepressant medication claims for Oregon Health Plan (OHP) members.

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 terms used for this review are available in **Appendix 2**. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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 – Antidepressants for Smoking Cessation
In a 2023 Cochrane review, the use of antidepressants for assisting long-term smoking cessation was studied. Comparisons between antidepressants, placebo and other active treatments were evaluated.[1] A literature search up till April 2022 identified 124 studies, enrolling 48,832 participants. A majority of participants were adults with four studies enrolling adolescents, ages 12-21 years old. Studies had at least 6 months of follow up. Thirty-four studies were found to be at high-risk of bias.

In trials evaluating bupropion compared to placebo, or no pharmacological treatment, high-quality evidence showed bupropion was associated with higher smoking cessation rates (RR 1.60; 95% CI, 1.49 to 1.72).[1] Serious adverse events were similar between groups (RR 1.16; 95% CI, 0.90 to 1.48) (moderate quality evidence).[1] There was no clear evidence that there was a difference in smoking cessation rates between bupropion 150 mg daily and 300 mg daily. Individuals taking bupropion were more likely to drop out of trials early compared to placebo or no pharmacological treatment (RR 1.44; CI, 1.27 to 1.65) (high quality evidence).[1] Fifteen RCTs comparing combination therapy of bupropion and nicotine replacement therapy (NRT) compared to NRT alone demonstrated similar smoking cessation rates (RR 1.17; 95% CI, 0.95 to 1.44) based on low quality evidence. Similar rates of severe adverse events and dropouts between the treatment groups were found based on low quality evidence.[1] Bupropion monotherapy may be less effective than varenicline alone (RR of 0.73; 95% CI, 0.67 to

0.80; moderate strength of evidence). Combinations of bupropion and varenicline demonstrated no statistical or clinical difference in smoking cessation rates compared to varenicline alone (RR of 1.21; 95% CI, 0.95 to 1.55; moderate quality of evidence).[1] Comparisons of bupropion to combination NRT (e.g., nicotine patches plus one other form of nicotine) demonstrated lower smoking cessation rates with combination NRT (RR 0.74; 95% CI, 0.55 to 0.98). No differences were found in severe adverse events and withdrawals due to treatment between the two treatment groups (low quality evidence).

There is low quality evidence that bupropion use may result in higher smoking cessation rates compared to nortriptyline; however, the results were not statistically significant and results were imprecise (RR 1.30; 95% CI, 0.93 to 1.82; 3 trials).[1] Data from 6 trials demonstrated that nortriptyline use was associated with higher smoking cessation rates compared to placebo (RR 2.03; 95% CI, 1.48 to 2.78). There was insufficient evidence to assess harms of nortriptyline. Evidence from 4 studies did not demonstrate evidence that SSRIs were effective for smoking cessation (RR 0.93; 95% CI, 0.71 to 1.22); however, there was a low number of studies available for analysis. Monoamine oxidase inhibitors were studied in 6 trials and found that they may to be more effective for smoking cessation than control, but results were not statistically significant due to imprecision (RR 1.29; 95% CI, 0.93 1.79).[1] Studies with venlafaxine and St. John's wort had insufficient evidence to support conclusions. There was insufficient evidence to effectively assess harms in studies with SSRIs, MAOIs, and St. John's wort. The link between depression and quit rates was not explored in most studies. Harms were difficult to estimate due to low event rates that caused them to be underpowered to determine a difference.

Cochrane – Antidepressants for Pain Management in Adults with Chronic Pain

A 2023 systematic review and network meta-analysis evaluated the use of antidepressants for managing chronic pain in adult patients.[2] There was a paucity of high-quality evidence from other other sources, so the conclusions from the network meta-analysis are included in this summary. There were 176 studies including 28,664 participants included in the review.[2] Literature was searched till January of 2022. Placebo and active treatments comparisons were studied. Antidepressants included in the review were: amitriptyline, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, imipramine, milnacipran, mirtazapine and nortriptyline. Pain conditions studied were: fibromyalgia (59 studies); neuropathic pain (49 studies); musculoskeletal pain (40 studies).[2] Pain due to headaches were excluded. The primary outcome was a 50% decrease in pain intensity, pain relief, mood and adverse events. Pain relief was measured by 0-10 visual analog scale (VAS), 0-100 VAS and the Brief Pain Inventory scale. The duration of the included RCTs was an average of 10 weeks.

Duloxetine was found to be most effective for pain based on moderate to high quality evidence. There is moderate quality evidence that duloxetine 60 mg daily provided a small to moderate effect for substantial pain relief (50% or more reduction in pain intensity from baseline) compared to placebo (RR 1.91; 95% CI, 1.69 to 2.17).[2] Investigators calculated the findings as a number needed to benefit (NNTB) of 7.1 for this outcome.[1] A reduction in continuous pain intensity was reduced more in those treated with duloxetine compared to placebo (standard mean difference [SMD] -0.31; 95% CI, -0.39 to -0.24).[2] Compared to placebo, duloxetine demonstrated a small improvement in mood based on moderate evidence (SMD -0.16; 95% CI, -0.22 to -0.1). Duloxetine 60 mg daily was found to be as effective as higher doses (duloxetine 120 mg daily).

Milnacipran 100 mg daily was found to be moderately effective for chronic pain (e.g., fibromyalgia) relief. There was a small reduction in pain intensity demonstrated with milnacipran compared to placebo (SMD -0.22; 95% CI, -0.39 to -0.06) (moderate quality of evidence).[2] There was low quality evidence that milnacipran provide substantial pain relief with a NNTB of 11, based on evidence from 2 studies. No additional benefit was demonstrated with doses higher than 100 mg.

All other antidepressants had insufficient evidence to draw conclusions on benefit for chronic pain. There was very low quality evidence available on adverse events for all therapies, therefore additional evidence is needed to determine strong conclusions.

After review, 6 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10–13]

New Guidelines:
High Quality Guidelines:

NICE – Esketamine Nasal Spray for Treatment-resistant Depression
A December 2022 Technology Appraisal Guidance from NICE evaluated the evidence for the use of esketamine.[3] The appraisal was primarily based on the 2 phase trials (TRANSFORM-2 and SUSTAIN-1). Additional supportive evidence was from 4 trials: TRANSFORM-1, TRAMSFORM-3, SUSTAIN-2 and SUSTAIN-3. Trials included patients 18 to 64 years of age with moderate to severe depression comparing esketamine plus an oral antidepressant to placebo plus an oral antidepressant.[3] The primary outcome was the change in MADRS score based on symptom response, which was a reduction in score of 50% or more from baseline. Remission rates were also a primary endpoint, defined as a MADRS score of 12 or less with minimal or no symptoms. The mean reduction in MADRS score from baseline in patients who had not responded to 2 antidepressants was 19.8 for esketamine and 15.8 for placebo (with concomitant oral antidepressant).[3] NICE felt that the evidence was limited by an unknown placebo response in the trials, short trial duration, subgroups could more clearly defined and small trial populations. Overall, NICE found that the evidence suggests that esketamine is more effective than placebo but the evidence is uncertain. The committee concluded that esketamine is not recommended for those with treatment-resistant depression.[3]

ACP – Nonpharmacological and Pharmacologic Treatments of Adults in Acute Phase of Major Depressive Disorder
In a 2023 guideline from the ACP provided guidance for the treatment of adults in the acute phase of major depressive disorder (MDD).[4] Major depressive disorder is characterized by at least 5 symptoms and is associated with more severe and an increased number of symptoms.[4] Acute phase encompasses treatment till remission, defined as resolution of symptoms. Recommendations were for pharmacological and non-pharmacological therapies used for treatment in the ambulatory care setting. Evidence for recommendations came from a systematic review and network meta-analysis performed in 2023. Methodology for the guideline followed ACP guideline process which includes assessment and grading of the literature using GRADE methodology. Recommendations for pharmacotherapy will be presented.

Recommendations from the ACP are for adults with MDD for initial and second-line treatments in the acute phase.[4]

- Monotherapy with cognitive behavioral therapy (CBT) or second-generation antidepressant therapy is recommended first-line in the acute phase of moderate to severe MDD (strong recommendations; moderate quality evidence).
- Combination of CBT and second-generation antidepressants as initial treatment of moderate to severe MDD is conditional recommendation based on low quality of evidence.
- In adults with mild MDD CBT is recommended as initial therapy (conditional recommendation based on low quality evidence).
- In patients that do not respond to initial treatment should be: 1) switching to or augmenting with CBT 2) switching to a different second-generation antidepressant or augmenting with a second antidepressant (conditional recommendation based on low quality of evidence). It is recommended that treatment selection be based on patient characteristics and potential treatment benefits and harms.

New Formulations or Indications:
None identified.

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)
Levomilnacipran[14]	FETZIMA	August 2023	Warnings and Precautions	Pediatric patients 7 years to less than 18 years of age treated with levomilnacipran was associated with an increased risk of new-onset hypertension (systolic and/or diastolic). The safety and efficacy of levomilnacipran has not been established in pediatric patients for the treatment of major depressive disorder.

Randomized Controlled Trials:
Citations were manually reviewed for relevant randomized controlled trials from the initial Medline 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 DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Zuranolone is a neuroactive steroid GABA A receptor positive modulator FDA-approved for the treatment of PPD in August of 2023.[15] The dose of zuranolone is 50 mg once daily in the evening for 14 days, taken with fat-containing food to increase absorption. Zuranolone can be used as monotherapy or as an adjunct to oral antidepressant treatment. Two phase 3 trials provided evidence for efficacy in those with PPD.[5,6] Results from the phase 3 trials will be presented as well as 2 additional studies in patients with MDD (not currently approved for this indication) (**Table 4**).

The phase 3 trials enrolled patients with severe PPD, characterized by severe depression (HAMD-17 scores of 26 points or more). Most of the participants were White and had a mean age of 28 to 31 years. Approximately 15% to 20% of patients were taking a concomitant antidepressant.[16] Participants had to cease lactating or temporarily stop providing breast milk to their infant before starting therapy and 7 days after the last dose. The primary endpoint in both studies was change from baseline of 17-point HAM-D score at day 15. Secondary outcomes included change in HAM-D at day 45 and change from baseline in MADRS score at day 15.[5,6]

Zuranolone 30 mg daily was evaluated in one PPD study and 50 mg daily in the second PPD study, both compared to placebo.[5] In both studies zuranolone and placebo were given for 14 days with the primary endpoint assessment at day15. There was a clinically and statistically significant reduction in HAM-D scores at day 15 in both studies compared to placebo (least square mean [LSM] of -4.0 to -4.2 points). Results out to day 45 demonstrated a 2.9 to 4.1 point decrease in HAM-D scores compared to placebo.[16] Changes in MADRS scores ranged from -4.6 to -5.1, which were clinically and statistically significant. Improvements in anxiety and CGI-I were also improved through day 45 in the those patients who received 50 mg zuranolone compared to placebo.[6] Changes in CGI-I at day 15 were reduced -2.2 points for zuranolone compared to -1.6 points for placebo (LSM -0.6; 95% CI, -0.9 to -0.2; p=0.005).[5]

Limitations to the evidence for PPD include lack of data for repeated course of zuranolone in patients who experience relapse of depressive symptoms. Long-term efficacy beyond 45 days is unknown. There is insufficient safety data for the use of zuranolone in individuals who breastfeed. External validity was limited in all studies due to lack of details on study sites and location.

Clinical Safety:

Common adverse reactions for those patients taking zuranolone are: somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infections **(Table 2**).[15] The discontinuation rates due to AE were low in both trials, ranging from 1%-4.1% for zuranolone and 0%-2% for placebo.[1,9] Severe adverse events occurred in 3%-4% of patients in the treatment group compared to 1%-4% in the placebo group. There is a FDA boxed warning for driving impairment due to central nervous system depressant effects. Patients should wait at least 12 hours after administration before driving. There is no evidence of sexual dysfunction with the use of zuranolone when studied in patients with MDD.[17] There is a risk of misuse, abuse, and substance use disorder, including addiction, with the use of zuranolone. The FDA has recommended that the DEA assign a schedule IV designation to zuranolone as there is some evidence that it may cause physical dependence; however final status is pending.[16] Patients with mild, moderate or severe substance use disorders within the previous 12 months were excluded from one trial and those with a history of alcohol or drug abuse were exclusionary criteria for the second trial. Nonclinical data shows a risk for major congenital malformations and neuronal apoptosis with fetal exposure so contraception is recommended for females of reproductive potential. There is insufficient data on long-term safety outcomes.

Table 2. Adverse Events of Zuranolone (2% or more of treated patients)[15]

Adverse Reaction	Placebo	Zuranolone
Somnolence	6%	36%
Dizziness	9%	13%
Diarrhea	2%	6%
Fatigue	2%	5%
Urinary tract infection	4%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Remission of depression
2) Reduction of depressive symptoms (e.g., HAM-D or MADRS score changes)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change from baseline in HAM-D scores

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	The mechanism of action is not fully understood but thought to be due to the positive allosteric modulation of $GABA_A$ receptors
Oral Bioavailability	Not described
Distribution and Protein Binding	Distribution is greater than 500 L Protein binding is greater than 99.5%
Elimination	45% urine and 41% feces
Half-Life	19.7 to 24.6 hours
Metabolism	CYP3A4 predominately

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. Deligiannidis, et al[6] DB, PC, PG, Phase 3, RCT	1. Zuranolone 50 mg/day 2. Placebo Study treatment: 14 days Follow-up: 45 days	Demographics: Mean Age: 31 years Mean Body mass index: 30.25 Mean HAM-D (17-point): 28.7 White: 69% Black: 21.5% Key Inclusion Criteria: - 18 to 45 years - HAM-D score of 26 points or more - Major depressive episode with onset during the third trimester of pregnancy or 4 weeks or less postpartum and were 12 months or less postpartum Key Exclusion Criteria: - Breastfeeding during study period - Bipolar disorder - Psychotic disorder - Attempted suicide - Risk of suicide in the current episode of PPD	ITT: 1. 98 2. 97 PP: 1. 86 2. 87 Attrition: 1. 12 (12%) 2. 10 (10%)	Primary Endpoint: Change from baseline in HAM-D score at day 15: 1. -15.6 points 2. -11.6 points LSM -4.0 points (95% CI, -6.3 to -1.7) P = 0.001 Secondary Endpoints: Change from baseline in HAM-D score at day 45: 1. -14.8 points 2. -12.5 points LSM -2.9 points (95% CI, -4.5 to 0) P=0.050 Change in MADRS score at day 15: 1. -19.7 points 2. -14.6 points LSM -5.1 points (95% CI, -8.4 to -1.7) P = 0.003	NA for all	Severe AE: 1. 3 (3.1%) 2. 1 (1.0%) AE leading to discontinuation: 1. 4 (4.1%) 2. 2 (2.0%) Somnolence: 1. 26 (26.5%) 2. 5 (5.1%) Dizziness: 1. 13 (13.1%) 2. 10 (10.2%) Sedation: 1. 11 (11.2%) 2. 1 (1.0%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Patients, clinicians, and study personnel were blinded to treatment allocation. Randomization process was not described. Performance Bias: (Unclear) Patients, clinicians, and study personnel blinded to treatment allocation. There was no information on if placebo was matching to active treatment. Detection Bias: (Unclear) Outcome assessment was not described. Attrition Bias: (High) Results were analyzed on ITT population, but attrition levels were above 10% in the treatment group. Assessment of missing data was not described. Reporting Bias: (Low) Study was performed as described and endpoints assessed as described. Other Bias: (Unclear) manufacturer funded. **Applicability**: Patient: Results are most applicable to patients with severe depression and without other mental health disorders. Intervention: Zuranolone dose is appropriate and is one of the dosing regimens recommended by the manufacturer. Comparator: Placebo comparison appropriate because efficacy had not been established yet and there is no gold standard treatment for PPD. Outcomes: Outcomes: The HAMD and MADRS are standard measurement tools in the treatment of depression. Setting: Not described.

2. Deligiannidis, et al[5] DB, PC, Phase 3, RCT	1. Zuranolone 30 mg/day 2. Placebo Study treatment: 14 days Follow-up: 45 days	Demographics: Mean Age: 28.35 years Mean Body mass index: 31 Mean HAM-D (17-point): 28.6 Baseline antidepressant use: 19.5% White: 42% Black: 31% Key Inclusion Criteria: - 18 to 45 years - 6 months or fewer post-partum - HAMD-17 score of 26 points or more - Major depressive episode with onset during the third trimester of pregnancy or 4 weeks or less postpartum - Stable psychotropic use for more than 30 days, if taking psychotropics Key Exclusion Criteria: - Breastfeeding during study period - Seizures - Psychotic disorder - Attempted suicide - Active alcoholism or drug addiction	ITT: 1. 77 2. 76 PP: 1. 76 2. 74 Attrition: 1. 1 (1%) 2. 2 (3%)	Primary Endpoint: Change from baseline in HAMD-17 total score at day 15: 1. -17.8 points 2. -13.6 points LSM -4.2 points (95% CI, -6.9 to -1.5) P = 0.003 Secondary Endpoints: Change from baseline in HAM-D score at day 45: 1. -15.6 points 2. -11.6 points LSM -4.1 points (95% CI, -6.7 to -1.4) p-value = 0.003 Change in MADRS score at day 15: 1. -17.8 points 2. -13.6 points LSM -4.6 points (95% CI, -8.3 to -0.8) P = 0.02	NA for all	Severe AE: 1. 3 (4%) 2. 3 (4%) AE leading to discontinuation: 1. 1 (1%) 2. 0 (0%) Somnolence: 1. 12 (15%) 2. 8 (11%) Dizziness: 1. 6 (8%) 2. 4 (6%) Sedation: 1. 4 (5%) 2. 0	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization 1:1 with randomization codes generated by an independent statistical vendor by an interactive response technology implementation. Baseline characteristics were well balanced. Performance Bias: (Low) Subjects, clinicians, and study team blinded to treatment allocation. Matched placebo capsules to maintain blinding. Detection Bias: (Unclear) No details provided on how outcomes were analyzed. Attrition Bias: (Low) Results were analyzed via ITT analysis and attrition rates were low. Reporting Bias: Study was performed as described and endpoints assessed as described. Other Bias: (Unclear) Funded by manufacturer. **Applicability**: Patient: Results are most applicable to patients who have severe depression and not on antidepressant therapy upon initiation. Intervention: Zuranolone dose was lower than previous studies but well tolerated. Comparator: Placebo comparison appropriate because efficacy had not been established yet and there is no gold standard treatment for PPD. Outcomes: The HAMD and MADRS are standard measurement tools in the treatment of depression. Setting: Thirty-three outpatient centers.
Abbreviations: AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; ITT = intention to treat; HAMD = Hamilton Depression Rating Scale; LSM = least square mean; MADRS = Montgomery-Asberg Depression Rating Scale: MD = mean difference; MDD = major depressive disorder; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PG = parallel group; PP = per protocol; PPD = postpartum depression; RCT = randomized controlled trial.								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION XL	TAB ER 24H	Y
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y
desipramine HCl	NORPRAMIN	TABLET	Y
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	Y
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
duloxetine HCl	CYMBALTA	CAPSULE DR	Y
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y

fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nefazodone HCl	NEFAZODONE HCL	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
amoxapine	AMOXAPINE	TABLET	V
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
citalopram hydrobromide	CITALOPRAM HBR	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
dextromethorphan HBr/bupropion	AUVELITY	TAB IR ER	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
esketamine HCl	SPRAVATO	SPRAY	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
paroxetine HCl	PAROXETINE HCL	ORAL SUSP	V
paroxetine HCl	PAXIL	ORAL SUSP	V

paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	V
selegiline	EMSAM	PATCH TD24	V
sertraline HCl	SERTRALINE HCL	CAPSULE	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	V
venlafaxine besylate	VENLAFAXINE BESYLATE ER	TAB ER 24	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vilazodone HCl	VILAZODONE HCL	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
brexanolone	ZULRESSO	VIAL	
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to September 07, 2023

Search terms

#	Searches	Results
1	amitriptyline.mp. or Amitriptyline/	9920
2	bupropion.mp. or Bupropion/	5621
3	citalopram.mp. or Citalopram/	7733
4	desipramine.mp. or Desipramine/	7977
5	desvenlafaxine.mp. or Desvenlafaxine Succinate/	545
6	doxepin.mp. or Doxepin/	1534
7	duloxetine.mp. or Duloxetine Hydrochloride/	3289
8	escitalopram.mp. or Escitalopram/	3270
9	fluoxetine.mp. or Fluoxetine/	15686

10	fluvoxamine.mp. or Fluvoxamine/	3321
11	imipramine.mp. or Imipramine/	13543
12	mirtazapine.mp. or Mirtazapine/	2726
13	nefazodone.mp.	802
14	nortriptyline.mp. or Nortriptyline/	3272
15	paroxetine.mp. or Paroxetine/	6844
16	sertraline.mp. or Sertraline/	6035
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	5014
18	amoxapine.mp. or Amoxapine/	487
19	clomipramine.mp. or Clomipramine/	4129
20	Dextromethorphan/ or dextromethorphan.mp.	3190
21	isocarboxazid.mp. or Isocarboxazid/	416
22	levomilnacipran.mp. or Levomilnacipran/	101
23	phenelzine.mp. or Phenelzine/	1688
24	protriptyline.mp. or Protriptyline/	415
25	selegiline.mp. or Selegiline/	3011
26	tranylcypromine.mp. or Tranylcypromine/	2311
27	trimipramine.mp. or Trimipramine/	548
28	vilazodone.mp. or Vilazodone Hydrochloride/	267
29	vortioxetine.mp. or Vortioxetine/	672
30	brexanolone.mp.	135
31	trazodone.mp. or Trazodone/	2349
32	esketamine.mp.	799

Appendix 3: Prescribing Information Highlights

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

ZURZUVAE™ (zuranolone) capsules, for oral use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

WARNING: IMPAIRED ABILITY TO DRIVE OR ENGAGE IN OTHER POTENTIALLY HAZARDOUS ACTIVITIES

See full prescribing information for complete boxed warning.

ZURZUVAE causes driving impairment due to central nervous system (CNS) depressant effects. Advise patients not to drive or engage in other potentially hazardous activities until at least 12 hours after administration. Patients may not be able to assess their own driving competence or the degree of impairment caused by ZURZUVAE *(5.1, 5.2)*.

INDICATIONS AND USAGE

ZURZUVAE is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. (1)

DOSAGE AND ADMINISTRATION

- Administer with fat-containing food. (2.1)
- Recommended dosage is 50 mg orally once daily in the evening for 14 days. (2.1)
- Dosage may be reduced to 40 mg once daily if CNS depressant effects occur. (2.1)
- ZURZUVAE can be used alone or as an adjunct to oral antidepressant therapy. (2.1)
- *Severe Hepatic Impairment:* Recommended dosage is 30 mg orally once daily in the evening for 14 days. (2.3, 8.6)
- *Moderate or Severe Renal Impairment:* Recommended dosage is 30 mg orally once daily in the evening for 14 days. (2.4, 8.7)

DOSAGE FORMS AND STRENGTHS

Capsules: 20 mg, 25 mg, and 30 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *CNS Depressant Effects:* ZURZUVAE can cause CNS depressant effects such as somnolence and confusion. If patients develop CNS depression, consider dosage reduction or discontinuation of ZURZUVAE. (5.2)
- *Suicidal Thoughts and Behavior:* Consider changing the therapeutic regimen, including discontinuing ZURZUVAE, in patients whose PPD worsens, or who experience emergent suicidal thoughts and behaviors. (5.3)
- *Embryo-fetal Toxicity:* May cause fetal harm. Advise a pregnant woman of the potential risk to an infant exposed to ZURZUVAE in utero. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during ZURZUVAE treatment and for one week after the final dose. (5.4, 8.1, 8.2, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and greater than placebo) were somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-987-9882 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- *CNS Depressants:* Concomitant use may increase impairment of psychomotor performance or CNS depressant effects. If use with another CNS depressant is unavoidable, consider dosage reduction.(7)
- *Strong CYP3A4 Inhibitors:* Concomitant use may increase the risk of ZURZUVAE-associated adverse reactions. Reduce the ZURZUVAE dosage to 30 mg orally once daily in the evening for 14 days when used concomitantly with a strong CYP3A4 inhibitor. (2.2, 7)
- *CYP3A4 Inducers:* Concomitant use may decrease the efficacy of ZURZUVAE. Avoid concomitant use. (2.2, 7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Appendix 4. Key Inclusion Criteria

Population	Patients with MDD and PPD
Intervention	Antidepressant treatment
Comparator	Placebo or active treatment comparison
Outcomes	Reduction in depressive symptoms and remission of symptoms
Setting	Outpatient

Appendix 5: Safety Edits

Zuranolone (Zurzuvae)

Goal(s):

- To ensure appropriate use of zuranolone in patients with post-partum depression.

Length of Authorization:

- One time use only.

Requires PA:

- Zuranolone requires a prior authorization approval due to safety concerns.

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 and age (e.g., ≥18 years)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have moderate to severe post-partum depression?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Has the patient been previously treated with zuranolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple courses of zuranolone have not been studied.	**No:** Approve for a single 14-day treatment.

P&T/DUR Review: 12/23 (KS)
Implementation: TBD

Brexanolone (Zulresso)

Goal(s):
- To ensure appropriate use of brexanolone in patients with post-partum depression.

Length of Authorization:
- One time use only.

Requires PA:
- Brexanolone requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and age (e.g., ≥15 years)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the patient with moderate to severe post-partum depression?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with brexanolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple doses of brexanolone have not been studied.	**No:** Go to #5
5. Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 12/23 (KS) 2/23 (KS), 2/21(SS) 7/19 (KS)
Implementation: TBD; 4/1/23; 8/19/19

Tricyclic Antidepressants

Goal(s):
- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:
- Up to 12 months

Requires PA:
- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
  - Patients with a claim for an SSRI or TCA in the last 6 months
  - Prescriptions identified as being written by a mental health provider

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

Table 1. FDA-Approved Indications of Tricyclic Antidepressants

Drug	FDA-Approved Indications	Maximum Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10
desipramine HCl	Depression	300 mg (150 mg for 10-19 years of age)	10
doxepin HCl	Depression Anxiety	150 mg	12
imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression Dysthymia Mixed anxiety and depressive disorder	225 mg	18
nortriptyline HCl	Depression	50 mg	12
protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for an FDA-approved indication and age (**Table 1**)?	**Yes:** Approve for up to 6 months	**No:** Go to #4
4. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	**Yes**: Approve for up to 6 months	**No:** Go to #5

Approval Criteria		
5. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	**Yes**: Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review:12/23 (KS), 2/23 (KS), 2/21(SS) 11/19
Implementation: TBD; 2/1/2020

Esketamine (Spravato)

Goal(s):
- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:
- Up to 6 months

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

Covered Alternatives:
8. Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
9. 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. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
6. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
7. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve requested doses (either 56 mg and/or 84 mg for titration) not to exceed 23 units total.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #4

Renewal Criteria		
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

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

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: sparsentan tablets, oral

Date of Review: December 2023
Generic Name: sparsentan

End Date of Literature Search: 09/12/2023
Brand Name (Manufacturer): Filspari™ (Travere Therapeutics, Inc)

Dossier Received: yes

Plain Language Summary:

- In 2023, the Food and Drug Administration (FDA) approved sparsentan, a medicine to treat a condition known as immunoglobulin A nephropathy (IgAN).
- Immunoglobulin A nephropathy is a type of kidney disease caused by buildup of a protein, called immunoglobulin, in the kidney. This causes damage to the kidneys and makes it harder for the kidneys to filter the blood.
- A small sample of tissue must be taken from the kidney to properly diagnose IgAN. Providers may also track levels of protein in the urine to help guide treatment.
- Treatment for IgAN includes:
    - Maintaining a healthy lifestyle including exercise, weight management, stopping smoking, and decreasing salt intake.
    - Keeping blood pressure under control. Some medicines that are normally used for blood pressure are given for kidney protection.
    - Prescribing medicines called glucocorticoids to reduce risk of kidney failure when the benefits of these medicines are greater than the risks of harmful side-effects.
- Sparsentan is a new medicine that lowers levels of protein in the urine for patients who have IgAN and are at risk of their disease worsening over a short time period. We do not know if sparsentan slows kidney decline in patients with IgAN.
- Studies with sparsentan showed that it may cause liver damage. Other side effects included arm and leg swelling, drops in blood pressure, dizziness, high potassium levels, and a low blood cell count that may have made patients feel weak and tired. Providers should not prescribe sparsentan for people who are pregnant or breastfeeding due to the possibility of harm to the developing baby.
- Use of sparsentan is only allowed under a special drug safety program (Risk Evaluation and Mitigation Strategies [REMS]) that is managed by the FDA. Prescribers, patients, and pharmacies must sign up for the program.
- We recommend that providers who prescribe sparsentan to a person enrolled in the Oregon Health Plan explain to the Oregon Health Authority why their patient needs sparsentan before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the evidence for efficacy of sparsentan in reducing proteinuria in adults with primary IgA nephropathy who are at risk of rapid disease progression?
2. What is the evidence for harms associated with the use of sparsentan?
3. Are there specific subpopulations that would be more likely to benefit or be harmed from the use of sparsentan?

Author: David Engen, PharmD

Conclusions:

- Persistent proteinuria is a modifiable prognostic indicator for IgAN progression.[1] Sparsentan was approved by the Food and Drug Administration (FDA) under the Accelerated Approval pathway in February of 2023.[1,2] Sparsentan is an endothelin type A receptor (ETAR) and angiotensin II type 1 receptor (AT1R) antagonist for use in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression due to proteinuria.[1,2]
- The safety and efficacy of sparsentan was evaluated in one ongoing, randomized, double-blind, phase 3 trial in patients with biopsy-proven IgAN (PROTECT).[1-3] The study enrolled 406 patients with evidence of proteinuria >1 g/day, an eGFR of >30 ml/min/1.73m^2, and who were on a stable dose of a maximum tolerated angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB).[1-3] Patients on their current ACEi or ARB were switched to oral doses of either sparsentan 400 mg or irbesartan 300 mg once daily over a period of 110 weeks. A prespecified, unblinded interim analysis was planned at 36 weeks and was the basis of FDA approval.[1-3]
- The FDA allowed the manufacturer to use the surrogate marker of urine protein-to-creatinine ratio (UPCR) for the primary efficacy endpoint.[1] It was determined that adults with primary IgAN may be at risk of rapid disease progression with a UPCR ≥ 1.5 g/g (normally 0.2 in unaffected individuals).[1] The change from baseline in proteinuria based on a 24-hour urine sample was evaluated for 281 patients at Week 36.[1-3] There was low-quality evidence that the adjusted mean percent change in urine protein to creatinine ratio (UPCR) compared to baseline was lower in the sparsentan group compared to the irbesartan group (-45% vs. -15%, respectively) with a mean ratio of 0.65 (95% CI, 0.55 to 0.77; p<0.0001).[1,2] There is insufficient efficacy data of sparsentan beyond 36 weeks.[1,2] It has not been established whether sparsentan slows kidney function decline in patients with IgAN.[1,2]
- The most common adverse events that occurred during treatment in the sparsentan and irbesartan groups, respectively, were peripheral edema (14% vs. 9%), hypotension/orthostatic hypotension (14% vs. 6%), dizziness (13% vs. 5%), hyperkalemia (13% vs. 10%), and anemia (5% vs. 2%).[1-3]
- Sparsentan prescribing information contains a boxed warning for risk of liver toxicity (up to 2.5% of patients) and embryo fetal toxicity (based on animal reproductive studies).[1,2]
- Data are limited for use in people with risk factors for or have preexisting hepatic dysfunction.
- Sparsentan use is restricted to the FILSPARI Risk Evaluation and Mitigation Strategy (REMS) Program.[1,2]

Recommendations:

- Implement prior authorization to ensure safe and appropriate use.
- Maintain sparsentan as non-preferred on the Oregon Health Plan (OHP) preferred drug list (PDL).

Background:

Immunoglobulin A nephropathy (IgAN) is a rare, progressive, inflammatory kidney disease that is the most common cause of end-stage renal failure in young adults.[4,5] Among the various types of renal conditions, IgAN, or Berger's disease, is among the most frequently encountered primary glomerular diseases worldwide but its geographic distribution is varied.[4,5] In the United States, it is estimated that the annual incidence of IgAN confirmed through biopsy is roughly 1 case per 100,000 persons.[4,6-8] Compared to the US, the incidence of IgAN is higher among East Asian and Pacific Rim populations and lower in Africa.[4,6-8] Certain risk factors such as a younger age of onset, male sex, hypertension, a decreased glomerular filtration rate (GFR), presence of proteinuria, and disease severity have all been identified as predictors of poor kidney prognosis in patients with IgAN.[9] Immunoglobulin A nephropathy is more likely to manifest between the ages of 16-35 years but may be observed in patients younger or older with variable symptomatic presentation.[10] Prevelance of IgAN is 2 to 6 times higher in males compared to females.[8] Roughly 15-20% of patients with IgAN progress to end stage renal disease/dialysis within 10 years of diagnosis and 30-40% progress to failure within 20-30 years (**Table 1**).[5,8,11-13]

Among the more prominent pathological features of IgAN is the deposition of IgA complexes in the mesangial region of the glomerulus.[4,14] IgA molecules are one of 5 primary glycosylated immunoglobulins and are key factors in the regulation of mucosal homeostasis and immunity.[4] IgA is secreted by plasma cells and provides a protective, anti-inflammatory function for the mucosa by inhibiting adhesion of pathogens and neutralizing toxins.[15] The two forms of IgA, IgA1 and IgA2, differ in structure, role, and location found in the body.[7] IgA1 makes up roughly 80% of the total IgA and is found mostly on the mucosal surfaces such as the lungs where it is more vulnerable to cleavage from bacterial proteases.[7] IgA2 is found primarily in the colon.[4] Deficiencies in IgA have been shown to result in a weakened mucosal barrier that is more susceptible to infection, especially in the gastrointestinal and upper respiratory tracts.[8] Some studies suggest IgAN may be the result of a multi-step process influenced by genetic predisposition and environmental factors.[4,15,16] When B-lymphocytes that produce galactose-deficient IgA1 enter systemic circulation and bone marrow, they raise the levels of serum Gal-deficient IgA1 (Gd-IgA1).[15,17] These circulating abnormal IgA1 trigger the formation of anti-glycan IgA1 antibodies and immune complexes (IC).[4,13] Due to the liver's inability to clear the aberrant IgA1, the ICs are deposited in the renal mesangium where they cause inflammation and lead to the glomerular damage.[4,13,18,19]

IgAN may present as a broad range of clinical manifestations. The early stages of IgAN are often asymptomatic, with some patients displaying mild microscopic hematuria and/or slight proteinuria (<0.5 g/day) that can be detected via screening.[10,18-20] Isolated microscopic hematuria with negligible proteinuria generally has a favorable prognosis.[10,18,19] However, many children and adolescents and about 10% to 15% of young adult patients with IgAN present with macroscopic hematuria and concurrent infection of the upper respiratory tract or a gastrointestinal illness.[10,18,19] As a progressive illness, IgAN rarely manifests with acute kidney failure.[20] Older adults with IgAN are more likely to present with a slow kidney decline with persistent proteinuria (e.g. >1 g/day), hematuria, hypertension, and a reduced estimated glomerular filtration rate (eGFR).[20] The classification of chronic kidney disease (CKD) stage according to GFR is listed in **Table 1**.[20] In adults 30 years of age or older, over half the patients with IgAN present with stage 3 to 5 progressive chronic kidney disease (CKD).[10,18,19] Other complications may be evident such as rapidly progressive glomerulonephritis (RPGN) which results in a 50% or more decline in eGFR over 3 months or less.[10,18,19] This rapid loss of kidney function is often associated with the presence of fibrous histological lesions known as cellular crescents.[18,19] There are reports that almost half of patients with RPGN develop kidney failure within 1 year of diagnosis even when on immunosuppressive therapy.[18,19]

Table 1: Stages of CKD[20]

CKD Staging	Description	eGFR (ml/min/1.73 m^2)
1	Normal or High	≥90
2	Mildly Decreased	60-89
3a	Mild to Moderately Decreased	45-59
3b	Moderately to Severely Decreased	30-44
4	Severely Decreased	15-29
5	Kidney Failure	<15
Abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate		

There are no validated diagnostic serum or urine biomarkers for IgAN and a definitive diagnosis is only possible through kidney biopsy.[20] Due to variations in the sample collection and timing of the procedure, IgAN may display diverse pathological findings.[14] Many studies have used kidney function and proteinuria as clinical outcome measures in patients with IgAN, but the findings are often difficult to distinguish from other acute inflammatory lesions that may produce sclerotic glomeruli or cellular crescents.[14,21,22] The Modified Oxford classification and MEST-C score system (described in **Table 2**) has been widely used to determine the risk of a 50% decline in eGFR or ESRD (typically over 5 years) in patients with IgAN.[23-25] Different pathologic variables comprise the MEST-C and

contribute to the overall prognosis.[23-25] MEST-C scoring assigns a numerical value of 0 or 1 based on the presence of mesangial and endocapillary hypercellularity, and segmental glomerulosclerosis, or a score of 0, 1, or 2 for tubular atrophy/interstitial fibrosis.[9,24,25]

Table 2. Oxford Classification/MEST-C Scoring System (modified)[9,24,25]

Histology	Score
Mesangial hypercellularity	M0: Presence of mesangial hypercellularity in <50% glomeruli M1: Presence of mesangial hypercellularity in >50% glomeruli
Endocapillary hypercellularity	E0: No endocapillary hypercellularity E1: Presence of any endocapillary hypercellularity
Segmental glomerulosclerosis	S0: No segmental glomerulosclerosis S1: Presence of any segmental glomerulosclerosis
Tubular atrophy and interstitial fibrosis	T0: 0–25% tubular atrophy/interstitial fibrosis in cortical area T1: 26–50% tubular atrophy/interstitial fibrosis in cortical area T2: >50% tubular atrophy/interstitial fibrosis in cortical area
Cellular or fibrocellular crescents	C0: no cellular or fibrocellular crescents C1: Presence of cellular/fibrocellular crescents in 1%-25% glomeruli C2: Presence of cellular/fibrocellular crescents in >25% glomeruli
Key: M: mesangial hypercellularity; E: endocapillary hypercellularity; S: segmental glomerulosclerosis; T: tubular atrophy and interstitial fibrosis; C: crescent formation.	

Although the presence of cellular crescents are noted in the pathologic scoring, prominent IgAN guidelines recommend that number of crescents should not be used to determine the likelihood for progression of IgAN.[9,20,24,25] The standardized MEST-C/Oxford Classification scores have been used to develop the International IgAN Prediction tool which, when combined with clinical data from kidney biopsy, assist clinicians in a more robust prognostic scoring system to help accurately predict risk of kidney decline in patients with IgAN.[25] The tool also considers other factors at the time of biopsy such as age, race, eGFR, blood pressure, presence of proteinuria, and supportive drug therapy (e.g. ACEi/ARB and immunosuppressive agent use) to predict risk of IgAN progression.[26] Other biomarkers have been proposed such as kidney inflammation, anemia, hyperuricemia, increased plasma osmolality, and elevated neutrophil:lymphocyte ratio but these markers have yet to be validated.[27] Even with advances in prediction models and diagnostic tools, there is still an unmet need for noninvasive biomarkers to support the evaluation of real-time disease activity in patients with IgAN.[27]

Proteinuria is a risk factor for renal disease and persistent proteinuria in excess of 1 g/d over 6 to 12 months is associated with increased risk of progression in IgAN.[9] In a study of 1155 patients, a statistically significant difference in 10-year kidney survival was demonstrated in patients with sustained proteinuria of 0.5-1 g/day compared to >1 g/d, which included a 10-year dialysis-free survival of 94% (95% CI: 90%–98%), and also a 20-year dialysis-free survival of 89% (95% CI: 82%–96%).[20] A 24-hour urine protein (24h-UP) is the standard test used to determine proteinuria.[26] Although the 24h-UP collection may be a challenge for some patients, it is particularly useful to discern small graduations of proteinuria given the association between increased disease risk and changes in proteinuria from 1-2 g/d and particularly >2 g/d.[26] Other less cumbersome methods to determine proteinuria include the urine protein to creatinine ratio (UPCR; normal ratio <0.2).[21] Since protein excretion and urinary creatinine are assumed to be constant over time, the UPCR from a single urine sample has been used as a substitute

for a 24h-UP.[21,26] The UPCR has been found to be reliable predictor of kidney function in a number of chronic renal disease studies.[5,21,26] However, there is also evidence to suggest that UPCR has a relatively poor correlation with 24 h-UP when proteinuria is over 1 g/d.[5,21,26]

Although treatment for IgAN is dependent upon stage and symptoms, comprehensive supportive care therapy is first-line to help preserve and slow decline of renal function.[20,28] Supportive care may necessitate lifestyle modifications such as increased exercise and weight management strategies, smoking cessation, and restriction of sodium intake (<2 g/d).[9,20,28] Maximum dose (or maximum tolerated dose) of renin-angiotensin-aldosterone system (RAAS) blockade with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) are recommended to decrease the risk of kidney failure by reducing proteinuria independent of the presence of hypertension.[20,28,29] For patients with IgAN and comorbid hypertension, the target blood pressure is 120/75 mm Hg and proteinuria <0.5 g/d (See **Table 3**).[5,15] Although RAAS blockade may provide a benefit in patients with IgAN and hypertension, the long-term impact on other renal and/or cardiovascular endpoints including mortality is unclear.[20] For patients with high risk of progressive CKD and already on maximal supportive care, a 6-month trial of glucocorticoid therapy may be warranted.[13,20] Immunosuppressive therapy with corticosteroids should be considered only when benefits of proteinuria reduction outweigh risks of toxicity.[20,28] Budesonide delayed-release (DR) capsules (TARPEYO) is a corticosteroid indicated to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression as defined by a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g.[30] Budesonide for IgAN treatment was approved based on a surrogate marker of proteinuria reduction although it has not been established whether oral budesonide slows kidney function decline in patients with IgAN.[30]

Table 3. Comprehensive Supportive Therapy for Patients with IgAN [5,15]

• ACEI or ARB irrespective of whether patients have high blood pressure →Target: blood pressure 120/75 mm Hg and proteinuria <0.5 g/d
• Statin therapy if persistent hyperlipidemia
• Low-sodium diet (<2 g/d) →24-hour urinary sodium excretion can be used to verify dietary consumption
• Advice on smoking cessation
• Avoidance of NSAIDs and other nephrotoxic drugs
• Healthy weight target

It has been reported that endothelin-1 and angiotensin II may contribute to the pathogenesis of IgAN via the endothelin type A receptor (ETAR) and angiotensin II type 1 receptor (AT1R) pathway, respectively, and that antagonism of these receptors may result in a reduction of proteinuria.[32] Sparsentan is an ETAR and AT1R antagonist approved by the FDA to treat patients with IgAN.[1,2] Both angiotensin II and certain isoforms of endothelin are strong vasoconstrictors and play a major role in the development of hypertension, CVD, and CKD.[32,33] Endothelin (ET) is a polypeptide produced by endothelial cells and is also present in the epithelial and mesangial cells within the renal system.[32,33] There are 3 known isoforms of ET and ET-1 has been shown to have the largest influence on renal vasoconstriction.[32,33] Various stimuli that increase renal ET-1 (e.g. acidosis, hyperglycemia, angiotensin II, pro-inflammatory cytokines, etc.) lead to toxic effects on renal function and eventual decline.[32,33] Inhibition of both RAAS and ET-1 may, therefore, be a potential target to slow the course of progressive kidney dysfunction in patient with IgAN.[32]

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

Clinical Efficacy:
Sparsentan was approved by the FDA under the Accelerated Approval pathway in February of 2023.[1,2] Sparsentan is indicated for adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g .[1,2] FDA labeling suggests that sparsentan should be used in people with IgAN confirmed through biopsy.[1,2] Prior to treatment, any use of renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists (ERAs), and/or aliskiren should be discontinued.[2]

Sparsentan is being studied in one ongoing, randomized, double-blind, phase 3 trial in patients with biopsy-proven IgAN (PROTECT).[1-3] The study enrolled 406 patients with evidence of proteinuria ≥1 g/day, an eGFR of ≥30 ml/min/1.73m^2, and who were on a stable dose of a maximum tolerated ACEi or ARB for at least 12 weeks or longer.[1-3] Per study protocol, patients discontinued their ACEi or ARB one day prior to the start of the study.[1,3] Although the trial design excluded participants with recent systemic corticosteroid and/or immunosuppressive therapy, if warranted, it was provided in addition to study medication at the discretion of the investigator.[1,3] Patients were randomized 1:1 to receive oral doses of either sparsentan 400 mg or irbesartan 300 mg once daily over a period of 110 weeks.[1,3] Doses for both sparsentan and irbesartan were titrated over a 2-week period until target doses were reached.[1,3] The protocol had a prespecified, unblinded interim analysis planned at 36 weeks.[1,3] The primary endpoint for the trial was the change in proteinuria from baseline based on a 24-hour urine sample at Week 36, while the confirmatory endpoint was the rate of change in eGFR over a 110-week period (approximately 2 years) after initiation of therapy.[1,3] At baseline, both the sparsentan and irbesartan groups had similar characteristics including mean eGFRs (57.1 mL/min/1.73 m^2 and 55.6 mL/min/1.73 m^2, respectively), mean urinary protein excretion (2.1 g/day and 2.2 g/day, respectively), and mean UPCR values (1.4 g/g and 1.5 g/g, respectively).[1,3]

Of the 406 participants enrolled, results of the first 281 patients were analyzed for the interim analysis.[1,2] At week 36, low-quality evidence showed the adjusted mean percent change in UPCR compared to baseline was lower in the sparsentan group compared to the irbesartan group (-45% vs. -15%, respectively) with a mean ratio of 0.65 (95%CI, 0.55 to 0.77; p<0.0001).[1,2] The clinical significance of this magnitude of change is unclear.

Trial findings were limited to the unblinded interim analysis at week 36 which included only a portion of all randomized participants (full study results not yet available). The mean age of subjects in the interim analysis set was 46 years of age. IgAN typically manifests in patients who are in their late teens to early 30s, therefore, the study may have included a high proportion of patients with more late-stage disease. It is unclear if younger patients on this therapy would respond in a similar manner. There was no evidence of participant assessment of a baseline MEST-C score or similar validated tool for between-group comparison. There were more individuals in the sparsentan group on maximum labeled dose of ACEis or ARBs as well as other hypertensive medications compared to the irbesartan group (65% vs 62%, and 44% vs 41%, respectively) but the effects of these slight differences on the outcome measures were unclear. The exclusion criteria around hepatotoxicity and CVD make safety and effectiveness uncertain in people with risk factors for these conditions. Also, the investigators were unable to perform a full assessment of important features such as microscopic or macroscopic hematuria given the use of a central laboratory for analysis. To date, there is limited data available whether the surrogate outcome of proteinuria reduction has a long-term clinical significance for patients with IgAN. To understand sparsentan's true place in therapy, additional research with a larger study population over a longer duration may be needed with an emphasis in primary survival endpoints and functional outcomes. The findings from the full confirmatory clinical trial will not be available until its completion (anticipated 10/2023; report to be submitted to FDA 02/2024).[1]

Clinical Safety:

There were 404 patients included in the safety population.[1-3] The proportion of serious adverse events (SAEs) and discontinuations due to an adverse event were similar between goups. There were no reported deaths. The most common adverse events that occurred during treatment in the sparsentan and irbesartan groups, respectively, were peripheral edema (14% vs. 9%), hypotension/orthostatic hypotension (14% vs. 6%), dizziness (13% vs. 5%), hyperkalemia (13% vs. 10%), and anemia (5% vs. 2%).[1-3] There were more participants in the sparsentan group that required dose reductions after titration compared to those treated with irbesartan (13% vs 9%, respectively). There was a decrease in hemoglobin (> 2 g/dL from baseline and below the lower limit of normal) observed in 11% of sparsentan and 5% of irbesartan recipients.[1-3] However, in the study no patient discontinued treatment because of anemia or decreased hemoglobin.[1-3] The adverse reactions reported during the PROTECT trial are summarized in **Table 4**.

Table 4. Adverse Reactions Reported In 5% Or More Of Patients Treated with Sparsentan Compared to Irbesartan[1-3]

Adverse Reactions	Sparsentan (n=202)	Irbesartan (n=202)
Peripheral edema	14%	9%
Hypotension (including orthostasis)	14%	6%
Dizziness	13%	5%
Hyperkalemia	13%	10%
Anemia	5%	2%

Sparsentan prescribing information contains a boxed warning of liver toxicity risk and embryo fetal toxicity.[2] Endothelin receptor antagonists are associated with risk of elevated aminotransferases and liver toxicity/failure.[2] Roughly 2% of patients of sparsentan-treated patients had increases in aminotransferases of more than three times the upper limit of normal, however, the increases were asymptomatic and reversible upon discontinuation of the drug.[2] Sparsentan is contraindicated during pregnancy due to animal studies that reported the possibility of fetal harm. Patients are also cautioned to avoid breastfeeding during sparsentan administration.[2] Sparsentan is available through a Risk Evaluation and Mitigation Systems (REMS) program due to observed hepatoxicity.[2] The REMS program requires documentation of serum aminotransferases and total bilirubin before treatment, monthly for 12 months, and then every 3 months in addition to pregnancy testing monthly for those with childbearing potential during treatment.[2] If patient has elevated aminotransferase levels greater than 3 times the upper limit of normal, treatment is not recommended.[2] Sparsentan use is contraindicated with concomitant RAAS inhibitors, ERAs, or aliskiren.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Improved survival
2) Stabilization of kidney function
3) Time to renal failure
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Mean percent change from baseline in urine protein-to-creatinine ratio

Table 5. Pharmacology and Pharmacokinetic Properties.[1,2]

Parameter	
Mechanism of Action	ETAR and AT1R antagonist. Endothelin-1 and angiotensin II are thought to contribute to the pathogenesis of IgAN via these receptors, and sparsentan has a high affinity for them, with a greater than 500-fold selectivity over the endothelin type B and angiotensin II subtype 2 receptors.
Oral Bioavailability	NA
Distribution and Protein Binding	Vd = 61.4L; Protein binding >99% (>90% binding to albumin)
Elimination	Feces (80%); Renal (2%)
Half-Life	9.6 hours
Metabolism	Cytochrome P450 3A

Abbreviations: AT1R = angiotensin II type 1 receptor; ETAR = Endothelin type A receptor; IgAN = immunoglobulin A nephropathy ; NA = not applicable; Vd = volume of distribution.

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Heerspink et al [1,3] DB, PG, AC, Phase 3, RCT	1. sparsentan 400 mg once daily 2. irbesartan 300 mg once daily 36 weeks	Demographics: Mean age: 46 years Male: 70% Race: -White 67% -Asian 29% -Black or African American 1% Hx of HTN: 70% Age at IgAN dx: 38.5 years Mean UPCR 1.4 g/g Urinary protein excretion: 1.8 g/day Mean eGFR: 57 ml/min/1.73m^2 Serum albumin: 41 g/L ACEi/ARB max dose: 63% Baseline concomitant agents: -Antihypertensive 42% -Lipid lowering 55% Key Inclusion Criteria: -Biopsy-proven IgAN	ITT: 1.202 2.202 mITT: 1.141 2.140 PP: 1.133 2.128 Attrition: 1. 23 (11%) 2. 39 (19%)	Primary Endpoint: Mean* percent change in UPCR from baseline to week 36: 1. -45% (95% CI -51% to -38%) 2. -15% (95% CI -24% to -4%) Mean ratio: 0.65 (95% CI 0.55 to 0.77) p-value <0.0001 *=adjusted geometric	NA for all	Any SAE 1. 28 (13.9%) 2. 27 (13.4%) Discontinued drug due to AE: 1. 16 (7.9%) 2. 9 (4.5%) Peripheral edema: 1. 29 (14%) 2. 19 (9%) Hypotension: 1. 28 (14%) 2. 12 (6%) Dizziness: 1. 27 (13%) 2. 11 (5%) Hyperkalemia: 1. 27 (13%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized using predefined computer-generated schedule. Randomization stratified via eGFR and UP excretion. Baseline characteristics similar between groups. Performance Bias: (Unclear) Study drug and active control identical in appearance and packaging. Participants, investigators and clinical staff blinded except for the data monitoring committee, SAE monitoring contact, and the "limited unmasked team" responsible for interim analysis (precluded from further participation). BP meds could be initiated/titrated at investigator's discretion until target goal reached (125/75 mmHg). Detection Bias: (Unclear) Proteinuria and albuminuria were assessed by 24-h urine collection at each study visit and analyzed at a central laboratory but blinding process not described. Attrition Bias: (Unclear) Only portion of randomized subjects (281/406) had 9-month UP/C measurement at the time of interim analysis; missing data was imputed using a multiple imputation (MI) procedure which was not described in detail.

		-24hr urine protein excretion ≥1.0 g/day after 12 weeks RAAS inhibition -eGFR ≥30 ml/min/1.73m^2 -BP ≤150/100 mmHg Key Exclusion Criteria: -IgAN secondary to another condition or IgA vasculitis -systemic immunotherapy (including corticosteroids) within previous 3 months - >25% glomeruli cellular crescents on renal biopsy within 6 mos of screening -CVD or major hepatic conditions -Concomitant use of any prohibited medications: RAAS inhibitors, endothelin inhibitors, Potassium-sparing diuretics, thiazolidinediones, SGLT-2 inhibitors, amphetamines, digoxin				2. 21 (10%)		Reporting Bias: (Low) Study followed original trial design. Other Bias: (High) Study was funded by the manufacturer. Funding source had role in data collection, data interpretation and analysis. **Applicability**: Patient: Results are most applicable to male patients in their mid-teens to mid-30s of East Asian/Pacific Rim or Northern European heritage. Study enrolled primarily male population with limited diversity (White 67%, Asian 29%). Study excluded 265/671 (39%) patients initially screened including participants recently prescribed glucocorticoids and also those with >25% glomeruli cellular crescents, which may have decreased proportion of patients with rapidly progressing disease. Intervention: The dose of sparsentan is appropriate based on phase 2 studies. Comparator: Active treatment with RAS inhibitor such as irbesartan in patients with proteinuria >0.5 g/d is standard of care. Outcomes: Substantial reduction in proteinuria as a reasonably likely surrogate endpoint for IgAN disease progression.[1] Setting: 156 sites, 18 countries

Abbreviations: AC=active control; ACEi = angiotensin converting enzyme inhibitors; AE = adverse event; ARB = angiotensin (II) receptor blocker; ARR = absolute risk reduction; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; DB = double blind; D/C = discontinued; eGFR = estimated glomerular filtration rate; GMR = Ratio of Geometric Mean; HTN = hypertension; IAS = interim analysis set; IgA(N) = Immunoglobulin A (nephropathy); ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PG = parallel group; PP = per protocol; RAAS = renin-angiotensin-aldosterone system; RCT = randomized controlled trial; SAE = serious adverse event; SGLT-2 = sodium glucose co-transporter-2 inhibitors; UP = urinary protein; UPCR = urine protein-to-creatinine ratio

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Appendix 1: Prescribing Information Highlights

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

FILSPARI™ (sparsentan) tablets, for oral use
Initial U.S. Approval: 2023

WARNING: HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **FILSPARI is only available through a restricted distribution program called the FILSPARI Risk Evaluation and Mitigation Strategies (REMS) because of these risks (5.3):**
- **Some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure (5.1).**
- **Measure liver aminotransferases and total bilirubin prior to initiation of treatment and ALT and AST monthly for 12 months, then every 3 months during treatment (2.2, 2.5, 5.1).**
- **Interrupt treatment and closely monitor patients developing aminotransferase elevations more than 3x Upper Limit of Normal (ULN) (2.2, 2.5).**
- **Based on animal data, FILSPARI can cause major birth defects if used during pregnancy (4, 5.2, 8.1).**
- **Pregnancy testing is required before, during, and after treatment (2.2, 4, 5.2, 8.1).**
- **Patients who can become pregnant must use effective contraception prior to initiation of treatment, during treatment, and for one month after (4, 5.3, 8.1, 8.3).**

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

FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g (1, 12.1).

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

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

- Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists (ERAs) or aliskiren (2.1, 4, 7.1).
- Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated. When resuming treatment with FILSPARI after an interruption, consider titration of FILSPARI, starting at 200 mg once daily. After 14 days, increase to the recommended dose of 400 mg once daily (2.3).
- Instruct patients to swallow tablets whole with water prior to the morning or evening meal (2.4).

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

Tablets: 200 mg and 400 mg (3).

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

- Pregnancy (4).
- Do not coadminister FILSPARI with angiotensin receptor blockers, endothelin receptor antagonists, or aliskiren (4).

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

- Hepatotoxicity (5.1)
- Embryo-Fetal Toxicity (5.2)
- Hypotension (5.4)
- Acute Kidney Injury (5.5)
- Hyperkalemia (5.6)
- Fluid Retention (5.7)

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

Most common adverse reactions (≥5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Travere Therapeutics at 1-877-659-5518 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Renin-Angiotensin System (RAS) inhibitors and ERAs: Contraindicated. Increased risk of hypotension, hyperkalemia (2.1, 4, 7.1).
- Strong CYP3A inhibitors: Avoid concomitant use. Increased sparsentan exposure (2.6, 7.2, 12.3).
- Moderate CYP3A inhibitors: Monitor adverse reactions. Increased sparsentan exposure (7.2, 12.3).
- Strong CYP3A inducers: Avoid concomitant use. Decreased sparsentan exposure (7.3, 12.3).
- Antacids: Avoid use within 2 hours before or after use of sparsentan. May decrease exposure to sparsentan (7.4, 11).
- Acid reducing agents: Avoid concomitant use. May decrease exposure to sparsentan (7.4).
- Nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase (COX-2) inhibitors: Monitor for signs of worsening renal function. Increased risk of kidney injury (7.5).
- CYP2B6, 2C9, and 2C19 substrates: Monitor for efficacy of the concurrently administered substrates. Decreased exposure of these substrates (7.6, 12.3).
- Sensitive P-gp and BCRP substrates: Avoid concomitant use. Increased exposure to substrates (7.7, 12.3).
- Agents Increasing Serum Potassium: Increased risk of hyperkalemia, monitor serum potassium frequently (5.6, 7.8).

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

- Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2023

Sparsentan

Goal(s):

- To promote use that is consistent with medical evidence and product labeling in patients with immunoglobulin A nephropathy (IgAN).
- To ensure appropriate use of sparsentan in populations with clinically definite IgAN.
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- Up to 12 months

Requires PA:

- Sparsentan

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 patient ≥ 18 years of age with diagnosis of IgAN confirmed by biopsy?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy for a patient who has received ≥ 6 months of initial therapy with this agent?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the medication going to be used in combination with any renin-angiotensin-aldosterone antagonists (e.g. angiotensin converting enzyme inhibitors or angiotensin receptor blockers), endothelin receptor antagonists [ERAs], or aliskiren?	**Yes:** Pass to RPh. Deny; medical appropriateness Use of sparsentan and any these agents is contraindicated.	**No:** Go to #6

Approval Criteria		
6. Is the prescriber a specialist in the management of IgAN (e.g. nephrologist)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient at high risk of disease progression, defined as a 24-hour urine collection that indicates: • Proteinuria > 1.0 g/day; -OR- • Urine protein-to-creatinine ratio ≥ 1.5 g/g?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Will the prescriber attest that the patient received the maximum or maximally tolerated dose of ONE of the following for ≥ 12 weeks prior to starting sparsentan: • Angiotensin converting enzyme inhibitor • Angiotensin receptor blocker -OR- is there documentation that the patient has an intolerance or contraindication to renin-aldosterone-angiotensin system (RAAS) inhibitors?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient received ≥ 3 months of optimized supportive care, including blood pressure management, lifestyle modification, and cardiovascular risk modification, according to the prescriber?	**Yes**: Approve for 9 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the prescriber documented a positive patient response to sparsentan therapy such as: • eGFR that is not declining? • Stabilization or improvement of proteinuria? • No progression to dialysis?	**Yes**: Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Antifungals

Date of Review: December 2023

Date of Last Review: February 2022 (oral); November 2019 (topical)
Dates of Literature Search: 09/01/2019 - 10/01/2023
Generic Name: oteseconazole
Brand Name (Manufacturer): Vivjoa (Mycovia Pharmaceuticals, Inc)
Dossier Received: no

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

Purpose for Class Update:
To evaluate new literature since the last reviews on oral and topical antifungal therapies. Evidence for the newly approved therapy for recurrent vulvovaginal candidiasis (RVVC), oteseconazole, will be critically evaluated and changes to the preferred drug list (PDL) will be updated if appropriate.

Plain Language Summary:
- Providers prescribe antifungal medicines to treat infections that are caused by fungus. Antifungals can be applied on the skin or taken by mouth.
- A high quality review looked at treatments for fungal infections in the vagina. Antifungals taken by mouth and antifungals applied topically into the vagina were similar in the short term (5 to 15 days) for improving symptoms of the infection.
- The Centers for Disease Control and Prevention (CDC) recommends either topical or oral antifungals to treat vaginal fungal infections.
- The Food and Drug Administration (FDA) approved a new medicine called oteseconazole to treat fungal infections in the vagina. The FDA approved oteseconazole for people that have 3 or more vaginal infections per year. Compared to a sugar pill (placebo), oteseconazole cured more vaginal infections.
- The Oregon Health Authority will pay for antifungals to treat serious fungal infections. Antifungals can be covered for minor fungal infections if people have conditions that could lead to complications. The Drug Use Research and Management group does not recommend any changes to this policy. We recommend that the Oregon Health Authority only pay for oteseconazole for patients who cannot get pregnant because of safety concerns. This process is called prior authorization.

Research Questions:
1. Is there new comparative evidence related to efficacy for the oral and topical antifungals for important outcomes (e.g., clinical cure or mycological cure)?
2. Is there new comparative evidence for harms for oral and topical antifungals?
3. What is the comparative evidence for efficacy and harms for oteseconazole?
4. Are there any subpopulations, such as people living in a congregate setting, who have more benefit or suffer more harm from antifungal therapy?

Author: Kathy Sentena, PharmD

Conclusions:

- There was one systematic review, one new guideline, one new drug, and 8 new safety warnings included in this review.
- A Cochrane review of the efficacy and safety of antifungals for the treatment of vulvovaginal candidiasis (VCC) found moderate quality of evidence that oral and intravaginal antifungal therapies had similar clinical cure rates in the short term (odds ratio [OR] 0.91; 95% confidence interval [CI], 0.91 to 1.43).[1] Oral therapies had higher mycological cure rates compared to intravaginal treatments in the short term (5-15 days) (OR 1.24; 95% CI, 1.03 to 1.50) and in the long term (OR 1.29; 95% CI, 1.05 to 1.60) (moderate quality evidence). All data for adverse events (AE) was considered to be of low quality.
- In 2021, the Centers for Disease Control and Prevention (CDC) published guidance for the treatment of VCC infections and RVVC infections.[2] Azole antifungals were recommended for acute treatment; however, there was no preference for one therapy over another.
- Since the last review, there have been 8 new FDA-issued safety warnings, detailed below, for the following drugs: fluconazole, flucytosine, ibrexafungerp, isavuconazonium, itraconazole, posaconazole, tinidazole, metronidazole, fexinidazole and voriconazole.
- Oteseconazole is a new therapy approved by the FDA for RVVC. There is moderate strength of evidence from 2 trials that oteseconazole is more effective than placebo to resolve symptoms of RVVC with a number to treat (NNT) of 3.[3,4] The most common adverse events (AEs) were nausea and headache.
- There was insufficient evidence on the use of antifungals in people living in congregate settings. Topical therapies are recommended for women who are pregnant.[2]

Recommendations:

- No changes to the preferred drug list (PDL) for oral and topical antifungals are recommended based on review of the evidence.
- Recommend renaming the topical antifungal class to reflect the inclusion of vaginal antifungal agents.
- Maintain oteseconazole as non-preferred and subject to prior authorization (PA) criteria.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Presentation of the evidence in the 2022 oral antifungal class update and in the 2019 topical antifungal class update resulted in no changes to the PDL.
- Clotrimazole, fluconazole and nystatin are preferred oral antifungals on the PDL and miconazole and nystatin are preferred topical agents (see **Appendix 1**).
- Griseofulvin, itraconazole, and terbinafine require a PA due to limited use beyond onychomycosis, which is an unfunded condition (see **Appendix 5**).
- Voriconazole and posaconazole are indicated for the treatment of invasive aspergillosis and require PA approval by a hematologist, oncologist or infectious disease specialist.
- Oregon Health Plan (OHP) does not fund the treatment of candidiasis of the mouth, skin, nails or dermatophytosis of nail, groin, scalp, and other dematophytosis in immune competent patients.
- Quarterly expenditures are modest for the antifungal class. Ninety-eight percent of claims were for preferred oral therapies and 78% claims for topical therapies were for preferred products.

Background:

Oral and topical antifungal drugs are used to treat a wide spectrum of infections. Serious fungal infections are usually seen in individuals with compromised immune systems, such as prolonged neutropenia, allogenic hematopoietic stem cell transplant and acquired immunodeficiencies. Serious fungal infections typically require oral or intravenous antifungal therapy.[5]

Antifungals can be categorized as azoles, echinocandins, polyenes, allylamines or nucleoside analogs.[6] Choice of antifungal depends on indication, causative organism and resistance patterns. Caspofungin, anidulafungin and micafungin are echinocandins with similar spectrum of action but differing dosing and drug interaction profiles. Echinocandins are most commonly used for serious fungal infections such as invasive candidiasis and as empiric therapy in patients with neutropenic fever.[7] Additionally, echinocandins have been used for salvage therapy in patients with invasive aspergillosis. Amphotericin deoxycholate, liposomal amphotericin and nystatin are polyene antifungals. Because high risk of nephrotoxicity is associated with systemic formulations of polyenes, these therapies are designated as second-line options for invasive aspergillosis and candidiasis infections. Allylamine antifungals consist of antofine and terbinafine. Flucytosine works by a different mechanism of action that allows for use in combination with amphotericin B for severe cryptococcal pneumonia and meningocephalitis, with a limited role in select invasive candidiasis infections. Due to high levels of resistance, flucytosine is not commonly used as monotherapy.[8] Drug interactions are common with antifungals and concomitant medications should be considered upon initiation.

Azole antifungals are categorized as either triazoles or imidazoles (e.g., fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole and ketoconazole). The azole antifungals are effective in treating several types of fungal infections: candidiasis, aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis. Fluconazole is most commonly recommended first-line for a majority of fungal infections due to efficacy and tolerability. Of the azole antifungals, posaconazole and isavuconazole have the broadest spectrum of action and are not associated with nephrotoxicity. There is wide variability between the different antifungals in their bioavailability and types of drug interactions (due to metabolism via the cytochrome P450 enzyme system).

Gastrointestinal issues are the most common adverse reactions associated with antifungal therapy. Hepatic manifestations from mild elevations in liver enzymes to hepatic failure have occurred. For these reasons, transaminase monitoring is recommended for patients receiving extended treatment with antifungal therapy. Drug monitoring is a recommended for itraconazole, voriconazole, and posaconazole to ensure efficacy and avoid toxicity. For the initial and salvage treatment of aspergillosis, triazole antifungals (e.g, voriconazole and posaconazole) are recommended.[5]

Antifungals are used for the treatment of VVC, which occurs in up to 75% of women in their lifetime.[9] *C. albicans* is the most common organism implicated in VVC infections, in which 80%-90% of resolve with the use of an azole antifungal.[9] Acute treatment recommendations include topical clotrimazole, miconazole, tioconazole, butoconazole and terconazole. Fluconazole is the only oral therapy for VVC. One of the components of this review is an evaluation of the efficacy and safety of a new drug for the treatment of RVVC, oteseconazole. Currently, there are no approved therapies for the treatment of RVVC. Recurrent VVC is defined as 3 or more infections within the previous 12 months. Guideline recommendations from the 2006 American College of Obstetricians and Gynecologists (ACOG) and the 2016 Infectious Disease Society of America (IDSA) (published prior to oteseconazole approval) for RVVC include using 2 therapies divided into induction regimens and longer maintenance regimens.[10] However, even maintenance regimens lasting up to 6 months do not guarantee a cure in the subsequent 6 months.

Important outcomes to determine antifungal efficacy include: symptom improvement, clinical cure (clinical symptoms), mycological cure (negative mycological test) and mortality. The FDA recommends that studies for VVC use a primary endpoint of complete absence of all signs and symptoms of VVC.[11] The vulvovaginal signs and symptom (VSS) score is a commonly used tool for determining the severity of VVC. The VSS score is used to access the signs and symptoms of VVC by a standardized, predefined scale, in which a numerical rating is assigned (absent = 0; mild = 1, moderate = 2, severe = 3). Vulvovaginal signs are edema, erythema, and excoriation and symptoms are defined as burning, itching, and irritation. Scores are calculated to determine a composite score, ranging from 0-18. Clinical cure is defined as a VSS score of 0 without additional antifungal treatment. Clinical improvement is defined as a score of 1 or less.[12]

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 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:
Cochrane – Oral versus Intra-vaginal Imidazole and Triazole Antifungal Treatment
A 2020 Cochrane review evaluated the use of antifungals in the treatment of VVC administered topically and vaginally. Women 16 years old and older with uncomplicated VVC with a mycological diagnosis (e.g., positive culture, microscopy for yeast, or both) were included.[1] Women with a diagnosis of HIV, or who were immunocompromised, pregnant, breast feeding or diabetic were excluded. Twenty-six trials were included (n=5007) with 23 trials evaluating acute VVC and 3 trials evaluating chronic VVC.[1] Follow-up ranged from 5 to 15 days (short term) for most trials. Two oral treatments were included, fluconazole and itraconazole, and six intravaginal treatments (butoconazole, clotrimazole, econazole, miconazole, sertaconazole, and terconazole) were studied. Main outcomes of interest were clinical cure (disappearance of symptoms either upon examination or by self-report), mycological cure (laboratory test determining no presence of VVC by mycological culture or microscopy), symptom reduction and side effects.

Clinical cure rate of candidiasis for oral compared to intra-vaginal therapy were no different in short term cure, 790 per 1000 versus 767 per 1000 (OR 0.91; 95% CI, 0.91 to 1.43) based on moderate quality evidence.[1] Long term (2 to 12 weeks) cure rates were also similar between oral and intravaginal treatments; OR 1.07 (95% CI, 0.77 to 1.50; moderate evidence). [1] There was moderate-quality evidence that mycological cure rates were higher in those treated with oral therapies compared to intravaginal treatments in the short term (OR 1.24; 95% CI, 1.03 to 1.50) and long term (OR 1.29; 95% CI, 1.05 to 1.60).[1] Withdrawals due to adverse events were reported by 3 trials, 2 withdrawals for intravaginal treatments and one for oral treatments (high quality of evidence). There was low-quality evidence of no difference for the number of AEs and preference to route of treatment.

After review, 3 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[13–16]

New Guidelines:
Centers for Disease Control - Sexually Transmitted Infections Treatment Guidelines
In 2021 the CDC updated guidance for the treatment of sexually transmitted infections (STIs), which included recommendations for the treatment of VVC.[2] The guidelines separate VVC into 2 severities; uncomplicated and complicated. Uncomplicated VVC is characterized by sporadic or infrequent VVC which is associated with mild to moderate symptoms most likely due to *C. albicans* in women who are non-immunocompromised. Complicated VVC is due to recurrent VVC (3 or more episodes of symptomatic VVC in less than 1 year) or severe VVC symptoms or due to an organism other than non-albicans candidiasis or women with diabetes, immunocompromising conditions, underlying immunodeficiency or immunosuppressive therapy.[2] Treatment options are outlined in **Table 1**.

Treatment recommendations for uncomplicated VVC include topical formulations, given as a single dose or 1-3 day regimens. Severe VVC should be diagnosed by vaginal culture or polymerase chain reaction (PCR) to determine organism and confirm diagnosis. Recurrent VVC caused by *C. albicans* should be treated with short-duration oral or topical azole therapy.[2] Initial therapy lasting 7-14 days for topicals or oral fluconazole 100 mg, 150 mg, or 200 mg every third dose for a total of 3 doses for recurrent VVC is recommended. Maintenance therapy, which may be indicated in some women, is typically oral fluconazole 100 mg, 150 mg or 200 mg weekly for 6 months. Severe VVC can be treated with 7-14 days of topical azoles or oral fluconazole 150 mg in 2 sequential oral doses (second dose 72 hours after initial dose).[2] Infections thought to be caused by non-albicans VVC should be treated with non-fluconazole azole (e.g., miconozole) regimens of 7-14 days (oral or topical).[2] If infection reoccurs then boric acid 600 mg administered vaginally daily for 3 weeks is recommended.

In women who are immunocompromised, treatment with a more prolonged course may be needed for acute VVC (7-14 days).[2] Women who are pregnant should be treated with topical azole therapy for 7 days.[2] Fluconazole is not recommended due to possible increase in spontaneous abortion.

Table 1. Centers for Disease Control and Prevention Recommended Treatments for Vulvovaginal Candidiasis[2]

Drug	Dose	Prescription status
Clotrimazole 1% cream	5 gm intravaginally daily for 7-14 days	OTC
Clotrimazole 2% cream	5 gm intravaginally daily for 3 days	OTC
Miconazole 2% cream	5 gm intravaginally daily for 7 days	OTC
Miconazole 4% cream	5 gm intravaginally daily for 3 days	OTC
Miconazole 100 mg vaginal suppository	1 suppository daily for 7 days	OTC
Miconazole 200 mg vaginal suppository	1 suppository daily for 3 days	OTC
Miconazole 1,200 mg vaginal suppository	1 suppository for 1 day	OTC
Tioconazole 6.5% ointment	5 gm intravaginally in a single application	OTC
Butoconazole 2% cream	5 gm intravaginally in a single application (single-dose bioadhesive product)	Prescription
Terconazole 0.4% cream	5 gm intravaginally daily for 7 days	Prescription
Terconazole 0.8% cream	5 gm intravaginally daily for 3 days	Prescription
Terconazole 80 mg vaginal suppository	1 suppository daily for 3 days	Prescription
Fluconazole 150 mg orally	1 tablet for 1 dose	Prescription
Abbreviations: OTC =over thee counter		

Adverse events experienced with topical treatments include itching and burning. Oral therapy can cause nausea, abdominal pain and headache. Liver enzyme elevations have been associated with oral azoles, unrelated to dose or duration of therapy. Topical products may weaken latex condoms and diaphragms and patients should refer to manufacturer recommendations on use.

New Formulations or Indications:
No new formulations or indications.

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Fluconazole[17]	DIFLUCAN	7/2023	Drug Interactions	Use with ivacaftor causes a 3-fold increase in ivacaftor. Reduction in ivacaftor dose is recommended. Use with lurasidone may increase lurasidone concentrations. Reduce dose of lurasidone if concomitant use cannot be avoided.
Flucytosine[18]	ANCOBON	2/2022	Contraindications	Use is contraindicated in people with complete dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.
Ibrexafungerp[19]	BREXAFEMME	11/2022	Boxed Warning	There is a new boxed warning of the risk of embryo-fetal toxicity with ibrexafungerp use. It is contraindicated in pregnancy due to fetal harm demonstrated in animal studies. Contraception should be used during treatment and 4 days after discontinuation.
Isavuconazonium[20]	CRESEMBA	12/2021	Warnings and Precautions	Anaphylaxis with fatal outcomes have been reported with the use of isavuconazonium and use should be discontinued if symptoms (e.g., hypotension, generalized erythema and flushing and urticaria) are reported.
Itraconazole[21]	SPORANOX	12/2022	Boxed Warning	Administration of itraconazole with venetoclax is contraindicated in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) during the dose initiation and ramp-up phase of venetoclax.
Posaconazole[22]	NOXAFIL	1/2022	Contraindications	Posaconazole should not be used with venetoclax at initiation and during ramp-up phase in patients with CLL or SLL due to increase in risk of tumor lysis syndrome.
Tinidazole[23] Metronidazole[24] Fexinidazole[25]	TINDAMAX FLAGYL	12/2021	Warnings and Precautions	Warnings against use in people with Cockayne Syndrome which can cause severe irreversible hepatotoxicity/acute liver failure and death.
Voriconazole[26]	VFEND	10/2022	Warnings and Precautions	Photosensitivity skin reactions have been reported. Direct sun exposure should be avoided. Reactions have ranged from premalignant conditions to cutaneous lupus erythematosus with a higher incidence in pediatric populations. An increased risk of skin toxicity with concomitant use of methotrexate has also been reported.

Randomized Controlled Trials:
A total of 204 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 DRUG EVALUATION: Oteseconazole (VIVJOA)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Oteseconazole is a selective inhibitor of fungal lanosterol demethylase, the enzyme required for fungal growth.[27] Oteseconazole is FDA-approved to reduce the incidence of recurrent VVC in females with a history of RVVC and are not of reproductive potential.[27] Oteseconazole can be used as induction therapy and maintenance therapy or in combination with fluconazole (as induction therapy). As monotherapy, oteseconazole is given as a single 600 mg dose on day 1 followed by a 450 mg dose on day 2.[27] Starting on day 14, oteseconazole 150 mg should be given once weekly for 11 weeks. If oteseconazole is given with fluconazole, the regimen should be the following: fluconazole 150 mg orally on day 1, day 4 and day 7; on days 14 thru 20 oteseconazole 150 mg once daily for 7 days then on day 28 give oteseconazole 150 mg once a week for 11 weeks.[27] Approval was based on 2 identical trials comparing oteseconazole to placebo (after fluconazole induction) and a third study comparing oteseconazole to placebo after either oteseconazole or fluconazole induction, specific trial details are provide in **Table 3**. Induction treatment is used to clear the acute VVC infection.

The VIOLET studies (n=656) were 2 identical phase 3, multi-center, double-blind, placebo-controlled randomized trials.[3] The majority of participants were generally healthy White women (89%), with a mean age of 34 years, that responded to treatment of an acute VVC episode with fluconazole (induction phase) who had a history of RVVC (defined as ≥3 episodes of VVC in a 12-month period).[3] Oteseconazole is contraindicated in females of reproductive potential due to the risk of embryo-fetal toxicity; however some females of reproductive potential were included in the trials. Participants were given 150 mg of oteseconazole daily for 7 days and then once weekly for 11 weeks or matching placebo for 12 weeks using the same dosing protocol. Participants that did not have resolution of infection during the induction phase did not enter the maintenance phase but were included in the intention to treat (ITT) analysis. The primary endpoint was the averaged percentage of patients with one or more RVVC episode through week 48.

Results from both trials included in VIOLET found oteseconazole to be superior to placebo for the primary endpoint at week 48. In study 1 there were 6.7% (n= 15) of participants that had one or more episodes of RVVC compared to 42.8% (n=93) of placebo treated patients (P<0.001)(CI not provided).[3] In the second study, 3.9% (n=9) of patients in the oteseconazole groups experienced one or more episodes of RVVC compared to 39.4% (n=86) of those treated with placebo (P<0.001).[3] In 87% of women with RVVC, the primary causative organism was *C. albicans*.

A third study evaluated the safety and efficacy of oteseconazole in the treatment of RVVC in a randomized, double-blind, multicenter trial. Patients were a mean age of 35 years old, 59% were White and 7% had diabetes. Patients were randomized to oteseconazole induction/oteseconazole maintenance phase or fluconazole induction/placebo maintenance phase. For the primary endpoint of the proportion of patients with 1 or greater culture-verified acute VVC episode through week 50, oteseconazole was superior to placebo (absolute risk reduction [ARR] 37.1%/NNT 3). A key secondary endpoint was the proportion of patients with a resolved acute VVC in the induction phase, which oteseconazole was non-inferior to fluconazole, 93.2% versus 95.8%, respectively (p-value not reported).

Trial limitations include insufficient evidence on repeat cycles of oteseconazole and use in women that have underlying disease states such as diabetes or HIV that are predisposed to developing VVC. The use of fluconazole 150 mg for induction could underestimate the treatment effect since a dose of 200 mg fluconazole is also appropriate.

Clinical Safety:
The most common adverse reactions experienced during clinical trials were headache and nausea.[27] Other AEs that occurred in 2% or less of people treated with oteseconazole included increased blood creatinine phosphokinase, dyspepsia, hot flush, dysuria, menorrhagia, and vulvovaginal irritation.[27] Oteseconazole may cause fetal harm based on animal studies and is contraindicated in people who are of reproductive age and if they are pregnant or lactating.[27] Oteseconazole has a half-life of 138 days and women should be informed of these implications before using. There were similar numbers of patients treated with oteseconazole and placebo that withdrew from RCTs due to treatment emergent adverse events (TEAE) and those with serious AEs.[27]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Clinical cure
2) Mycological cure
3) Recurrent infections
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Proportion of patients with ≥1 culture-verified acute VVC episode (positive fungal culture for Candida species associated with a clinical signs and symptoms score of ≥3)

Table 3. Pharmacology and Pharmacokinetic Properties.[27]

Parameter	
Mechanism of Action	Azole metalloenzyme inhibitor targeting the fungal sterol, 14α demethylase (CYP51) with a lower affinity for human CYP enzymes
Oral Bioavailability	73% - 100% (with food)
Distribution and Protein Binding	423 L 99.5 to 99.7% bound to plasma proteins
Elimination	56% in the feces and 26% in the urine
Half-Life	138 days
Metabolism	Not significantly metabolized

Abbreviations: CYP = cytochrome; L = liter

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. Martens, et al[4] (ultraVIOLET) DB, MC, Phase 3, RCT	1. Oteseconazole 600 mg on day 1 and 450 mg on day 2 then oteseconazole 150 mg weekly for 11 weeks† 2. Fluconazole 150 mg every 72 hours for 3 doses then placebo weekly for 11 weeks Treatment: 2-week induction phase followed by maintenance phase for 11 weeks* † Maintenance dose of oteseconazole 150 mg or placebo weekly Follow-up: 37 weeks	Demographics: Age: 35 years White: 59% Black: 34% Hispanic or Latino: 26% Diabetes: 7% Acute VVC in past 12 months:5 Candida Albicans at baseline: 40% Key Inclusion Criteria: - Women and girls 12 years and older - History of RVVC (defined as 3 or more episodes of acute VVC in the past 12 months) - Active vulvovaginal candidiasis infection (at least 1 episode documented positive by culture, PCR, Affirm test, KOH test, positive vaginal smear or other approved diagnostic test; confirmation of acute VCC defined by total score of 3 or greater for vulvovaginal signs and symptoms; positive KOH wet mount preparation from vaginal smear with hyphae or pseudohyphae and/or budding yeast cells) - Negative pregnancy test Key Exclusion Criteria: - Vaginal infection other than acute VVC - use of systemic antifungal therapy 7 or less days before screening immunosuppressive therapy - Major organ disease - Absence of contraception	ITT: 1. 147 2. 72 PP: 1. 103 2. 51 Attrition: 1. 44 (30%) 2. 21 (29%)	Primary Endpoint: Proportion of participants with 1 or greater culture-verified acute VVC episode through week 50: Oteseconazole: 8 (5.1%) Fluconazole: 31 (42.2%) (CI not provided) P<0.001 Secondary Endpoints: Resolved acute VVC infection at day 14 : Oteseconazole: 93.1% (n=96) Fluconazole: 50 98.3% (n=50) MD 5.2% (95% CI, -10.7 to 0.2) Lower limit of non-inferiority margin was above -12.5; non-inferiority achieved	ARR 37.1%/ NNT 3 NA	Serious TEAE: 1. 3 (2%) 2. 1 (1%) Discontinuations due to TEAE: 1. 1 (<1%) 2. 0 Urinary tract infections: 1. 18 (12%) 2. 12 (17%) Bacterial vaginosis: 1. 16 (11%) 2. 11 (15%) Skin and subcutaneous tissue disorders: 1. 10 (7%) 2. 3 (4%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 2:1 by interactive web response system. Baseline characteristics were similar between groups. Performance Bias: (Low) Blinded with use of matching placebo. Same number of capsules provided per group. Detection Bias: (Unclear) Not described. Attrition Bias: (High) High attrition in both groups due to induction failure (14%) and lost to follow-up (5%). Missing values were imputed by multiple imputation. Primary analysis was done on the ITT population and secondary analysis was done on the per protocol population to determine non-inferiority. Reporting Bias: (High) Trial conducted as stated. Lack of CI limits ability to interpret results. Other Bias: (Unclear) Manufacturer funded. **Applicability**: Patient: Results are most applicable to women with recurrent VVC and in their 30's without diabetes. Seventy-six percent of RVVC isolates were *C albicans*. Intervention: Oteseconazole dose was appropriate based on other trials and FDA labeling. Comparator: Active treatment comparison to fluconazole in induction phase was appropriate; however a 200 mg dose is also appropriate. There were a high number of non-albicans Candida at baseline, in which optimal treatment is unknown however a non-fluconazole regimen is recommended. Placebo comparison in the maintenance phase was appropriate since fluconazole is not approved for RVVC. Outcomes: Outcomes are appropriate to determine efficacy of antifungal treatment. Setting: Thirty-eight US sites.

2. Sobel, et al‡[3] VIOLET (2 trials with same design) DB, MC, PC, Phase 3, RCT	1. Oteseconazole 150 mg daily for 7 days and then once weekly for 11 weeks* 2. Matching placebo for 12 weeks* * All patients entered an induction phase of fluconazole 150 mg every 72 hours for 3 doses (with matching placebo capsules) Follow up: 48 weeks	Demographics (pooled): Age: 34 years White: 80.5% Black: 11.5% Hispanic or Latino: 11.5% Diabetes: 2.5% Acute VVC episodes in past 12 months: 4 Candida Albicans: 51% Key Inclusion Criteria: - Women 12 and older with 3 or more symptomatic acute VCC within the previous 12 months (recurrent VVC) presenting with acute VVC - screening episode cleared with fluconazole induction therapy Key Exclusion Criteria: - Vaginal infection other than acute VVC - Use of systemic antifungal therapy 7 or less days before screening - Renal or hepatic impairment	ITT: 1. 435 2. 217 PP: 1. 324 2. 162 Attrition: 1. 111 (25.5%) 2. 55 (25.3%)	Study 1: Primary Endpoint: Averaged percentage of participants with 1 or greater culture-verified acute VVC episode through week 48. 1. 15 (6.7%) 2. 47 (42.8%) CI not reported P<0.001 Study 2: Primary Endpoint: Averaged percentage of participants with 1 or greater culture-verified acute VVC episode through week 48. 1. 9 (3.9%) 2. 43 (39.4%) CI not reported P<0.001 Secondary Endpoints: Study 1: Time to first recurrence of culture-verified VVC through week 48: 1. 45.7 weeks 2. 27.8 weeks HR 0.11 95% CI, 0.06 to 0.21 P<0.001 Study 2: Time to first recurrence of culture-verified VVC through week 48: 1. 47.2 weeks 2. 33.1 weeks HR 0.08 95% CI, 0.04 to 0.17 P<0.001	ARR 36%/ NNT 3 ARR 36%/ NNT 3	Serious TEAE: 1. 10 (2.3%) 2. 8 (3.6%) Discontinuations due to TEAE: 1. 3 (<1%) 2. 1 (<1%) Urinary tract infections: 1. 24 (5.5%) 2. 11 (5.0%) Bacterial vaginosis: 1. 28 (6.5%) 2. 17 (7.8%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized design through an IWRS used to assign subjects in a 2:1 ratio to the dose regimen of oteseconazole or placebo. Baseline characteristics were well matched. Performance Bias: (Low) Participants and trial personnel were blinded to treatment assignment. Placebo and oteseconazole were identical in appearance. Detection Bias: (Unclear) Not described. Attrition Bias: (High) More than 10% attrition in both groups. Primary endpoint was analyzed via ITT. Missing values were imputed by multiple imputation. Reporting Bias: (Low) Trial was conducted as reported. Other Bias: (Unclear) Manufacturer funded. **Applicability**: Patient: Applies mostly to patients with RVVC who are White that responded to initial fluconazole therapy. Intervention: Dose of oteseconazole was appropriate based on data from phase 2 studies. Comparator: Placebo comparison appropriate since there are no other approved treatments for RVVC. Outcomes: Recurrent VVC episode is an appropriate primary endpoint. Setting: In one study 97 sites were in North America, Japan and Europe and in the second study 84 centers were in North America and Europe. Thirty-eight percent of participants in the first trial and 36% of participants in the second trial were from the US.

Key: * Only participants with resolved acute VC infection (clinical signs and symptoms score of <3) entered the maintenance phase; ‡ Pooled results from 2 identical trials

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; ITT = intention to treat; IWRS = interactive web response system; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; RVVC = recurrent vulvovaginal candidiasis; VVC = vulvovaginal candidiasis

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Antifungals, Oral

Generic	Brand	Form	PDL
clotrimazole	CLOTRIMAZOLE	TROCHE	Y
fluconazole	DIFLUCAN	SUSP RECON	Y
fluconazole	FLUCONAZOLE	SUSP RECON	Y
fluconazole	DIFLUCAN	TABLET	Y
fluconazole	FLUCONAZOLE	TABLET	Y
nystatin	MYCOSTATIN	ORAL SUSP	Y
nystatin	NYSTATIN	ORAL SUSP	Y
nystatin	NYSTATIN	TABLET	Y
flucytosine	ANCOBON	CAPSULE	N
flucytosine	FLUCYTOSINE	CAPSULE	N
griseofulvin ultramicrosize	GRISEOFULVIN ULTRAMICROSIZE	TABLET	N
griseofulvin, microsize	GRISEOFULVIN	ORAL SUSP	N
griseofulvin, microsize	GRISEOFULVIN	TABLET	N
ibrexafungerp citrate	BREXAFEMME	TABLET	N
isavuconazonium sulfate	CRESEMBA	CAPSULE	N
itraconazole	TOLSURA	CAP SD DSP	N
itraconazole	ITRACONAZOLE	CAPSULE	N
itraconazole	SPORANOX	CAPSULE	N
itraconazole	ITRACONAZOLE	SOLUTION	N
itraconazole	SPORANOX	SOLUTION	N
ketoconazole	KETOCONAZOLE	TABLET	N
miconazole	ORAVIG	MA BUC TAB	N
oteseconazole	VIVJOA	CAPSULE	N
posaconazole	NOXAFIL	ORAL SUSP	N
posaconazole	POSACONAZOLE	ORAL SUSP	N
posaconazole	NOXAFIL	SUSPDR PKT	N
posaconazole	NOXAFIL	TABLET DR	N
posaconazole	POSACONAZOLE	TABLET DR	N
terbinafine HCl	TERBINAFINE HCL	TABLET	N
voriconazole	VFEND	SUSP RECON	N
voriconazole	VORICONAZOLE	SUSP RECON	N
voriconazole	VFEND	TABLET	N
voriconazole	VORICONAZOLE	TABLET	N

Antifungals, Topical

Generic	Brand	Form	PDL
miconazole nitrate	MICONAZOLE NITRATE	CREAM (G)	Y
nystatin	NYSTATIN	CREAM (G)	Y
nystatin	NYSTATIN	OINT. (G)	Y
acetic ac/resorcino/salicyl ac	ANTIFUNGAL NAIL	TINCTURE	N
butenafine HCl	BUTENAFINE HCL	CREAM (G)	N
butenafine HCl	MENTAX	CREAM (G)	N
ciclopirox	CICLOPIROX	GEL (GRAM)	N
ciclopirox	CICLOPIROX	SHAMPOO	N
ciclopirox	LOPROX	SHAMPOO	N
ciclopirox	CICLODAN	SOLUTION	N
ciclopirox	CICLOPIROX	SOLUTION	N
ciclopirox olamine	CICLODAN	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	CREAM (G)	N
ciclopirox olamine	LOPROX	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	SUSPENSION	N
ciclopirox olamine	LOPROX	SUSPENSION	N
ciclopirox/skin cleanser no.28	CICLODAN	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	KIT SS-CLN	N
ciclopirox/urea/camph/men/euc	CICLODAN	SOLUTION	N
ciclopirox/urea/camph/men/euc	CICLOPIROX	SOLUTION	N
clotrimazole	ANTIFUNGAL	CREAM (G)	N
clotrimazole	ATHLETE'S FOOT	CREAM (G)	N
clotrimazole	CLOTRIMAZOLE	CREAM (G)	N
clotrimazole	FUNGOID	CREAM (G)	N
clotrimazole	LOTRIMIN AF	CREAM (G)	N
clotrimazole	MICOTRIN AC	CREAM (G)	N
clotrimazole	MYCOZYL AC	CREAM (G)	N
clotrimazole	ALEVAZOL	OINT. (G)	N
clotrimazole	CLOTRIMAZOLE	SOLUTION	N
clotrimazole	FUNGOID	SOLUTION	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	CREAM (G)	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	LOTION	N
econazole nitrate	ECONAZOLE NITRATE	CREAM (G)	N
efinaconazole	JUBLIA	SOL W/APPL	N
ketoconazole	KETOCONAZOLE	CREAM (G)	N
ketoconazole	EXTINA	FOAM	N

ketoconazole	KETOCONAZOLE	FOAM	N
ketoconazole	KETODAN	FOAM	N
ketoconazole	KETOCONAZOLE	SHAMPOO	N
ketoconazole/skin cleanser 28	KETODAN	COMBO. PKG	N
luliconazole	LULICONAZOLE	CREAM (G)	N
luliconazole	LUZU	CREAM (G)	N
miconazole nitrate	ATHLETE'S FOOT SPRAY	AERO POWD	N
miconazole nitrate	THERA ANTIFUNGAL	CREAM(ML)	N
miconazole nitrate	ALOE VESTA	OINT.(ML)	N
miconazole nitrate	ANTIFUNGAL POWDER	POWDER	N
miconazole nitrate	MICONAZORB AF	POWDER	N
miconazole nitrate	MICOTRIN AP	POWDER	N
miconazole nitrate	MYCOZYL AP	POWDER	N
miconazole nitrate	THERA ANTIFUNGAL	POWDER	N
miconazole nitrate	MICONAZOLE NITRATE	SOL W/APPL	N
miconazole nitrate	FUNGOID TINCTURE	TINCTURE	N
miconazole nitrate/zinc ox/pet	MICONAZOLE-ZINC OXIDE-PETROLTM	OINT. (G)	N
miconazole nitrate/zinc ox/pet	VUSION	OINT. (G)	N
naftifine HCl	NAFTIFINE HCL	CREAM (G)	N
naftifine HCl	NAFTIFINE HCL	GEL (GRAM)	N
naftifine HCl	NAFTIN	GEL (GRAM)	N
nystatin	NYAMYC	POWDER	N
nystatin	NYSTATIN	POWDER	N
nystatin	NYSTOP	POWDER	N
nystatin/triamcinolone acet	MYCONEL	CREAM (G)	N
nystatin/triamcinolone acet	MYTREX	CREAM (G)	N
nystatin/triamcinolone acet	N.T.A.	CREAM (G)	N
nystatin/triamcinolone acet	NYSTATIN-TRIAMCINOLONE	CREAM (G)	N
nystatin/triamcinolone acet	MYTREX	OINT. (G)	N
nystatin/triamcinolone acet	N.T.A.	OINT. (G)	N
nystatin/triamcinolone acet	NYSTATIN-TRIAMCINOLONE	OINT. (G)	N
oxiconazole nitrate	OXICONAZOLE NITRATE	CREAM (G)	N
oxiconazole nitrate	OXISTAT	LOTION	N
sertaconazole nitrate	ERTACZO	CREAM (G)	N
sulconazole nitrate	EXELDERM	CREAM (G)	N
sulconazole nitrate	EXELDERM	SOLUTION	N
tavaborole	KERYDIN	SOL W/APPL	N
tavaborole	TAVABOROLE	SOL W/APPL	N
terbinafine HCl	ATHLETE'S FOOT	CREAM (G)	N
terbinafine HCl	ATHLETE'S FOOT AF	CREAM (G)	N

terbinafine HCl	TERBINAFINE	CREAM (G)	N
tolnaftate	ATHLETE'S FOOT	AERO POWD	N
tolnaftate	TOLNAFTATE	AERO POWD	N
tolnaftate	ANTIFUNGAL CREAM	CREAM (G)	N
tolnaftate	FUNGOID-D	CREAM (G)	N
tolnaftate	TOLNAFTATE	CREAM (G)	N
tolnaftate	TOLNAFTATE	POWDER	N
tolnaftate	ANTIFUNGAL	SOLUTION	N
tolnaftate	MICOTRIN AL	SOLUTION	N
tolnaftate	MYCOZYL AL	SOLUTION	N
tolnaftate	TOLNAFTATE	SOLUTION	N
undecylenic ac/zinc undecylena	ANTIFUNGAL CREAM	CREAM (G)	N
undecylenic ac/zinc undecylena	UNDEX-25	OINT. (G)	N
clotrimazole	VOTRIZA-AL	LOTION	
econazole/triamcinolone	TRIAMAZOLE	CMB ONT CR	
gentian violet/brgreen/proflav	TRIPLE DYE	MED. SWAB	
gentian violet/brilliant green	TRIPLE DYE	LIQUID	

Antifungals, Vaginal

Generic	Brand	Form
butoconazole nitrate	GYNAZOLE 1	CRM/PF APP
clotrimazole	VAGINAL 3-DAY	COMBO. PKG
clotrimazole	3-DAY VAGINAL CREAM	CREAM/APPL
clotrimazole	CLOTRIMAZOLE	CREAM/APPL
clotrimazole	CLOTRIMAZOLE-3	CREAM/APPL
clotrimazole	CLOTRIMAZOLE	TABLET
miconazole nitrate	MICONAZOLE 3	CMB PF CRM
miconazole nitrate	MICONAZOLE 7	CREAM/APPL
miconazole nitrate	MICONAZOLE NITRATE	CREAM/APPL
miconazole nitrate	MICONAZOLE-7	CREAM/APPL
miconazole nitrate	YEAST-X	CREAM/APPL
miconazole nitrate	MICONAZOLE 1	KIT
miconazole nitrate	MICONAZOLE 3	KIT
miconazole nitrate	MICONAZOLE 3	SUPP.VAG
miconazole nitrate	MICONAZOLE 7	SUPP.VAG
miconazole nitrate	MICONAZOLE NITRATE	SUPP.VAG
terconazole	TERCONAZOLE	CREAM/APPL
terconazole	TERCONAZOLE	SUPP.VAG
tioconazole	TIOCONAZOLE-1	OIN/PF APP

Appendix 2: Medline Search Strategy

#	Searches	Results
1	clotrimazole.mp. or Clotrimazole/	3272
2	fluconazole.mp. or Fluconazole/	16337
3	Nystatin/ or nystatin.mp.	5543
4	flucytosine.mp. or Flucytosine/	4010
5	griseofulvin.mp. or Griseofulvin/	4059
6	ibrexafungerp.mp.	111
7	isavuconazonium.mp.	91
8	Itraconazole/ or itraconazole.mp.	11838
9	ketoconazole.mp. or Ketoconazole/	9831
10	miconazole.mp. or Miconazole/	3480
11	oteseconazole.mp.	32
12	posaconazole.mp.	3503
13	terbinafine.mp. or Terbinafine/	3490
14	voriconazole.mp. or Voriconazole/	8632
15	Nystatin/ or nystatin.mp.	5543
16	acetic.mp.	59749
17	butenafine.mp.	109
18	ciclopirox.mp. or Ciclopirox/	704
19	econazole.mp. or Econazole/	1053
20	efinaconazole.mp.	240
21	luliconazole.mp.	194
22	naftifine.mp.	220
23	oxiconazole.mp.	122
24	sertaconazole.mp.	164
25	sulconazole.mp.	99
26	tavaborole.mp.	145
27	tolnaftate.mp. or Tolnaftate/	304
28	undecylenic.mp.	394
29	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	116475
30	limit 29 to (english language and humans and yr="2019 -Current")	6996
31	limit 30 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	204

Appendix 3: Prescribing Information Highlights

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

VIVJOA™ (oteseconazole) capsules, for oral use
Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------
VIVJOA™ is an azole antifungal indicated to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are NOT of reproductive potential. (1)

----------DOSAGE AND ADMINISTRATION----------
- There are two recommended VIVJOA dosage regimens: a VIVJOA-only regimen and a Fluconazole/VIVJOA regimen. Use one of these two dosage regimens. (2.1)
  - Administer VIVJOA orally with food. (2.1)
- For the *VIVJOA-only Dosage Regimen*: (2.2)
  - **On Day 1:** Administer VIVJOA 600 mg (as a single dose), then
  - **On Day 2:** Administer VIVJOA 450 mg (as a single dose), then
  - **Beginning on Day 14**: Administer VIVJOA 150 mg once a week (every 7 days) for 11 weeks (Weeks 2 through 12).
- For the *Fluconazole/VIVJOA Dosage Regimen*, prescribe fluconazole and: (2.3)
  - **On Day 1**, **Day 4**, and **Day 7**: Administer fluconazole 150 mg orally, then
  - **On Days 14 through 20**: Administer VIVJOA 150 mg once daily for 7 days, then
  - **Beginning on Day 28**: Administer VIVJOA 150 mg once a week (every 7 days) for 11 weeks (Weeks 4 through 14).

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 150 mg of oteseconazole (fluconazole is not supplied in the carton). (3)

----------CONTRAINDICATIONS----------
- Females of Reproductive Potential (4), (5.1), (8.3)
- Pregnant and Lactating women (4), (8.1), (8.2)
- Hypersensitivity to oteseconazole (4)

----------WARNINGS AND PRECAUTIONS----------
Embryo-Fetal Toxicity: Based on animal studies, VIVJOA may cause fetal harm. The drug exposure window of approximately 690 days (based on 5 times the half-life of oteseconazole) precludes adequate mitigation of the embryo-fetal toxicity risks. Advise patients that VIVJOA is contraindicated in females of reproductive potential, and in pregnant and lactating women because of potential risks to a fetus or breastfed infant. (5.1, 8.1, 8.2, 8.3)

----------ADVERSE REACTIONS----------
The most frequently reported adverse reactions (incidence > 2%) were headache and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mycovia Pharmaceuticals, Inc. at 1-855-299-0637 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
BCRP (Breast Cancer Resistance Protein) Substrates: Concomitant use of VIVJOA with BCRP substrates may increase the exposure of drugs that are BCRP substrates, which may increase the risk of adverse reactions associated with these drugs. Use the lowest possible starting dose of the BCRP substrate or consider reducing the dose of the substrate drugs and monitor for adverse reactions. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Renal Impairment: Not recommended in severe renal impairment or ESRD (with or without dialysis). (8.6)
- Hepatic Impairment: Not recommended in moderate or severe hepatic impairment. (8.7)

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

Revised: 4/2022

Appendix 4: Key Inclusion Criteria

Population	Patients with active fungal infection
Intervention	Antifungals
Comparator	Placebo or active treatment
Outcomes	Mycological cure
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Antifungals

Goal(s):

- Approve use of antifungals only for OHP-funded diagnoses. Minor fungal infections of skin, such as dermatophytosis and candidiasis are only funded when complicated by an immunocompromised host.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- See criteria

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/

Table 1: Examples of FUNDED indications (10/19/23)

ICD-10	Description
B37.3	Candidiasis of vulva and vagina (vaginitis and cervicitis)
B37.1	Candidiasis of the lung
B37.7	Disseminated Candidiasis
B37.5-37.6, B37.81-37.84, B37.89-37.90	Candidiasis of other specified sites
B38.0-B38.4, B38.7, B38.9	Coccidiomycosis various sites

B39.0-39.5, B39.9, G02, I32, I39, J17	Histoplasmosis, subacute meningitis, acute bacterial meningitis
B40.9,B41.0, B41.9, B48.0	Blastomycosis
B42.0-42.9,, B43.9, B44.9-45.0, B45.7, B45.9, B46.9, B48.1-48.2~~,~~ ~~B48.8~~, B49	Rhinosporidiosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycosis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
B48.8	Mycosis, Opportunistic
B44.81	Bronchopulmonary Aspergillus, Allergic
N73.9-75.1~~, N75.9~~, N76.0-N77.1	Acute inflammatory pelvic disease~~Inflammatory disease of cervix vagina and vulva~~
L03.019,L03.029, L03.039, L03.049	Cellulitis and abscess of finger and toe
P37.5	Neonatal Candida infection
B37.42,B37.49	Candidiasis of other urogenital sites

Table 2: Examples of NON-FUNDED indications (12/16/21)

ICD-10	Description
L2.083, L2.10-2.11, L21.8-21.9,	Erythematosquamous dermatosis
L22	Diaper or napkin rash
L20.0-20.84, L20.89-20.9	Other atopic dermatitis and related conditions
L24.0-24.2, L25.1-25.5, L57.8, L57.9, L23.0, L23.81, L24.81, L25.0, L25.2, L25.8-25.9, L55.1-55.2 , L56.8, L58.9	Contact dermatitis and other eczema
L53.0-53.2, L51.0, L51.8-51.9, L52, L71.0-71.1, L71.8, L93.0, L93.2, L49.0-L49.9, L26, L30.4, L53.8, L92.0, L95.1, L98.2, L53.9	Erythematous conditions
L43.8,L44.1-44.3, L44.9,L66.1	Lichen Planus
L70.0-70.2, L70.8	Rosacea or acne
B35.1	Tinea unguium (onychomycosis)
B36.0	Pityriasis versicolor
B36.2	Tinea blanca
B36.3	Black piedra

B36.8, B36.9	Mycoses, superficial
B37.2	Cutaneous candidiasis
B37.9	Candidiasis, unspecified
R21	Rash and other nonspecific skin eruption

Table 3: Criteria driven diagnoses (12/16/21)

ICD-10	Description
B35.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
B35.2	Dermatophytosis of hand (tinea manuum)
B35.6	Dermatophytosis of groin and perianal area (tinea cruris)
B353	Dermatophytosis of foot (tinea pedis)
B35.5	Dermatophytosis of body (tinea corporis / tinea imbricate)
B35.8	Deep seated dermatophytosis
B35.8-B35.9	Dermatophytosis of other specified sites - unspecified site
B36.1	Tinea nigra
B37.83	Candidiasis of mouth

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by OHP? (See examples in Table 1).	**Yes:** Go to #3	**No:** Go to #7#4
3. Is the request for oteseconazole?	**Yes:** Go to #4	**No:** Go to #6
4. Does the patient have a diagnosis of recurrent vulvovaginal candidiasis (RVVC) defined as a history of 3 or more episodes of acute vulvovaginal candidiasis (VCC) in the previous 12 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the patient of reproductive potential?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 18 capsules for 12 months
6. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Approve for 3 months or course of treatment.
7. Is the prescriber a hematology, oncology or infectious disease specialty prescriber requesting voriconazole or posaconazole?	**Yes:** Approve for 3 months or course of treatment.	**No:** Go to #8
8. Is the diagnosis not funded by OHP? (see examples in Table 2).	**Yes:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by OHP Current age < 21 years: Go to #9	**No:** Got to #96
9. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	**Yes:** Go to #107	**No:** Current age ≥ 21 years: Go to #141 Current age < 21 years: Go to #141

Approval Criteria		
10. Is the patient immunocompromised (examples below)? • Does the patient have a current (not history of) diagnosis of cancer **AND** is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment. **OR** • Does the patient have a diagnosis of HIV/AIDS? **OR** • Does the patient have sickle cell anemia? • Poor nutrition, elderly or chronically ill? • Other conditions as determined and documented by a RPh.	**Yes:** Record ICD-10 code. Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Go to #11~~8~~

<table>
<tr><th colspan="3">Approval Criteria</th></tr>
<tr>
<td>11. Is the patient currently taking an immunosuppressive drug? Document drug.

Pass to RPh for evaluation if drug not in list.

Immunosuppressive drugs include but are not limited to:
<table>
<tr><td>azathioprine</td><td>leflunomide</td></tr>
<tr><td>basiliximab</td><td>mercaptopurine</td></tr>
<tr><td>cyclophosphamide</td><td>methotrexate</td></tr>
<tr><td>cyclosporine</td><td>mycophenolate</td></tr>
<tr><td>etanercept</td><td>rituximab</td></tr>
<tr><td>everolimus</td><td>sirolimus</td></tr>
<tr><td>hydroxychloroquine</td><td>tacrolimus</td></tr>
<tr><td>infliximab</td><td></td></tr>
</table>
</td>
<td>Yes: Approve as follows: (immunocompromised patient)

ORAL & TOPICAL
• Course of treatment.
• If length of therapy is unknown, approve for 3 months.</td>
<td>No: Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP

Current age < 21 years: Go to #129</td>
</tr>
<tr>
<td>12. 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)?</td>
<td>Yes: Go to #130</td>
<td>No: Pass to RPh. Deny; medical necessity.</td>
</tr>
</table>

Approval Criteria		
13. 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? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class and process appropriate PA.
14. RPh only: All other indications need to be evaluated to see if it is an OHP-funded diagnosis: • If funded: may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only. • If not funded: ○ If current age< 21 years; Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)? ▪ Is yes, may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only. ▪ If No, Deny (medical appropriateness) ○ If current age ≥ 21 years, Deny; not funded by the OHP. ▪ Deny non-fungal diagnosis (medical appropriateness) ▪ Deny fungal ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP). ▪ Forward any fungal ICD-10 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.		

P&T Review: *12/23 (KS);12/22; 2/22 (KS); 11/19 (KS); 7/15; 09/10; 2/06; 11/05; 9/05; 5/05*
Implemented: *TBD; 1/1/23; 4/1/22; 5/1/16; 8/15; 1/1/11; 7/1/06; 11/1/0; 9/1/0*