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, June 5, 2025 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

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

A. Quarterly Utilization Report
B. Oncology Prior Authorization Updates
C. Orphan Drug Policy Updates
    1. Public Comment

1:25 PM III. DUR ACTIVITIES

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

1. New and Emerging Therapies for Metabolic Dysfunction-Associated Steatotic Liver Disease/Metabolic DysfunctionAssociated Steatohepatitis (MASLD/MASH) in Adults
2. Update on the Biosimilar Landscape in the United States Market
3. Review of Off-Label Use of Gabapentin and Pregabalin

IV. NEW BUSINESS

1:40 PM	A. Actinic Keratosis Class Review	D. Moretz (OSU)

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

2:10 PM	B. Egrifta SV® (tesamorelin) Prior Authorization Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:25 PM	C. Drugs for Dry Eye Disease 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:45 PM	D. Spravato® (esketamine) Prior Authorization Update and Drug Use Evaluation 1. Prior Authorization Criteria 2. Drug Use Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
3:05 PM	BREAK	
3:20 PM	E. Journavx™ (suzetrigine) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
3:35 PM	F. Topical Drugs for Molluscum Contagiosum 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
3:50 PM	G. Nutritional Supplements Prior Authorization Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
4:00 PM	H. Nuedexta® (dextromethorphan/quinidine) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
4:15 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

Drug Use Research & Management Program
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Office of Delivery System Innovation
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2025
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2025
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2025
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2026
Bridget Bradley, PharmD, BCPP	Pharmacist	Kaiser Northwest Psychiatry	Beaverton	December 2026
Samara Stevens, ND	Public	Mental Health Naturopath	Portland	December 2026
Jeanne Savage, MD	Physician	Medical Director, Trillium	Portland	December 2026
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2027
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2027
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2027
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2027

OREGON HEALTH AUTHORITY

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Health Systems Division
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Phone 503-947-5220 | Fax 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, April 3rd, 2025
1:05 PM - 4:15 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; Bridget Bradley, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Cat Livingston, MD; Eddie Saito, PharmD; Jeanne Savage, MD; Samara Stevens, ND

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

Audience: Sajani Barot*, Idorsia Pharmaceuticals, Amanda Rendall*, Neurelis; Pam Eads*, UCB; Jay Mehta*, Axsom Therapeutics; Erin Nowak*, Abbvie; Rochelle Yang*, Teva; Marc Parker, Viking; Leif Bruce, Novo Nordisk; Leanne Yantis, AllCare; Cathy Simpson, AbbVie; Jessica Grussing, Neurelis; Ray Kong, Neurocrine Bioscience; Andrea Willcuts, Idorsia; Brett Fushimi, UCB; Dan O'Donnell, Axsome Therapeutics; Kim Eggert; Jennifer Lankford; Georgette Dzwilewski, Indivior; Erin Scow, OHA; Shauna Durbin, CEbP; Jim Slater, CareOregon; Andrea Vintro, CEbP; Jen Tamburo, AstraZeneca; Jennifer Lankford, Eli Lilly; Elva Van Devender, Umpqua Health; Gary Parenteau, Dexcom; Greg Kitchens, Artia Solutions; Melissa Snider, Gilead; Bryan Armstrong, CareOregon; Chris Ferrin, IHN; Nirmal Ghuman, J&J; Lisa Pulver, J&J; Rosalie Elliott, Umpqua Health; Mark Kantor, AllCare Health; Brett Freund; Amy Breen, Teva

(*) Provided verbal testimony

I. CALL TO ORDER

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

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

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

D. Department Update provided by Andrew Gibler, PharmD

E. Legislative Update provided by Dee Weston, JD

II. CONSENT AGENDA TOPICS

A. Orphan Drug Policy Updates
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Lenmeldy™ (atidarsagene autotemcel); Ctexli™ (chenodiol); Crenessity™ (crinecefont); Camzyos® (mavacamten); Gomekli™ (mirdametinib) based on their FDA-approved label

III. NEW BUSINESS

A. Drugs for Weight Management PA Update for Obstructive Sleep Apnea: Kathy Sentena, PharmD
Recommendation:
- Amend Weight Management Drugs PA criteria to allow coverage of tirzepatide for patients with OSA and obesity
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

B. Tryvio™ (aprocitentan) New Drug Evaluation: Megan Herink, PharmD
Recommendations:
- Implement PA for aprocitentan to ensure safe and appropriate use
Public Comment: Sajani Barot, Indorsia Pharmaceuticals
ACTION: Motion to approve, 2nd, all in favor

C. Oncology Drug Policy Evaluation: Courtney Ho, PharmD Candidate
Recommendations:
- Continue to require PA for newer antineoplastic medications due to high costs, ongoing accelerated approvals, and no evidence of a barrier to access, or delay in therapy resulting from the PA policy
- Add new FDA-approved antineoplastic agent Romvimza™ (vimseltinib) to Table 1 in the Oncology Agents PA criteria
- Encourage cost effective evidence-based step therapy for certain cancer indications supported by clinical guidelines
ACTION: Motion to approve, 2nd, all in favor

D. Antiepileptics, Noninjectable Class Update: Deanna Moretz, PharmD
Recommendations:
- Retire Clobazam PA criteria based on compendia support for treatment resistant seizures and make at least one formulation of clobazam preferred
- Revise Pregabalin PA criteria to include medically appropriate use for fibromyalgia for patients with the EPSDT Benefit
- Evaluate comparative costs in executive session
Public Comment: Amanda Rendall, Neurelis; Pam Eads, UCB
ACTION: Motion to approve, 2nd, all in favor

E. Headache Prevention and Treatment Class Update: Kathy Sentena, PharmD

Recommendations:

- No changes to the PDL are recommended based on review of the evidence
- Update the CGRP Antagonist and Antimigraine - Serotonin Agonist PA criteria with clerical updates and new drug additions
- Implement the Butalbital Containing Products PA criteria
- Evaluate costs in executive session

Public Comment: Jay Mehta, Axsome Therapeutics; Erin Nowak, Abbvie; Rochelle Yang, Teva

ACTION: The Committee recommended removing question #10 and modifying question #15 to add subcutaneous sumatriptan and intranasal zolmitriptan as an option in the CGRP PA criteria. The Committee also recommended increasing the Symbravo quantity to #9 to match the package size

Motion to approve, 2nd, all in favor

F. Treatments for Hyperhidrosis Class Review: Sarah Servid, PharmD

Recommendations:

- Implement PA criteria for topical anticholinergics and onabotulinumtoxinA to limit use to people with:
    - Diagnosis of primary axillary hyperhidrosis
    - Severe symptoms that interfere with daily activities
    - When prescribed by, or in consultation with, a dermatologist
    - When symptoms have failed to respond to non-pharmacologic lifestyle management
- Recommend onabotulinumtoxinA as a preferred option for treatment of hyperhidrosis based on large treatment effect size and relatively long duration of effect
- Make topical anticholinergics non-preferred

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

G. Botulinum Toxins Class Update: Sara Fletcher, PharmD

Recommendations:

- No changes to policy for use in migraine headache, strabismus, or other previously reviewed and funded indications
- Update the Botulinum Toxins PA criteria to incorporate coverage for chronic anal fissures
- Evaluate costs in executive session

IV. EXECUTIVE SESSION

Members Present: Bridget Bradley, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Cat Livingston, MD; Jeanne Savage, MD; Samara Stevens, ND

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

V. RECONVENE for PUBLIC RECOMMENDATIONS

Drug Use Research & Management Program
OHA Health Systems Division
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A. Drugs for Weight Management

Recommendation: Make Zepbound version of tirzepatide preferred and subject to PA criteria pending acceptance of a SR offer for OSA

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

B. Antiepileptics, Noninjectable Class

Recommendations: Make generic clobazam tablets and oral suspension preferred; make pregabalin capsules and generic levetiracetam ER 24H tablets preferred; and make carbamazepine oral suspension non-preferred

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

C. Headache Prevention and Treatment Class

Recommendations: Make rizatriptan tablets and rapid tablets, and eletriptan tablets preferred

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

D. Botulinum Toxins Class

Recommendations: Remove PDL status for all products

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

VI. ADJOURN

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: October 2023 - September 2024

Eligibility	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
Total Members (FFS & Encounter)	1,432,279	1,432,128	1,423,066	1,276,290	1,264,099	1,268,663	1,249,346	1,239,354	1,231,095	1,226,816	1,235,264	1,241,007	1,293,284
FFS Members	146,187	137,146	137,961	118,187	112,962	110,868	105,128	103,204	102,443	98,771	97,509	96,865	113,936
OHP Basic with Medicare	18,735	13,793	12,274	9,270	9,176	9,007	8,737	8,820	8,839	8,606	8,437	8,250	10,329
OHP Basic without Medicare	10,282	9,803	9,773	9,779	9,707	9,663	9,533	9,402	9,417	9,308	9,241	9,221	9,594
ACA	117,170	113,550	115,914	99,138	94,079	92,198	86,858	84,982	84,187	80,857	79,831	79,394	94,013
Encounter Members	1,286,092	1,294,982	1,285,105	1,158,103	1,151,137	1,157,795	1,144,218	1,136,150	1,128,652	1,128,045	1,137,755	1,144,142	1,179,348
OHP Basic with Medicare	91,865	98,460	100,763	104,359	105,114	105,811	106,369	106,771	106,835	107,175	107,413	106,294	103,936
OHP Basic without Medicare	66,719	66,924	66,747	67,029	67,008	67,065	67,120	66,762	66,760	66,835	66,785	66,566	66,860
ACA	1,127,508	1,129,598	1,117,595	986,715	979,015	984,919	970,729	962,617	955,057	954,035	963,557	971,282	1,008,552

Gross Cost Figures for Drugs	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	YTD Sum
Total Amount Paid (FFS & Encounter)	$128,232,366	$124,797,008	$123,866,587	$132,782,333	$123,815,891	$128,487,740	$132,708,729	$135,357,917	$111,255,209	$119,997,131	$130,684,653	$132,795,197	$1,524,780,761
Mental Health Carve-Out Drugs	$10,522,262	$10,645,708	$10,326,136	$11,471,366	$10,671,275	$10,977,468	$11,511,020	$11,707,881	$10,972,278	$11,918,353	$11,627,547	$11,385,643	$133,736,939
OHP Basic with Medicare	$65	$28	$15	$2,188	$84	$10,494	$6,864	$10,110	$13,507	$3,368	$20	$6,729	$53,473
OHP Basic without Medicare	$3,689,843	$3,732,121	$3,660,908	$4,019,549	$3,687,727	$3,668,080	$3,976,169	$3,983,083	$3,782,258	$4,041,367	$4,035,605	$3,790,219	$46,066,929
ACA	$6,633,705	$6,696,761	$6,404,361	$6,968,543	$6,435,886	$6,864,639	$7,011,462	$7,194,306	$6,736,154	$7,371,050	$7,150,024	$7,136,641	$82,603,531
FFS Physical Health Drugs	$6,600,222	$6,389,793	$6,103,428	$9,167,285	$8,195,078	$8,106,153	$8,123,812	$8,194,273	$7,294,157	$7,522,002	$6,885,929	$6,682,805	$89,264,937
OHP Basic with Medicare	$215,171	$224,476	$237,075	$311,240	$285,274	$275,866	$289,731	$314,571	$257,177	$299,649	$291,775	$251,425	$3,253,429
OHP Basic without Medicare	$1,451,837	$1,474,023	$1,407,854	$1,641,197	$1,386,981	$1,362,550	$1,443,649	$1,417,784	$1,266,998	$1,466,439	$1,276,324	$1,236,643	$16,832,279
ACA	$4,707,633	$4,445,162	$4,162,459	$6,810,004	$6,105,145	$6,056,354	$5,900,415	$6,025,126	$5,390,861	$5,412,417	$4,998,489	$4,828,127	$64,842,192
FFS Physician Administered Drugs	$1,307,830	$1,401,090	$1,492,171	$2,156,717	$1,537,570	$1,582,584	$1,414,156	$1,125,581	$1,270,185	$1,278,472	$1,489,820	$914,260	$16,970,437
OHP Basic with Medicare	$256,295	$189,803	$128,103	$204,370	$189,728	$99,221	$147,873	$106,697	$107,210	$126,452	$158,975	$145,979	$1,860,705
OHP Basic without Medicare	$247,202	$419,136	$455,923	$273,828	$337,079	$296,179	$267,064	$214,989	$490,949	$192,471	$295,895	$51,480	$3,542,195
ACA	$377,382	$457,237	$548,541	$987,683	$517,153	$602,802	$388,585	$374,478	$335,201	$411,987	$454,833	$448,827	$5,904,708
Encounter Physical Health Drugs	$82,652,387	$81,227,023	$80,567,932	$83,314,536	$78,118,936	$81,986,986	$86,101,106	$87,951,824	$79,008,893	$88,271,133	$87,059,919	$87,077,365	$1,003,338,041
OHP Basic with Medicare	$335,093	$314,309	$302,334	$401,908	$385,599	$414,934	$387,784	$375,755	$370,397	$390,333	$389,281	$398,084	$4,465,810
OHP Basic without Medicare	$18,268,817	$17,828,648	$17,584,769	$18,432,688	$16,795,435	$17,667,114	$18,648,154	$18,990,291	$17,195,475	$19,372,608	$19,026,844	$18,240,408	$218,051,252
ACA	$59,119,621	$57,861,190	$56,578,482	$55,696,350	$51,227,558	$53,998,080	$56,232,445	$57,475,023	$51,537,910	$57,105,750	$56,609,386	$57,528,337	$670,970,132
Encounter Physician Administered Drugs	$27,149,664	$25,133,394	$25,376,920	$26,672,428	$25,293,032	$25,834,549	$25,558,635	$26,378,357	$12,709,695	$11,007,171	$23,621,437	$26,735,123	$281,470,406
OHP Basic with Medicare	$1,025,782	$922,762	$882,649	$1,332,340	$1,206,383	$993,515	$1,051,128	$856,722	$448,388	$675,190	$966,764	$970,752	$11,332,375
OHP Basic without Medicare	$4,464,249	$5,333,017	$5,125,914	$4,990,103	$5,287,698	$5,157,193	$5,234,661	$4,744,208	$2,526,288	$2,525,187	$5,178,848	$5,391,087	$55,958,453
ACA	$19,900,840	$16,853,049	$17,123,634	$16,671,920	$15,438,594	$15,903,406	$16,079,632	$18,020,094	$8,246,354	$6,240,859	$14,485,147	$16,688,886	$181,652,414

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

Last Updated: April 18, 2025

Drug Use Research & Management Program
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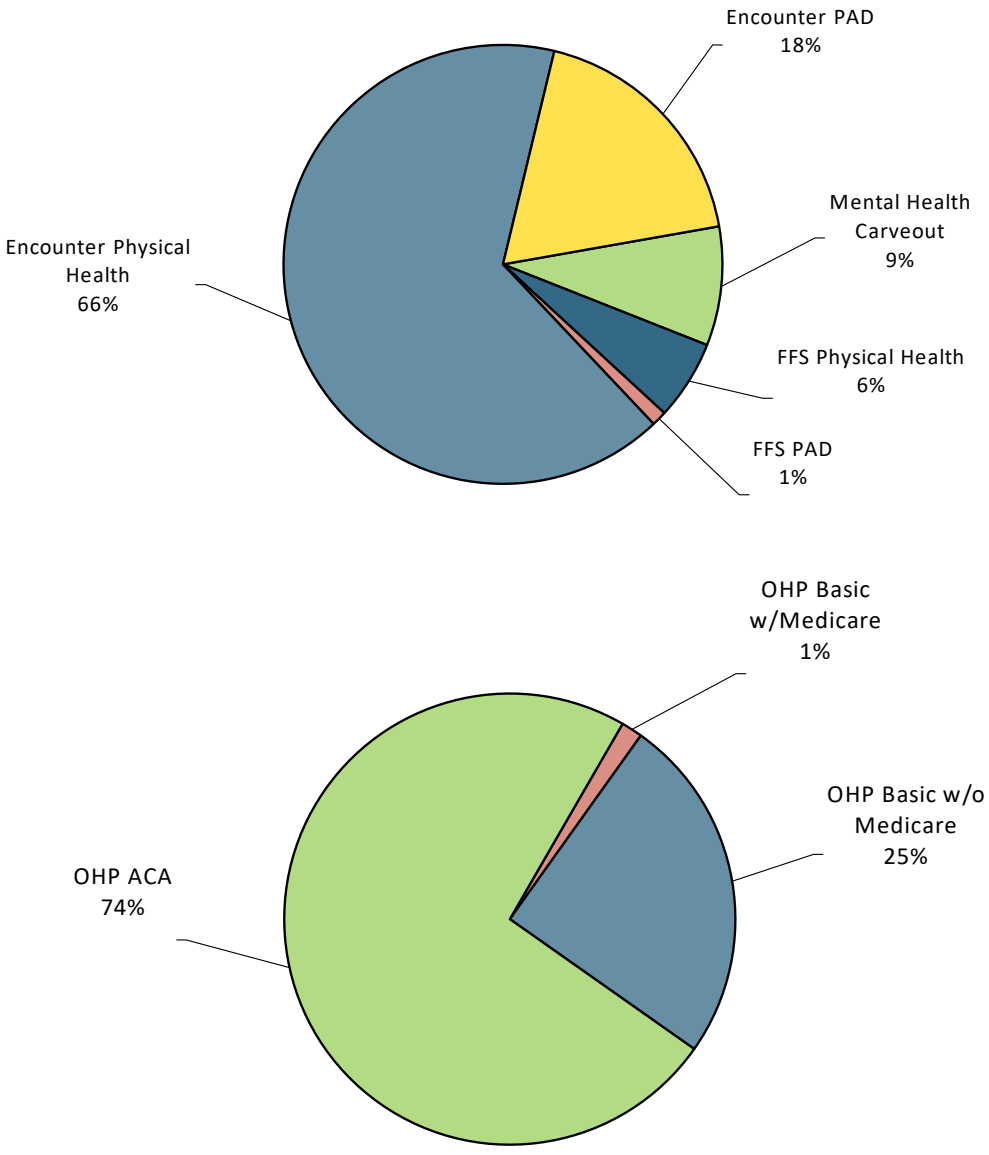
Pharmacy Utilization Summary Report: October 2023 - September 2024

YTD Percent Paid Amounts



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

Last Updated: April 18, 2025

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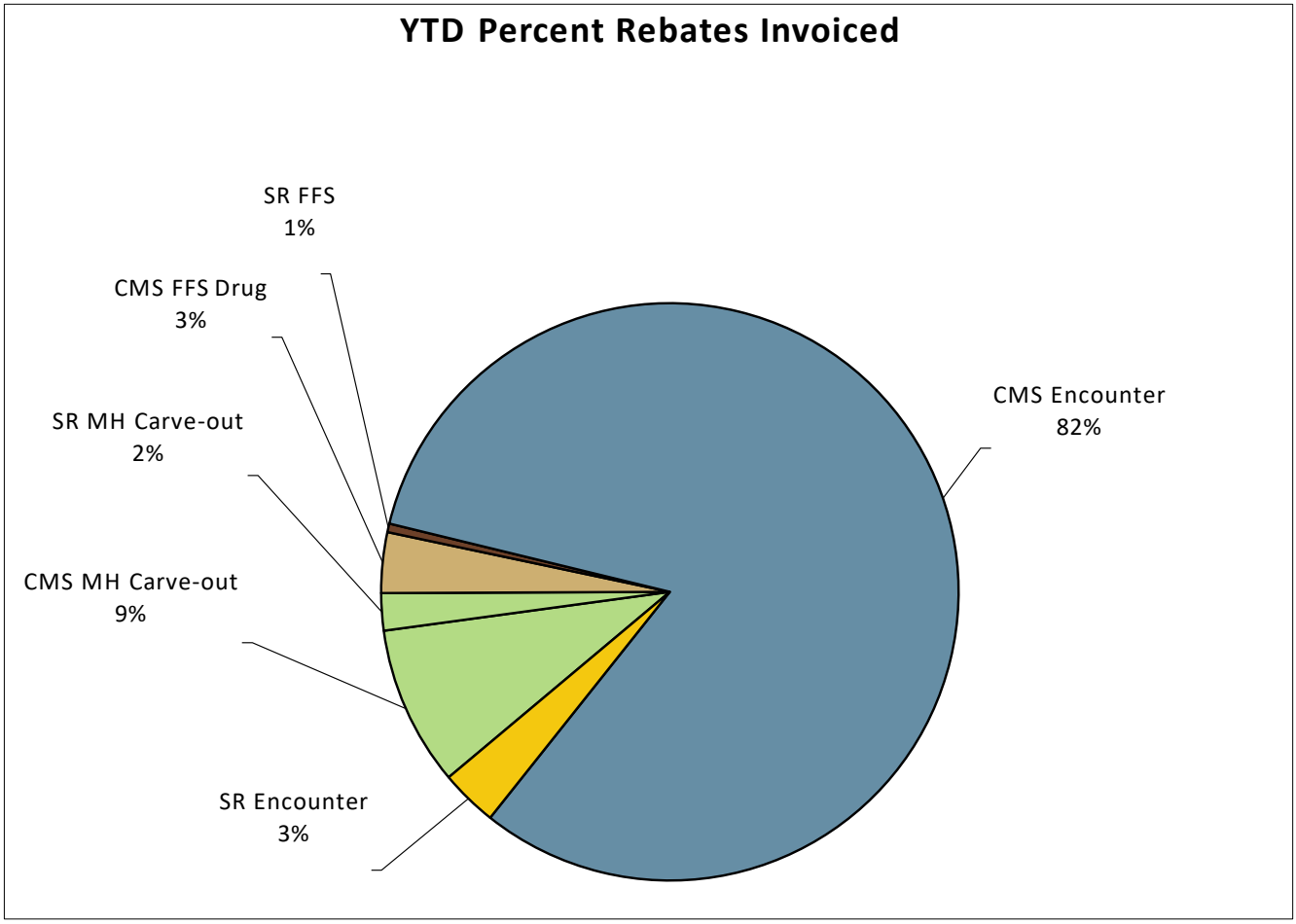
Pharmacy Utilization Summary Report: October 2023 - September 2024

Quarterly Rebates Invoiced	2023-Q4	2024-Q1	2024-Q2	2024-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$128,530,305	$129,831,672	$131,298,672	$123,478,122	$513,138,772
CMS MH Carve-out	$10,498,011	$12,024,097	$11,778,233	$11,672,423	$45,972,763
SR MH Carve-out	$2,488,739	$2,381,715	$2,880,506	$2,934,264	$10,685,225
CMS FFS Drug	$4,244,643	$4,964,300	$4,372,307	$3,811,894	$17,393,143
SR FFS	$614,191	$685,908	$643,229	$526,700	$2,470,028
CMS Encounter	$104,805,149	$105,777,165	$108,319,784	$101,305,635	$420,207,733
SR Encounter	$5,879,573	$3,998,486	$3,304,614	$3,227,206	$16,409,880

Quaterly Net Drug Costs	2023-Q4	2024-Q1	2024-Q2	2024-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$248,365,656	$255,254,292	$248,023,183	$259,998,859	$1,011,641,989
Mental Health Carve-Out Drugs	$18,507,357	$18,714,297	$19,532,440	$20,324,857	$77,078,951
FFS Phys Health + PAD	$18,435,701	$25,095,179	$22,406,629	$20,434,695	$86,372,203
Encounter Phys Health + PAD	$211,422,598	$211,444,816	$206,084,114	$219,239,307	$848,190,835



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

Last Updated: April 18, 2025

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: October 2023 - September 2024

Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$89.53	$87.14	$87.04	$104.04	$97.95	$101.28	$106.22	$109.22	$90.37	$97.81	$105.79	$107.01	$98.62
Mental Health Carve-Out Drugs	$7.35	$7.43	$7.26	$8.99	$8.44	$8.65	$9.21	$9.45	$8.91	$9.71	$9.41	$9.17	$8.67
FFS Physical Health Drugs	$45.15	$46.59	$44.24	$77.57	$72.55	$73.12	$77.28	$79.40	$71.20	$76.16	$70.62	$68.99	$66.90
FFS Physician Administered Drugs	$8.95	$10.22	$10.82	$18.25	$13.61	$14.27	$13.45	$10.91	$12.40	$12.94	$15.28	$9.44	$12.54
Encounter Physical Health Drugs	$64.27	$62.72	$62.69	$71.94	$67.86	$70.81	$75.25	$77.41	$70.00	$78.25	$76.52	$76.11	$71.15
Encounter Physician Administered Drugs	$21.11	$19.41	$19.75	$23.03	$21.97	$22.31	$22.34	$23.22	$11.26	$9.76	$20.76	$23.37	$19.86

Claim Counts	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
Total Claim Count (FFS & Encounter)	1,258,721	1,228,095	1,208,356	1,286,166	1,232,871	1,283,827	1,322,316	1,336,622	1,221,871	1,286,792	1,257,743	1,244,590	1,263,998
Mental Health Carve-Out Drugs	212,387	207,419	203,144	218,442	202,868	210,543	215,106	215,915	198,146	214,852	209,498	206,291	209,551
FFS Physical Health Drugs	38,797	37,038	36,256	44,845	40,956	41,983	41,742	41,650	36,320	36,313	32,955	32,448	38,442
FFS Physician Administered Drugs	8,552	8,232	8,073	10,088	9,749	9,926	9,125	9,458	8,523	8,572	7,964	7,708	8,831
Encounter Physical Health Drugs	877,314	856,727	844,804	886,965	853,524	889,280	920,205	931,382	851,739	895,096	876,408	872,258	879,642
Encounter Physician Administered Drugs	121,671	118,679	116,079	125,826	125,774	132,095	136,138	138,217	127,143	131,959	130,918	125,885	127,532

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$101.88	$101.62	$102.51	$103.24	$100.43	$100.08	$100.36	$101.27	$91.05	$93.25	$103.90	$106.70	$100.52
Mental Health Carve-Out Drugs	$49.54	$51.32	$50.83	$52.51	$52.60	$52.14	$53.51	$54.22	$55.37	$55.47	$55.50	$55.19	$53.19
FFS Physical Health Drugs	$170.12	$172.52	$168.34	$204.42	$200.09	$193.08	$194.62	$196.74	$200.83	$207.14	$208.95	$205.95	$193.57
FFS Physician Administered Drugs	$152.93	$170.20	$184.83	$213.79	$157.72	$159.44	$154.98	$119.01	$149.03	$149.15	$187.07	$118.61	$159.73
Encounter Physical Health Drugs	$94.21	$94.81	$95.37	$93.93	$91.53	$92.19	$93.57	$94.43	$92.76	$98.62	$99.34	$99.83	$95.05
Encounter Physician Administered Drugs	$223.14	$211.78	$218.62	$211.98	$201.10	$195.58	$187.74	$190.85	$99.96	$83.41	$180.43	$212.38	$184.75

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$24.99	$25.01	$24.88	$26.53	$26.09	$26.36	$26.96	$27.14	$26.60	$27.12	$27.05	$26.89	$26.30
Mental Health Carve-Out Drugs	$17.47	$17.26	$17.11	$17.78	$17.84	$17.62	$17.69	$17.60	$17.48	$17.36	$17.14	$17.18	$17.46
FFS Physical Health Drugs	$118.78	$117.72	$115.69	$152.47	$149.51	$146.46	$147.28	$152.89	$151.43	$149.11	$153.92	$150.35	$142.13
Encounter Physical Health Drugs	$23.09	$23.29	$23.23	$22.82	$22.56	$23.14	$24.04	$24.11	$23.79	$24.93	$25.07	$25.09	$23.76

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$659.54	$694.17	$735.38	$764.71	$760.71	$772.01	$784.16	$792.50	$774.07	$811.21	$800.12	$710.87	$754.95
Mental Health Carve-Out Drugs	$1,334.43	$1,384.99	$1,362.13	$1,387.97	$1,390.75	$1,404.99	$1,433.67	$1,439.99	$1,461.61	$1,437.08	$1,441.33	$1,428.86	$1,408.98
FFS Physical Health Drugs	$428.44	$456.92	$455.50	$512.81	$513.37	$502.49	$516.84	$491.13	$515.24	$567.34	$540.28	$486.27	$498.89
Encounter Physical Health Drugs	$639.74	$671.44	$716.95	$743.88	$738.48	$750.29	$759.94	$770.04	$745.83	$783.81	$772.58	$682.80	$731.31

Generic Drug Use Percentage	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
Generic Drug Use Percentage	90.0%	90.4%	90.9%	91.4%	91.5%	91.7%	91.7%	91.7%	91.6%	91.5%	91.3%	90.1%	91.1%
Mental Health Carve-Out Drugs	97.6%	97.5%	97.5%	97.5%	97.5%	97.5%	97.5%	97.4%	97.4%	97.3%	97.3%	97.3%	97.4%
FFS Physical Health Drugs	83.4%	83.8%	84.5%	85.6%	86.1%	86.9%	87.2%	87.0%	86.4%	86.1%	85.8%	83.4%	85.5%
Encounter Physical Health Drugs	88.5%	89.0%	89.6%	90.1%	90.4%	90.5%	90.6%	90.6%	90.4%	90.3%	90.1%	88.6%	89.9%

Preferred Drug Use Percentage	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Avg Monthly
Preferred Drug Use Percentage	90.19%	90.04%	89.93%	90.04%	90.02%	90.07%	90.03%	89.99%	89.92%	88.95%	88.64%	88.59%	89.7%
Mental Health Carve-Out Drugs	92.90%	92.80%	92.75%	92.70%	92.60%	92.68%	92.53%	92.49%	92.39%	86.73%	86.69%	86.53%	91.1%
FFS Physical Health Drugs	95.77%	95.70%	95.63%	95.49%	95.36%	95.36%	95.25%	95.42%	95.43%	95.35%	95.37%	95.11%	95.4%
Encounter Physical Health Drugs	89.33%	89.17%	89.05%	89.16%	89.19%	89.24%	89.25%	89.21%	89.14%	89.27%	88.89%	88.88%	89.1%

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

Last Updated: April 18, 2025

Drug Use Research & Management Program
DHS - Health Systems Division
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Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2025

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	VRAYLAR*	Antipsychotics, 2nd Gen	$6,133,431	11.9%	4,520	$1,357	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$5,558,608	10.7%	2,040	$2,725	Y
3	REXULTI*	Antipsychotics, 2nd Gen	$3,047,949	5.9%	2,185	$1,395	V
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,867,197	5.5%	1,160	$2,472	Y
5	Inj Delandistrogene Mox Rokl	Physican Administered Drug	$1,843,440	3.6%	1	$1,843,440	
6	CAPLYTA*	Antipsychotics, 2nd Gen	$1,549,169	3.0%	1,047	$1,480	V
7	INVEGA TRINZA	Antipsychotics, Parenteral	$1,487,788	2.9%	179	$8,312	Y
8	SPRAVATO*	Antidepressants	$1,146,528	2.2%	928	$1,235	V
9	ARISTADA	Antipsychotics, Parenteral	$1,051,151	2.0%	411	$2,558	Y
10	TRINTELLIX	Antidepressants	$1,036,789	2.0%	2,230	$465	V
11	BUPROPION XL	Antidepressants	$760,635	1.5%	56,125	$14	Y
12	AUVELITY	Antidepressants	$737,246	1.4%	783	$942	V
13	SERTRALINE HCL	Antidepressants	$716,403	1.4%	63,558	$11	Y
14	ABILIFY ASIMTUFII	Antipsychotics, Parenteral	$695,407	1.3%	132	$5,268	Y
15	LYBALVI*	Antipsychotics, 2nd Gen	$676,818	1.3%	450	$1,504	V
16	TRAZODONE HCL	Antidepressants	$631,682	1.2%	54,428	$12	V
17	DULOXETINE HCL	Antidepressants	$619,997	1.2%	40,188	$15	Y
18	ESCITALOPRAM OXALATE	Antidepressants	$610,409	1.2%	48,708	$13	Y
19	FLUOXETINE HCL	Antidepressants	$598,005	1.2%	49,082	$12	Y
20	QELBREE*	ADHD Drugs	$461,607	0.9%	1,030	$448	Y
21	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$413,514	0.8%	31,545	$13	
22	LAMOTRIGINE	Antiepileptics, Outpatient	$390,336	0.8%	31,365	$12	Y
23	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$345,875	0.7%	22,959	$15	Y
24	INVEGA HAFYERA	Antipsychotics, Parenteral	$322,232	0.6%	18	$17,902	Y
25	BUPROPION XL	Antidepressants	$311,467	0.6%	1,763	$177	V
26	ATOMOXETINE HCL*	ADHD Drugs	$284,681	0.6%	10,532	$27	Y
27	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$281,851	0.5%	22,101	$13	Y
28	BIKTARVY	HIV	$272,648	0.5%	93	$2,932	Y
29	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$243,230	0.5%	22	$11,056	Y
30	VENLAFAXINE HCL ER	Antidepressants	$240,884	0.5%	18,744	$13	Y
31	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	$225,193	0.4%	397	$567	N
32	OLANZAPINE*	Antipsychotics, 2nd Gen	$211,750	0.4%	14,397	$15	Y
33	SERTRALINE HCL	Antidepressants	$211,626	0.4%	1,347	$157	V
34	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$205,132	0.4%	177	$1,159	Y
35	MIRTAZAPINE	Antidepressants	$203,256	0.4%	14,215	$14	Y
36	DAYBUE*	STC 99 - Miscellaneous	$199,860	0.4%	10	$19,986	N
37	Inj Pembrolizumab	Physican Administered Drug	$190,359	0.4%	48	$3,966	
38	GUANFACINE HCL ER	ADHD Drugs	$186,997	0.4%	13,328	$14	Y
39	LAMOTRIGINE ER	Antiepileptics, Outpatient	$184,951	0.4%	4,496	$41	V
40	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$181,610	0.4%	95	$1,912	Y
		Top 40 Aggregate:	**$37,337,713**		**516,837**	**$48,342**	
		All FFS Drugs Totals:	**$51,754,038**		**777,650**	**$1,603**	

*** Drug requires Prior Authorization**

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

Last updated: April 18, 2025

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - First Quarter 2025

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Inj Delandistrogene Mox Rokl	Physican Administered Drug	$1,843,440	14.3%	1	$1,843,440	
2	BIKTARVY	HIV	$272,648	2.1%	93	$2,932	Y
3	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$243,230	1.9%	22	$11,056	Y
4	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	$225,193	1.7%	397	$567	N
5	DAYBUE*	STC 99 - Miscellaneous	$199,860	1.5%	10	$19,986	N
6	Inj Pembrolizumab	Physican Administered Drug	$190,359	1.5%	48	$3,966	
7	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$181,610	1.4%	95	$1,912	Y
8	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$181,552	1.4%	12	$15,129	
9	TRIKAFTA*	Cystic Fibrosis	$175,073	1.4%	27	$6,484	N
10	PAXLOVID	Coronavirus Antivirals	$166,310	1.3%	128	$1,299	Y
11	IBRANCE*	Antineoplastics, Newer	$158,627	1.2%	8	$19,828	
12	EVEROLIMUS*	Antineoplastics, Newer	$153,859	1.2%	13	$11,835	
13	Gammagard Liquid Injection	Physican Administered Drug	$149,199	1.2%	49	$3,045	
14	JARDIANCE	Diabetes, SGLT-2 Inhibitors	$138,598	1.1%	371	$374	Y
15	HUMIRA(CF) PEN*	Targeted Immune Modulators	$136,676	1.1%	33	$4,142	Y
16	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$132,525	1.0%	1	$132,525	
17	IMCIVREE*	Weight Management Drugs	$132,103	1.0%	4	$33,026	
18	ELIQUIS	Anticoagulants, Oral and SQ	$121,625	0.9%	305	$399	Y
19	FINTEPLA*	Antiepileptics, Outpatient	$119,348	0.9%	25	$4,774	N
20	VITAMIN D3	Calcium/Vit D Replacement, Oral	$115,287	0.9%	1,693	$68	Y
21	Injection, Pertuzumab, 1 Mg	Physican Administered Drug	$114,559	0.9%	17	$6,739	
22	EPIDIOLEX*	Antiepileptics, Outpatient	$107,398	0.8%	89	$1,207	N
23	RAVICTI	Urea Cycle Disorders	$100,548	0.8%	1	$100,548	N
24	TRULICITY*	Diabetes, GLP-1 Receptor Agonists and GIP The	$95,827	0.7%	152	$630	Y
25	Iron Sucrose Injection	Physican Administered Drug	$83,911	0.6%	165	$509	
26	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$83,212	0.6%	2,458	$34	Y
27	Canakinumab Injection	Physican Administered Drug	$78,729	0.6%	2	$39,365	
28	KISQALI*	Antineoplastics, Newer	$76,472	0.6%	5	$15,294	
29	Aflibercept Injection	Physican Administered Drug	$74,083	0.6%	158	$469	
30	BRIXADI	Substance Use Disorders, Opioid & Alcohol	$71,599	0.6%	43	$1,665	Y
31	Inj Heparin Sodium Per 1000u	Physican Administered Drug	$70,622	0.5%	80	$883	
32	VENCLEXTA*	Antineoplastics, Newer	$69,731	0.5%	6	$11,622	
33	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$69,463	0.5%	1,069	$65	Y
34	Factor Viii Recombinant Nos	Physican Administered Drug	$68,392	0.5%	3	$22,797	
35	Inj Fam-Trastu Deru-Nxki 1mg	Physican Administered Drug	$67,236	0.5%	8	$8,405	
36	CHOLBAM*	Bile Therapy	$65,104	0.5%	2	$32,552	N
37	SKYRIZI*	Targeted Immune Modulators	$64,840	0.5%	3	$21,613	N
38	RINVOQ*	Targeted Immune Modulators	$63,672	0.5%	26	$2,449	N
39	SYMBICORT	Corticosteroids/Beta-Agonist Combination, Inh	$61,615	0.5%	241	$256	Y
40	LISDEXAMFETAMINE DIMESYLATE*	ADHD Drugs	$59,157	0.5%	822	$72	Y
		Top 40 Aggregate:	**$6,583,294**		**8,685**	**$59,599**	
		All FFS Drugs Totals:	**$12,929,821**		**101,817**	**$1,694**	

*** 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: April 18, 2025

Drug Use Research & Management Program
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Prior Authorization Criteria Update: Oncology

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

Table 1. New oncology drugs

Generic Name	Brand Name
Datopotamab deruxtecan-dlnk	DATROWAY

Recommendation:

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

Author: Sara Fletcher, PharmD, MPH, BCPS June 2025

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 provider 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/

Table 1: National Comprehensive Cancer Network (NCCN) Categories for Recommendations

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy (if specified) or 12 months, (if duration is unspecified).	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy (if specified) or 12 months (if duration is unspecified).	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No: If not eligible for EPSDT review:** Pass to RPh. Deny; not funded by the OHP **If eligible for EPSDT review:** Go to #5.

5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity.
6. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Go to #8	**No:** Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Go to #8	**No:** Go to #9
8. Are there equally or higher recommended alternative agents based on NCCN categories of evidence (Table 1) for the requested indication and place in therapy?	**Yes:** Pass to RPh. Approve for length of therapy (if specified) or 12 months (if duration is unspecified) Note: When efficacy is similar, the choice of agent should be determined by safety, and then cost. In the absence of a safety concern, the prescriber is expected to use the least costly alternative.	**No:** Pass to RPh. Approve for length of therapy (if specified) or 12 months (if duration is unspecified).
9. Is there documentation based on chart notes that the patient is enrolled in a 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 #10

10. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.

11. All other diagnoses must be evaluated for evidence of clinical benefit.

    The prescriber must provide the following documentation:
    - medical literature or guidelines supporting use for the condition,
    - clinical chart notes documenting medical necessity, and
    - documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy.

      RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Table 1. Oncology agents which apply to this policy (Updated 3/4/2025)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

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

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

Generic Name	Brand Name
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lazertinib	LAZCLUZE
lenvatinib mesylate	LENVIMA
lifileucel	AMTAGVI
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
melphalan hcl/hepatic delivery kit (HDS)	HEPZATO KIT
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mobecertinib	EXKIVITY
momelotinib	OJJAARA
mosunetuzumab-axgb	LUNSUMIO
motixafortide	APHEXDA
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib and abiraterone acetate	AKEEGA
niraparib tosylate	ZEJULA
nirogacestat hydrobromide	OGSIVEO
nivolumab	OPDIVO
nivolumab and hyaluronidase-nvhy	OPDIVO QVANTIG
nivolumab; relatlimab-rmbw	OPDUALAG
nogapendekin alfa inbakicept-pmln	ANKTIVA
obecabtagene autoleucel	AUCATZYL
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
omidubicel-onlv	OMISIRGE

Generic Name	Brand Name
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
quizartinib	VANFLYTA
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYX
repotrectinib	AUGTYRO
retifanlimab-dlwr	ZYNYZ
revumenib	REVUFORJ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
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

Generic Name	Brand Name
talquetamab-tgvs	TALVEY
tarlatamab-dlle	IMDELLTRA
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tislelizumab-jsgr	TEVIMBRA
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
toripalimab-tpzi	LOQTORZI
tovorafenib	OJEMDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
trastuzumab-strf	HERCESSI
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vimseltinib	ROMVIMZA
vismodegib	ERIVEDGE
vorasidenib	VORANIGO
zanidatamab-hrii	ZIIHERA
zanubrutinib	BRUKINSA
zenocutuzumab-Zbco	BIZENGRI
ziv-aflibercept	ZALTRAP

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

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. Updated orphan drugs

Generic Name	Brand Name
Axatilimab-csfr	NIKTIMVO
Diazoxide choline	VYKAT XR
Remestemcel-L-rknd	RYONCIL

Recommendation:

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

Author: Sara Fletcher, PharmD, MPH, BCPS

June 2025

Orphan Drugs

Goal(s):

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

Length of Authorization:

- Up to 6 months

Requires PA:

- See Table 1 (pharmacy and provider administered claims)

Covered Alternatives:

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

Table 1. Included orphan drugs

ADAMTS13, recombinant-krhn (ADZYNMA)
Allogeneic processed thymus tissue-agdc (RETHYMIC)
Alpelisib (VIJOICE)
arimoclomol citrate (MIPLYFFA)
Atidarsagene autotemcel (LENMELDY)
Avacopan (TAVNEOS)
Axatilimab-csfr (NIKTIMVO)
Belumosudil (REZUROCK)
Beremagene geperpavec-svdt (VYJUVEK)
Birch triterpenes (FILSUVEZ)
Burosumab-twza (CRYSVITA)
Cerliponase alfa (BRINEURA)
Chenodiol (CTEXLI)
Crinecefont (CRENESSITY)
Crovalimab-akkz (PIASKY)
Danicopan (VOYDEYA)
Diazoxide choline (VYKAT XR)
Eculizumab (SOLIRIS)
Eculizumab-aagh (EPYSQLI)
Eculizumab-aeeb (BKEMV)
Eladocagene exuparvovec-tneq (KEBILDI)
Elafibranor (IQIRVO)
Elapegademase-lvlr (REVCOVI)

Elivaldogene autotemcel (SKYSONA)
Fosdenopterin (NULIBRY)
Givosiran (GIVLAARI)
Inebilizumab-cdon (UPLIZNA)
Iptacopan (FABHALTA)
Leniolisib (JOENJA)
Levacetylleucine (AQNEURSA)
Levoketoconazole (RECORLEV)
Lonafarnib (ZOKINVY)
Lumasiran (OXLUMO)
Luspatercept (REBLOZYL)
Maralixibat (LIVMARLI)
Mavacamten (CAMZYOS)
Mavorixafor (XOLREMDI)
Mirdametinib (GOMEKLI)
Mitapivat (PYRUKYND)
Nedosiran (RIVFLOZA)
Odevixibat (BYLVAY)
Olipudase alfa-rpcp (XENPOZYME)
Palovarotene (SOHONOS)
Palopegteriparatide (YORVIPATH)
Pegcetacoplan (EMPAVELI)
Plasminogen, human-tvmh (RYPLAZIM)
Pozelimab-bbfg (VEOPOZ)
Ravulizumab-cwvz (ULTOMIRIS)
Remestemcel-L-rknd (RYONCIL)
Rozanolixizumab-noli (RYSTIGGO)
Satralizumab-mwge (ENSPRYNG)
Seladelpar (LIVDELZI)
Sodium thiosulfate (PEDMARK)
Sutimlimab-jome (ENJAYMO)
Tofersen (QALSODY)
Trientine tetrahydrochloride (CUVRIOR)
Velmanase alfa-tycv (LAMZEDE)
Zilucoplan (ZILBRYSQ)

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

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

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

P&T/DUR Review: 6/25; 4/25; 2/25; 12/24; 10/24; 8/24; 4/24; 12/23; 10/23; 6/23; 2/23; 12/22; 6/22; 4/22; 12/21; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: 5/12/25; 3/10/25; 1/1/25; 9/1/24; 5/1/24; 1/1/24; 11/1/23; 7/1/23; 4/1/23; 1/1/23; 7/1/22; 5/1/22; 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20

ProDUR Report for January through March 2025
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	2	0	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	2,210	607	0	1,601	1.1%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	10,427	3,351	0	7,040	5.5%	N/A
ER (Early Refill)	**Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)**	**Set alert/Deny claim**	**116,766**	**27,578**	**154**	**89,034**	**62.6%**	**23.6%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	42,347	12,308	0	29,980	22.7%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	976	239	0	737	0.5%	N/A
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	4	4	0	0	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	816	264	0	552	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	386	133	0	252	0.2%	N/A
PA (Drug/Age Precaution)	Products containing Codeine being billed and patient is less than 18 years of age	Set alert/Pay claim	15	6	0	9	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**157**	**66**	**0**	**91**	**0.0%**	**42.0%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	12,161	3,699	0	8,445	6.5%	N/A
		Totals	**186,267**					

ProDUR Report for January through March 2025
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	9,133	1,991	7,142	90,394	10.1%	21.8%
ER	Prozac (Fluoxetine)	6,848	1,536	5,312	72,709	9.4%	22.4%
ER	Lexapro (Escitalopram)	6,644	1,309	5,335	67,136	9.8%	19.7%
ER	Celexa (Citalopram)	2,030	476	1,554	23,130	8.7%	23.4%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	9,760	1,972	7,788	98,077	9.9%	20.2%
ER	Trazodone	8,750	2,107	6,643	75,462	11.6%	24.1%
ER	Cymbalta (Duloxetine)	6,185	1,455	4,730	55,484	11.1%	23.5%
ER	Effexor (Venlafaxine)	3,148	661	2,487	31,800	9.8%	21.0%
ER	Remeron (Mirtazapine)	2,486	563	1,923	19,842	12.4%	22.6%
ER	Elavil (Amitriptyline)	1,971	562	1,409	20,199	9.7%	28.5%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	5,817	1,666	4,151	39,270	14.7%	28.6%
ER	Abilify (Aripiprazole)	4,930	1,066	3,864	35,872	13.7%	21.6%
ER	Zyprexa (Olanzapine)	3,411	904	2,507	24,054	14.1%	26.5%
ER	Risperdal (Risperidone)	2,404	591	1,813	15,435	15.6%	24.6%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	4,683	1,071	3,612	44,487	10.5%	22.9%
ER	Lorazepam	436	155	281	13,298	3.2%	35.6%
ER	Alprazolam	222	59	163	7,479	2.9%	26.6%
ER	Diazepam	128	39	89	4,567	2.8%	30.5%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	8,028	1,844	6,184	40,605	14.3%	23.0%
ER	Intuniv (Guanfacine ER)	2,370	440	1,930	18,944	12.4%	18.6%
ER	Depakote (Divalproex)	2,024	614	1,410	13,470	15.0%	30.3%
ER	Suboxone (Buprenorphine/Naloxone)	92	36	56	1,567	5.8%	39.1%

ProDUR Report for January through March 2025
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC-Other
ER	January	6,259	104	267	778	6	4,861	26	3	214
ER	February	5,846	120	247	713	8	4,530	31	5	192
ER	March	7,461	157	287	802	11	5,954	43	0	207
	Total	**19,566**	**381**	**801**	**2,293**	**25**	**15,345**	**100**	**8**	**613**
	Percentage of Total Overrides		**1.9%**	**4.1%**	**11.7%**	**0.1%**	**78.4%**	**0.5%**	**0.0%**	**3.1%**

ProDUR Report for January through March 2025			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
January	DD	14	$2,274.73
	ER	113	$46,187.18
	ID	20	$2,752.75
	LR	3	$985.97
	TD	3	$799.51
	January Total	**153**	**$53,000.14**
February	DA	1	$231.99
	DD	26	$7,463.15
	ER	146	$48,259.85
	HD	1	$62.99
	ID	16	$2,271.39
	TD	5	$792.58
	February Total	**195**	**$59,081.95**
March	DD	20	$2,437.67
	ER	54	$12,049.15
	ID	14	$2,560.06
	LR	1	$11.86
	MX	1	$15.23
	TD	2	$172.24
	March Total	**92**	**$17,246.21**
	Total 1Q2025 Savings		**$129,328.30**

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Billing Correction Review	High Cost OCC 3	Total Patients Identified	56	52	8	
		Total Claims Identified	59	53	8	
		Claims reviewed	3	1		
		Estimated Savings	$0	$0		
	OCC 4 with OCC 2 for different NDC	Total Patients Identified	16	20	2	
		Total Claims Identified	17	20	2	
	OCC 4 with OCC 2 for the same NDC	Total Patients Identified	6	20		
		Total Claims Identified	6	22		
	OCC 4 with Primary Payer Rejection Code	Total Patients Identified	4	5	1	
		Total Claims Identified	4	5	1	

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

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	11	11	6	
		Unique Patients Identified	11	11	6	
		Total Faxes Successfully Sent	8	8	4	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	2	4		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$565	$937		
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	96	72	47	
		Unique Patients Identified	96	72	49	
		Total Faxes Successfully Sent	79	43	36	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	39	22	6	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$26,468	$7,965	$1,218	

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

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	1	1		
		Total Faxes Successfully Sent	1	1		
		Prescriptions Unchanged after 3 Months of Fax Sent	1			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0			

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

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	876	915	300	
		High risk patients identified	9	7	4	
		Prescribers successfully notified	8	7		
		Patients with change in antipsychotic drug in following 90 days	1	1		
		Patients with continued antipsychotic therapy in the following 90 days	8	6		

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

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	62	53	5	
		Total prescribers identified	60	53	5	
		Prescribers successfully notified	60	53	3	
		Patients with claims for the same antipsychotic within the next 90 days	33	23		
		Patients with claims for a different antipsychotic within the next 90 days	2	2		

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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	63	55		
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	18	25		
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	156	188		
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	35	20		
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	22	23		
		Letters Sent To Providers	15	16		
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	28	23		
		Letters Sent To Providers	31	25		
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	23	24		
		Letters Sent To Providers	16	13		
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	23	23		
		Letters Sent To Providers	5	9		
	Lock-In	RetroDUR Profiles Reviewed	8	8		
		Locked In	0	0		

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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	15	17	9	
		Total prescribers identified	14	16	9	
		Prescribers successfully notified	13	13	6	
		Patients with paid claims within next 60 days	10	13	1	
		Patients with denied claim within next 60 days	12	10	1	

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

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	71	47	15	
		Total prescribers identified	71	47	15	
		Prescribers successfully notified	67	45	3	
		Patients with discontinuation of therapy within next 90 days	19	15	15	
		Patients with new prescription for naloxone within next 90 days		1		
		Average number of sedative drugs dispensed within next 90 days	23	16	0	
		Average number of sedative prescribers writing prescriptions in next 90 days	23	16	0	
	Oncology Denials	Total patients identified	3	2		
		Total prescribers identified	3	2		
		Prescribers successfully notified	2	2		
		Patients with claims for the same drug within the next 90 days	2	1		
		Patients with claims for any oncology agent within the next 90 days	2	1		
	TCAs in Children	TCA Denials in Children	35	36	9	
		Total patients identified	11	12	4	
		Total prescribers identified	11	11	3	
		Prescribers successfully notified	6	5	1	
		Patients with claims for a TCA within the next 90 days	2	3		
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days		1		

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New and Emerging Therapies for Metabolic Dysfunction-Associated Steatotic Liver Disease/Metabolic Dysfunction-Associated Steatohepatitis (MASLD/MASH) in Adults

Sara Fletcher, PharmD, MPH, BCPS, Oregon State University Drug Use Research and Management Group

Introduction

The American Association for the Study of Liver Diseases (AASLD) introduced new nomenclature for fatty liver disease in June 2023. Steatotic liver disease is the new umbrella term describing hepatic steatosis, with subcategories that include metabolic dysfunction-associated steatotic liver disease (MASLD) and MASLD with increased alcohol intake (MetALD).[1] The terms MASLD and metabolic dysfunction-associated steatohepatitis (MASH) were introduced in place of nonalcoholic fatty liver disease (NAFLD) and its subcategory nonalcoholic steatohepatitis (NASH).[1-3] MASLD is defined by the presence of hepatic steatosis on imaging or biopsy and at least one cardiometabolic risk factor of: increased body mass index (BMI) or waist circumference; increased fasting glucose or hemoglobin A1C (HbA1C) or type 2 diabetes (T2D); hypertension; elevated plasma triglycerides; or decreased high-density lipoprotein (HDL).[1]

MASH is a subcategory of MASLD which includes inflammation and hepatocyte injury (e.g., hepatocyte ballooning), with or without evidence of liver fibrosis.[4] MASLD affects about 25% of people worldwide, and 12-14% of those with MASLD are estimated to have MASH.[4] Complications can include cirrhosis, hepatic decompensation, and death.

Fibrosis Stage

Once diagnosed, MASH is described by stages of fibrosis (**Table 1**).

Table 1. Stages of MASH Fibrosis[4,5]

Fibrosis Stages	Description
No Fibrosis (F0)	None
Stage 1, Mild (F1) • F1A • F1B • F1C	Perisinusoidal OR periportal fibrosis • Mild perisinusoidal fibrosis • Moderate perisinusoidal fibrosis • Only portal/periportal fibrosis
Stage 2 Moderate (F2)	Perisinusoidal AND portal/periportal fibrosis
Stage 3, Severe (F3)	Bridging fibrosis
Stage 4, Cirrhosis (F4)	Cirrhosis

Treatment

Historically no medications have been specifically indicated for MASH. Treatment focuses on cardiometabolic risk factor management including guideline-directed therapy for T2D, dyslipidemia, obesity, metabolic syndrome, prediabetes, hypertension, and cardiovascular disease.[4]

Pioglitazone and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for people with T2D and biopsy-proven MASH and should be considered when there is increased risk of MASH based on presence of risk factors and likelihood of fibrosis using non-invasive tests (e.g., fibrosis-4 index [FIB-4]).[4,6] However, pioglitazone has notable side effects, including weight gain and potential risk for worsening heart failure which may preclude use in general practice.[4,6] In large phase III trials, pioglitazone did not improve liver histology or fibrosis in non-cirrhotic MASH, though multiple smaller studies with lower quality evidence have shown improvement in fibrosis.[3,7] In people with T2D and MASLD, American Academy of Clinical Endocrinology (AACE) recommends providers consider pioglitazone, GLP-1 RAs, or sodium-glucose cotransporter-2 (SGLT2) inhibitors for cardiometabolic benefit, though there is no evidence of benefit for liver related outcomes with SGLT2 inhibitors.[4] Some guidelines also suggest vitamin E for people with MASH but without comorbid T2D or advanced fibrosis.[4,8] Not all organizations recommend vitamin E because of potential long-term side effects (i.e., cardiovascular disease, prostate cancer) and large phase 3 trials did not show robust improvement in histologic outcomes compared to placebo.[3,7]

Weight Management

Lifestyle interventions (e.g., diet and exercise) are recommended for all adults with MASLD.[4] In adults with MASLD and overweight, weight loss of at least 5% reduces liver fat and has cardiometabolic benefits, 7-10% reduces liver inflammation, and 10% or more improves fibrosis and may reverse steatohepatitis.[3,4]

For people with MASLD and BMI of at least 27 kg/m^2, the AACE recommends the addition of semaglutide 2.4 mg/week or liraglutide 3 mg/day when weight management goals are not effectively achieved by lifestyle interventions alone.[4] Hepatic histologic benefit could be expected if substantial weight loss is induced by GLP-1 RAs. There is a similar a safety profile for use in patients with MASH (including compensated cirrhosis) and they are recommended for use with indications of T2D and obesity due to cardiometabolic benefits.[3] Bariatric surgery is also an option to treat MASLD and improve cardiometabolic health in some patients.[3,4]

Medicaid compendia (i.e., Micromedex) support use of semaglutide and liraglutide for MASH in adults with overweight or obesity based on results of phase 2 studies.[9,10] A phase 2 trial supporting tirzepatide in MASH is also published.[11] Semaglutide in patients with fibrosis stage 4 did not improve fibrosis or resolution of MASH.[12] A phase 2 study of daily dosed injectable semaglutide (0.1 mg, 0.2 mg, 0.4 mg) in stage 1, 2, or 3 showed improvement for MASH resolution and fibrosis improvement at week 72 compared to placebo (**Table 2**). The phase 2 SYNERGY-NASH study of weekly dosed tirzepatide (5 mg, 10 mg, 15 mg) in stage 2 or 3 fibrosis also showed resolution of MASH and improvement of fibrosis (**Table 2**) at week 52.[11] Though not a primary endpoint, a 10.7-15.6% weight loss was seen in tirzepatide treated patients and 5-13% in semaglutide treated patients.[11,13] Studies of liraglutide included fewer participants and evaluated slightly different outcomes. Details of these studies are available at: https://www.orpdl.org/durm/meetings/meetingdocs/2024_08_01/archives/2024_08_01_Rezdiffra_NDE.pdf.

Table 2. Selected GLP-1 RA phase 2 studies*[11,13]

	MASH Resolution	Fibrosis Improvement
Semaglutide 0.1 mg	40% OR 3.36 (95% CI 1.29-8.86)	49% OR 1.96 (95% CI 0.86-4.51)
Semaglutide 0.2 mg	36% OR 2.71 (95% CI 1.06-7.56)	32% OR 1.00 (95% CI 0.43-2.32)
Semaglutide 0.4 mg	59% OR 6.87 (95% CI 2.60-17.63)	43% OR 1.42 (95% CI 0.62-3.28)
Placebo	17%	33%
Tirzepatide 5 mg	44% Difference 34% (95% CI 17-50)	55% Difference 25% (95% CI 5-46)
Tirzepatide 10 mg	56% Difference 46% (95% CI 29-62)	51% Difference 22% (95% CI 1-42)
Tirzepatide 15 mg	62% Difference 53% (95% CI 36-69)	51% Difference 21% (95% CI 1-42)
Placebo	10%	30%

*Results from unique studies; not for direct comparison
CI=confidence interval; MASH=metabolic dysfunction-associated steatohepatitis; OR=odds ratio

Resmetirom

Resmetirom, a partial agonist of the thyroid hormone receptor-beta (THR-β) was approved by the FDA in March 2024 through the FDA accelerated approval pathway. It is indicated, in conjunction with diet and exercise, for the treatment of adults with MASH who have moderate to advanced liver fibrosis (F2 to F3).[14] Per FDA guidance, fibrosis staging and NAFLD activity score (NAS) are used in clinical trials as critical inclusion criteria and surrogate outcomes for testing.[15] Improved mortality has not yet been demonstrated from histologic changes.[3] The NAS is an unweighted composite 0 to 8 point score determined by the summation of three components: steatosis grade, lobular inflammation, and ballooning scores.[4] Continued approval is contingent upon verification and description of clinical benefit (e.g., death from any cause, liver transplantation, hepatic decompensation events) in confirmatory trials.[14] Evidence for efficacy and safety of resmetirom is from an ongoing phase 3 trial which enrolled adults who had at least 3 of 5 metabolic risk factors, biopsy confirmed MASH, and a NAS total score of 4 or more with presence of histological steatosis, lobular inflammation, and ballooning.[16] The intention-to-treat primary population (N=966) consisted of all randomized patients with F1B, F2, and F3 fibrosis stage, and the primary biopsy analysis population (N=955) included those with paired biopsies.[16] Patients were White (89.3%), with mean BMI of more than 35 kg/m^2, T2D (67% with baseline HbA1C ~6.6%), hypertension (78.1%), and dyslipidemia (71.3%), and no history of atherosclerotic cardiovascular disease (ASCVD) (5.9%).[16] For those with T2D, 21% were on a GLP-1 RA, 20% on an SGLT2 inhibitor, and 18.2% on insulin. Those with an HbA1C of more than 9% were excluded.[16] For those with dyslipidemia, 68.7% were taking a statin. [16]

There were two primary endpoints: MASH resolution and fibrosis improvement. MASH resolution at week 52 was defined as achievement of hepatocellular ballooning score of 0, lobular inflammation score of 0 to 1, and reduction of NAS by 2 or more points with no worsening of fibrosis.[16] The second primary endpoint was defined as improvement in fibrosis by at least one stage without worsening of NAS.[16] Results compared to placebo are in **Table 3**. There was no effect on body weight or heart rate.[16] Most adverse events were mild to moderate, with diarrhea (27-33.4%) lasting a median of 15-20 days being most common. Discontinuation due to adverse events were more frequent in the resmetirom 100 mg group (6.8%) than resmetirom 80mg (1.8%) or placebo (2.2%).[16] Dosing in the study was randomly assigned; dosing by FDA label is weight-based with the 100 mg dose reserved for people weighing 100 kg or more. Drug interactions (e.g., certain statins) may require dose reduction. Long-term safety remains unknown.

Table 3. MAESTRO-NASH Primary Endpoints Results OHP Policy

	MASH Resolution	Fibrosis Improvement
Resmetirom 80 mg	25.9% 95% CI 11.0 to 21.8% p<0.001	24.2% 95% CI 4.8 to 15.7% p<0.001
Resmetirom 100 mg	29.9% 95% CI 15.3 to 26.2% p<0.001	25.9% 95% CI 6.4 to 17.2% p<0.001
Placebo	9.7%	14.2%
CI=confidence interval; MASH=metabolic-dysfunction steatohepatitis		

Use of resmetirom is available with prior authorization for eligible patients with Oregon Health Plan (OHP) open card benefits. Use of GLP-1 RAs with compendia support for MASH can be covered with prior authorization for Medicaid members with both overweight/obesity and MASH. OHP will continue to cover GLP-1 RAs for people with T2D who are taking or have contraindications to metformin.

Conclusion

MASH is an important cause of liver disease which is increasing in prevalence as metabolic risk factors increase. Risk factor management is a primary component of care for patients with MASH. A novel medication, resmetirom, has received accelerated approval for treatment of stage F2 or F3 MASH in conjunction with lifestyle changes. It was tested in patients with multiple risk factors and HbA1C less than 9% and demonstrated histologic improvements in MASH and fibrosis in some patients compared to placebo. Efficacy for other clinical outcomes is unknown. Additionally, evidence supporting the use of certain GLP-1 RAs is increasing. It is unclear if GLP-1 RA induced weight loss is the primary driver for improvements seen in MASH and fibrosis in phase 2 studies. OHP will cover resmetirom, liraglutide, and semaglutide for Oregon fee-for-service members who have MASH and who meet prior authorization criteria.

Key Points

- Management of modifiable risk factors, including weight loss, is important for treatment of MASH.
- Resmetirom is a new medication approved for MASH based on histologic improvement in a phase 3 study.
- Liraglutide, semaglutide, and tirzepatide have phase 2 evidence of histologic improvement in MASH.
- Prior Authorization criteria for resmetirom and certain GLP-1 RAs are available at: https://www.orpdl.org/drugs/

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Update on the Biosimilar Landscape in the United States Market

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Introduction

A biosimilar is a biologic medication that is highly similar to and has no clinically meaningful differences in safety and efficacy from an existing Food and Drug Administration (FDA)-approved biologic, called a reference product.[1] Biologics include injectable monoclonal antibodies, insulin, vaccines, and colony stimulating factors. Although the overall number of prescriptions for biologics is relatively modest compared to oral small-molecule medications, their use is associated with significant financial impact.[2] Since biologic medication structures are more complex than those of small-molecule medications (e.g. methotrexate) and because they come from living organisms (e.g., bacteria, yeast), variations can occur from batch to batch.[1] As a result, biologics are complicated and expensive to purify, process, and manufacture, which often affects their marketed price.[1] Biosimilars can mitigate the cost pressures of reference biologic therapy because they are typically priced at least 25% lower, providing a means to administer biologic therapy, while also managing cost of care.[3] Since 2015, the United States (US) health care system has saved an estimated $23.6 billion through use of biosimilars in place of reference products.[3] This newsletter will review recent trends in the biosimilar market and present changes in Oregon Health Plan (OHP) fee-for-service (FFS) biosimilar policies for the class of biologics called the Targeted Immune Modulators (TIMs) for Autoimmune Conditions including rheumatoid arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, and Crohn's disease.

Targeted Immune Modulators

Targeted Immune Modulators include biologic disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs. Biologic DMARDs are large, complex, proteins that must be administered parentally. In contrast, targeted synthetic DMARDs are small chemical molecules that can be taken orally. DMARDs for auto-immune conditions are classified according to their mechanism of action as outlined in **Table 1.**

Table 1. Mechanism Of Action for DMARDs

Mechanism Of Action	Disease Modifying Antirheumatic Drugs (DMARDs)
Injectable Biologic DMARDs	
Tumor Necrosis Factor Inhibitors	Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, Infliximab
Interleukin Antagonists	Anakinra, Bimekizumab, Brodalumab, Canakinumab Guselkumab, Ixekizumab, Mirkizumab, Risankizumab, Sarilumab, Spesolimab, Secukinumab, Tildrakizumab, Tocilizumab, Ustekinumab
Integrin Receptor Antagonists	Vedolizumab, Natalizumab
Lymphocyte Antagonists	Abatacept, Rituximab
Oral Targeted Synthetic DMARDs	
Janus Kinase Inhibitors	Baricitinib, Tofacitinib, Upadacitinib
Phosphodiesterase-4 Inhibitor	Apremilast, Roflumilast

Some TIMs have narrow indications while others are FDA-approved for a broad spectrum of autoimmune conditions. For example, adalimumab (HUMIRA) is FDA-approved to treat 9 conditions including ankylosing spondylitis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, hidradenitis suppurativa, non-infectious uveitis, Crohn's disease, and ulcerative colitis. In comparison, ustekinumab (STELARA) is approved to treat 4 conditions including Crohn's disease, plaque psoriasis, psoriatic arthritis, and ulcerative colitis. As of October 2024, the FDA has approved biosimilars for 5 reference TIMs: used to treat autoimmune conditions: adalimumab (HUMIRA), etanercept (ENBREL), infliximab (REMICADE), rituximab (RITUXAN), and ustekinumab (STELARA).

FDA Guidance for Biosimilar Approval

The Biologics Price Competition and Innovation (BPCI) Act of 2009 was included as part of the Affordable Care Act (ACA) health-care-reform legislation enacted in 2010.[4] The BPCI Act created an abbreviated licensure pathway for biological products shown to be biosimilar with an FDA-licensed reference product. This regulation allowed the FDA to approve a biologic product based on less than a full complement of preclinical and clinical data if the sponsor could provide analytic studies showing its product was "highly similar" to an approved product.[4] All FDA-approved biosimilars are deemed safe and effective relative to the innovator product.[5] There are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency.[6]

Trends in Biosimilar Product Approvals

In 2023, the top 5 specialty drugs in US mail-order pharmacies by volume and total expenditure were all biologics: adalimumab, ustekinumab, dupilumab, risankizumab, and etanercept.[7] According to the

FDA biosimilars dashboard, the agency has approved 50 biosimilar products from different classes since 2015.[5] Additionally, nearly 100 products are enrolled in the agency's product development program for biosimilars pipeline.[5]

In the overall US market, adalimumab is one of the top 5 drugs by expenditure.[8] Adalimumab is the first self-administered biologic product with a significant number of biosimilar competitors.[8] The patent on adalimumab expired in 2016, but because of legal challenges related to many patents asserted on manufacturing processes, the first adalimumab biosimilar did not enter the US market until 2023.[3] There are now 9 FDA-approved biosimilars for adalimumab (HUMIRA).[7] There are 2 different concentrations of adalimumab commercially available, high concentration (100 mg/mL) and low concentration (50 mg/mL). Although adalimumab biosimilars became available in 2023, this introduction had minimal impact on overall adalimumab expenditures.[8] For example, in clinic settings in 2023, $5.6 million was spent on adalimumab biosimilars versus $1.6 billion in expenditures for brand name adalimumab (HUMIRA).[8]

Interchangeable Products

Biosimilars that the FDA classifies as "interchangeable" have met additional requirements and, as with generic drugs, they can be substituted for the innovator product without consulting a prescriber.[5] The regulatory concept of interchangeability creates confusion for prescribers and patients and also complicates decisions by manufacturers about whether and how to develop their biosimilar products.[5] An interchangeable biological product is a product that has been shown to be biosimilar to the reference product, and can be expected to produce the same clinical result as the reference product in any given patient.[9]

In the US, substitution policies are determined by state laws, not by the FDA. In Oregon, biosimilar legislation is addressed in OAR 855-139-0300 Oregon Administrative Rules[10] A pharmacy or pharmacist filling a prescription for a biological product may substitute a biosimilar product for the prescribed biological product if all of the following conditions are met:[10]

- The biosimilar product has been determined by the FDA to be interchangeable with the prescribed biological product.[10]
- The prescribing practitioner has not designated on the prescription that substitution is prohibited.[10]
- The patient for whom the biological product is prescribed is informed of the substitution prior to dispensing the biosimilar product.[10]
- The pharmacy or pharmacist provides written, electronic or telephonic notification of the substitution to the prescribing practitioner or the prescribing practitioner's staff within 3 business days of dispensing the biosimilar product.[10]

The "Biosimilar Red Tape Elimination Act" (S.2305), currently under review in the US Senate, could deem FDA-approved biosimilars as interchangeable without requiring additional switching study evidence.[11] The FDA Purple Book provides a listing of all originator, biosimilar, and interchangeable biosimilar products currently approved by the FDA.[12]

As of July 2024, 13 biosimilars are FDA-approved as interchangeable with the reference product. There are 2 biosimilar, interchangeable products for insulin glargine (LANTUS) and 5 products for adalimumab (HUMIRA). One interchangeable product is available for ranibizumab (LUCENTIS), which is used to prevent vision loss in people with macular degeneration. The most recent interchangeable biosimilar was approved for eculizumab (SOLIRIS), which is approved to prevent complications in people with paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. **Table 2** presents a list of adalimumab biosimilars and highlights the 5 products are interchangeable with the reference adalimumab product (HUMIRA).

Table 2. FDA-Approved Adalimumab Biosimilars[6]

Biosimilar Product	Interchangeable
Abrilada (adalimumab-afzb)	Yes
Amjevita (adalimumab-atto)	Yes
Cyltezo (adalimumab-adbm)	Yes
Hadlima (adalimumab-bwwd)	No
Hulio (adalimumab-fkjp)	No
Hyrimoz (adalimumab-adaz)	Yes
Idacio (adalimumab-aacf)	No
Simlandi (adalimumab-ryvk)	Yes
Yuflyma (adalimumab-aaty)	No
Yusimry (adalimumab-aqvh)	No

Oregon Health Plan Policy Updates

At the August 2024 meeting, the Oregon Drug Use Review/Pharmacy & Therapeutics Committee reviewed the prior authorization (PA) criteria for TIMs used to treat autoimmune conditions. The committee agreed to implementation of 3 separate tiers for the TIMs in this class:

- Tier 1 agents are preferred, first line medications.
- Tier 2 agents are preferred, second line medications.
- Tier 3 agents are nonpreferred, third line medications.

All TIMs are subject to PA before OHP FFS will pay for the claims. After executive session, where overall comparative costs and drug rebates were assessed, the following recommendations for updating the Preferred Drug List (PDL) were approved by the Committee and will become effective January 1, 2025:

- Current preferred products adalimumab (HUMIRA) and etanercept (ENBREL) will be designated as Tier 1 in the TIMs for autoimmune conditions class of medications.
- Four biosimilar products including infliximab-axxq (AVSOLA), adalimumab-ryvk (SIMLANDI), adalimumab-atto (AMJEVITA 100 mg/mL), and adalimumab-fkjp 50 mg/mL will be designated as Tier 1 TIMs.
- Ixekizumab (TALTZ), apremilast (OTEZLA), and tofacitinib citrate (XELJANZ) will be designated as Tier 2 TIMs.
- Secukinumab (COSENTYX) will be changed from preferred to non-preferred, Tier 3.
- All other TIMS will be designated as non-preferred, Tier 3.
- All other biosimilar products will be designated as non-preferred, Tier 3.

The OHP FFS Drug Class list and PA criteria can be accessed at this website: https://orpdl.org/drugs/

Oregon Health Plan Biosimilar Prior Authorization Criteria

- All biosimilars used for TIMS require a PA.
- Certain biosimilars for adalimumab and infliximab are preferred, Tier 1 agents in the class of Targeted Immune Modulators for autoimmune conditions.
- Oncology biosimilars are all preferred with no PA restrictions.
- Colony stimulating factor biosimilars are non-preferred.

Conclusion

Biosimilar products have the potential to increase accessibility and expand the use of biologic therapies in a cost-effective manner. The impact of biosimilars reaches beyond savings to the health care system, by increasing health equity, and could help improve patients' access to medications that previously may not have been covered by their insurance or were otherwise unaffordable.[9] The OHP FFS program has recently revised the PDL status of specific biosimilars to encourage adoption and utilization of these cost-effective products.

Peer Reviewed By: Adam Saulles, PharmD, BCACP, CSP, Senior Manager, Clinical Pharmacy Services, CredenaHealth and Alex Ortega Loayza, MD, MCR, Professor of Dermatology, OHSU School of Medicine

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Review of Off-Label Use of Gabapentin and Pregabalin

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Introduction

Gabapentinoids, including gabapentin and pregabalin, are approved by the Food Drug Administration (FDA) for the treatment of partial seizures, postherpetic neuralgia (PHN), and other neuropathic conditions (**Table 1**).[1,2] However, there is substantial use for off-label conditions (**Table 2).**[3,4] In a 2022 study, approximately 1 in 5 United States (U.S.) adults with chronic pain received a gabapentinoid.[4] This is likely a result of a need for alternatives to opioids. Center for Disease Control and Prevention (CDC) guidance includes gabapentinoids as an option for nonopioid therapy for subacute or chronic pain.[5] However, they are associated with small to moderate improvement in pain and have potential adverse events.[5]

Table 1: FDA Approved Indications.[1,2]

Indications	Gabapentin	Pregabalin
Diabetic peripheral neuropathy		✓
Fibromyalgia		✓
Partial-onset seizures	✓	✓
Postherpetic neuralgia	✓	✓
Spinal cord injury pain		✓

Gabapentin and pregabalin bind to the alpha2-delta subunit of voltage gated calcium channels resulting in anti-nociceptive and anticonvulsant effects.[1,2] Despite an increased bioavailability and faster onset of action with pregabalin compared to gabapentin, there is insufficient evidence that one agent is more effective than the other.[6] This newsletter will summarize the efficacy and safety of gabapentin and pregabalin for their use in select off-label conditions, including neuropathic pain and generalized anxiety disorder (GAD).

Neuropathic Pain

Gabapentin and pregabalin are commonly used for various types of neuropathic pain, despite differences in their labeled indications. The FDA denied approval of gabapentin for a broad neuropathic pain indication, and later approved it only for PHN based on two supportive studies .[6] A Cochrane systematic review concluded that there is moderate evidence that gabapentin is more effective than placebo over 4-12 weeks, as measured by a 50% or more reduction in pain associated with PHN (relative risk [RR]: 1.7, 95% confidence interval [CI]: 1.4-2.0) with a number needed-to-treat (NNT) of 7 (95% CI 5.5 to 9.4) and diabetic peripheral neuropathy (RR:1.7, CI: 1.4-2.0; NNT 6; 95% CI 5.0 to 9.7).[7] Despite different study populations and durations, this effect is comparable to the NNT seen with tricyclic antidepressants (NNT 3-4) and serotonin norepinephrine reuptake inhibitors (NNT 6).[8] However, in positive trials in diabetic peripheral neuropathy, gabapentin results in a difference of only about 1 point on a 1-to-10-point pain scale and there have been at least two negative studies of gabapentin in diabetic peripheral neuropathy.[3,9] A minimum clinically important difference (MCID) in the numerical pain scale is at least 2 points.[10] There is limited evidence for use of gabapentin in other neuropathic pain conditions, including central neuropathic pain, neuropathic back pain, HIV neuropathy, spinal cord injury, radicular leg pain, and cancer-related neuropathic pain.[7]

Table 2: Off-Label Uses of Gabapentinoids.

Gabapentin	Pregabalin
Compendia* supported off-label uses	
• Alcohol dependence • Diabetic peripheral neuropathy • Postoperative pain • Uremia pruritus • Vasomotor symptoms	• Generalized anxiety disorder • Postoperative pain • Restless leg syndrome** • Social anxiety disorder • Uremia pruritus
Off-label uses with insufficient or very low-quality evidence	
• Cancer related neuropathy • Fibromyalgia** • Generalized anxiety disorder • Neuropathic pain related to spinal cord injury • Panic disorder • Refractory cough • Social anxiety disorder • Trigeminal neuralgia	• Cancer-associated neuropathy • Familial dysautonomia • Obsessive-compulsive disorder • Panic disorder • Refractory cough • Ureteral stent symptoms • Vasomotor symptoms
Off-label uses with evidence of no benefit	
• HIV neuropathy • Back pain • Migraine prophylaxis	• HIV neuropathy • Back pain

*Compendia supported uses are supported by Micromedex with Level A or B evidence
**Unfunded Conditions on the Oregon Health Plan prioritized list of health services

A Cochrane systematic review concluded that pregabalin is more effective than placebo, as measured by a 50% or more reduction in pain, for the treatment of PHN based on moderate-quality evidence (pregabalin 300 mg daily RR: 2.5, CI: 1.9-3.4, NNT: 6; pregabalin 600 mg daily RR: 2.7, CI: 2.0-

3.5, NNT: 4) and peripheral diabetic neuropathy (pregabalin 300 mg daily RR: 1.3, CI: 1.2-1.5, NNT: 14; pregabalin 600 mg daily RR: 1.6, CI: 1.4-1.9, NNT: 7).[11] There is low-quality evidence for pregabalin 600 mg in central neuropathy (RR: 1.5, CI: 1.2-1.9, NNT: 8) and moderate-quality evidence that pregabalin is not more effective than placebo for the treatment of HIV neuropathy.[11] There is insufficient evidence for the efficacy of pregabalin in neuropathic cancer pain, painful polyneuropathy and back pain with radiculopathy.[11]

Generalized Anxiety Disorder

In February 2022, the Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG) developed treatment guidance for GAD.[12] The algorithm is included in **Appendix 1** and the full guidance can be found here: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/Pages/MHCAG-Recommendations.aspx.[13] The algorithm recommends pregabalin as first-line adjunct treatment for patients with GAD in conjunction with a selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).[12]

Moderate-quality evidence shows that pregabalin at doses of 300-600 mg/day may improve anxiety symptoms compared to placebo, as measured by the Hamilton Anxiety Rating Scale (HAM-A), based on studies of short duration (4-8 weeks) with high risk of attrition bias.[14] HAM-A measures the severity of anxiety symptoms and consists of 14 items with a total score ranging from 0-56. No MCID has been established for the HAM-A.[14] Studies demonstrate a medium effect size for anxiety reduction that is similar to SSRIs and SNRIs. One study evaluated pregabalin as adjunctive treatment in patients who had not adequately responded to a SSRI or SNRI over 8 weeks.[15] Subjects on pregabalin had a higher responder rate on the HAM-A than those on placebo (47.5% vs. 35.2%; odds ratio [OR] 1.77; 95% CI 1.12-2.79).[15] There are limited data evaluating the efficacy or safety of pregabalin for GAD in patients with comorbid substance use or other mental health disorders. There is also insufficient evidence supporting the use of gabapentin for the use of GAD.

Non-Neuropathic Pain

A systematic review of perioperative gabapentinoid for postoperative pain found a statistically significant reduction in postoperative pain compared to placebo at all time points from 6 hours to 48 hours postoperatively.[16] However, the mean difference was not clinically meaningful. The mean difference in pain score on a 100-point scale ranged from 2 to 10 with most relief seen within 6 hours.[16] The investigators noted that a difference of at least 10 points is needed for a MCID.

Another systematic review found limited evidence of no benefit with gabapentin and pregabalin for the treatment of chronic low back pain.[17] Overall, there is limited evidence to support the use of gabapentin and pregabalin in non-neuropathic pain indications in both acute and chronic settings.

Other

Vasomotor Symptoms

There is low-quality evidence that gabapentin reduces frequency of hot flashes associated with menopause compared to placebo at 12 weeks (mean difference [MD] -2.77; 95% CI -4.29 to -1.24) with no difference in duration or severity score of vasomotor symptoms.[18] Trials did not consistently meet the MCID for vasomotor symptom frequency (3.57 per day).[19] The North American Menopause Society recommends gabapentin for menopausal women who cannot tolerate hormone therapy.[20]

Alcohol Dependence

There is low-quality evidence of no significant difference in improved alcohol abstinence with gabapentin at varying doses compared to placebo (RR 1.33; 95% CI 0.84 to 2.10) and no significant benefit on relapse to heavy drinking (RR 0.80; 95% CI 0.57 to 1.13).[21] Low-quality evidence shows that gabapentin may reduce the percentage of heavy drinking days, decrease alcohol consumption, and decrease acute alcohol withdrawal symptoms.[22,23] Patients with more mild alcohol withdrawal symptoms that are stable enough to be treated in an outpatient setting may benefit from gabapentin.

Safety and Tolerability

For all off-label uses of gabapentin and pregabalin, there is a consistent trend toward higher rates of discontinuations due to adverse events compared to placebo, with the most common adverse events of dizziness, somnolence, headache, and sedation. Additional adverse events can include blurred vision, negative cognitive effects, sedation, weight gain, peripheral edema and increased risks of these events when used in combination with opioids. Rates of serious adverse effects in published trials are low.

The FDA issued a warning in 2010 of increased risk of respiratory depression when gabapentinoids are used with opioids or other central nervous system (CNS) depressants.[24] Observational studies have shown an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk for overdose, with higher risks at increased doses.[24] Pregabalin is a Schedule V controlled substance, defined as a drug with low potential for abuse and dependence. Although there may be low abuse potential in the general population, data suggests this risk is much higher among patients with substance use disorders, particularly opioid use disorder.[25,26]

Current Policies

In the Oregon Health Plan (OHP) fee-for-service (FFS) Medicaid program, prior authorization (PA) is required for

pregabalin. The goal of the PA is to limit use to FDA-approved and OHP-funded indications. Common conditions that are unfunded on the Health Evidence Review Commission (HERC) prioritized list include restless leg syndrome, fibromyalgia, and some polyneuropathies. Gabapentin is currently a preferred product and available without PA. In June 2024, the PA criteria was modified to allow use of pregabalin for GAD as adjunct to first-line treatment with a SSRI or SNRI, consistent with the MHCAG GAD treatment guidance.

Conclusion

Gabapentin and pregabalin are commonly used for off-label indications with limited evidence. Trials are short in duration (4-12 weeks), often have high placebo response rates, and result in modest benefit with a relatively small effect size. For the treatment of GAD, adjunctive pregabalin may be beneficial for those who cannot tolerate or have not benefit on first-line therapy alone.

Providers and patients should weigh the potential benefit of gabapentinoids with their side effects, risk of misuse and abuse in those at high risk for substance use disorder, risk for respiratory depression when used in combination with opioids, and risk of fetal harm when used in pregnancy.

When determined that it is appropriate to use a gabapentinoid off-label in clinical practice, patient education should be provided regarding limited evidence and potential adverse events. A reasonable time frame to evaluate clinical effects (6-8 weeks) of the medication should be determined, and if no clinical benefit is observed, the drug should be deprescribed.

Peer Reviewed By: Andrew Gibler, Pharm.D., RPh, Clinical Pharmacy Policy and Programs Manager, Oregon Health Authority, Health Policy and Analytics Division and Robert Hughes, DO, Family Medicine, Samaritan Health Services

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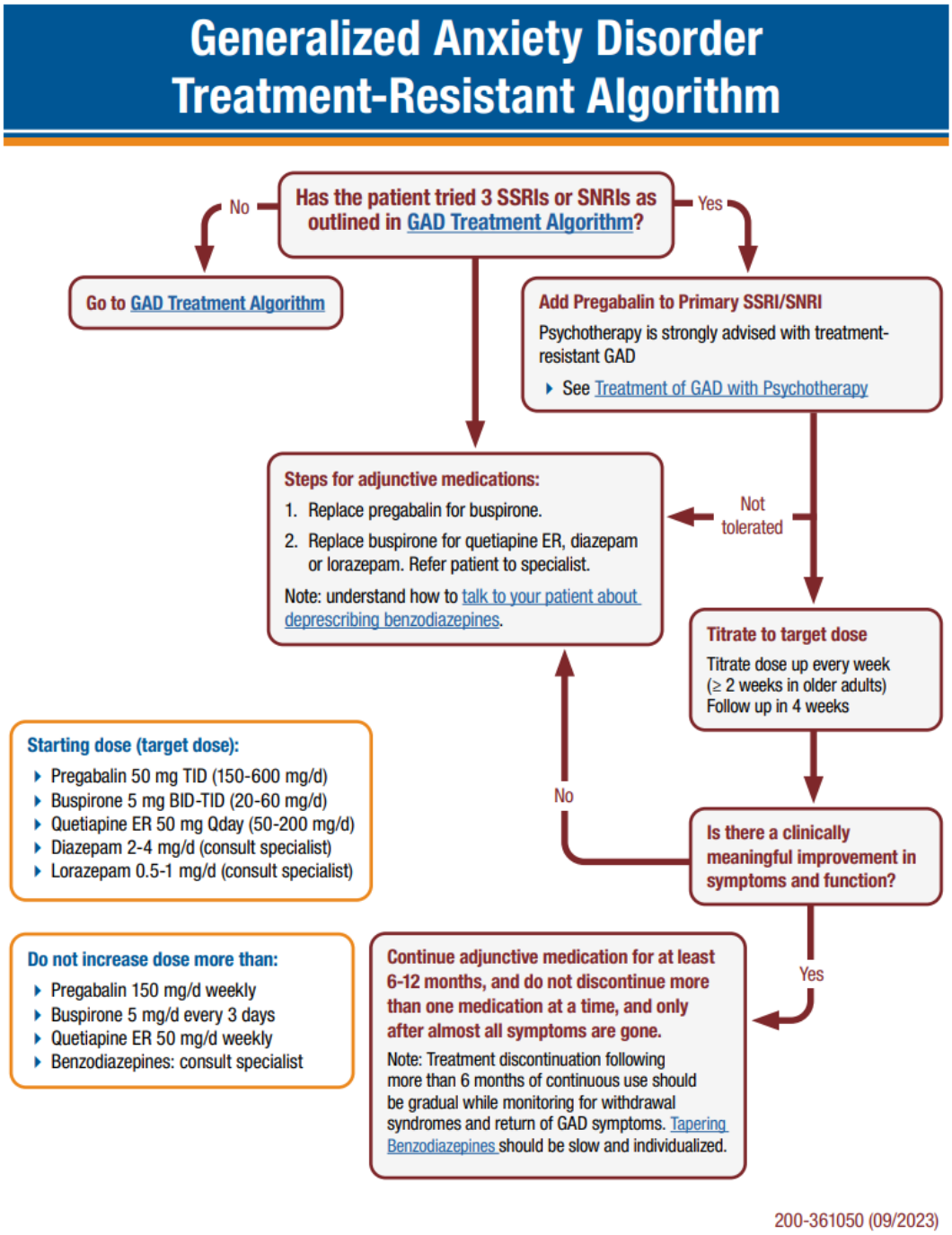
Appendix 1: Oregon Health Authority Mental Health Clinical Advisory Group Generalized Anxiety Disorder Treatment-Resistant Algorithm



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Drug Class Review: Actinic Keratosis

Date of Review: June 2025 **End Date of Literature Search:** 03/07/2025

Purpose for Class Review:
Evaluate evidence for treatment of actinic keratosis (AK), which is not funded according to the 2025 Health Evidence Review Commission (HERC) List of Prioritized Health Services.[1] Develop prior authorization (PA) criteria to provide a medical necessity pathway to coverage for AK in people with the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit.

Plain Language Summary:
- Actinic keratosis is a skin condition caused by sun damage. Because sun damage builds up over time, actinic keratosis is more common in older people. It appears as scaly, rough, or bumpy spots on the skin. Actinic keratosis is most common in people who have fair skin, have blonde or red hair, have freckles, or sunburn easily.
- Anyone can get actinic keratosis, but it is more common in males than in females. Common places for actinic keratosis to appear include: the scalp in people who are bald or have thinning hair, face, neck, hands, and arms.
- Without treatment, actinic keratosis can grow, spread, and may turn into skin cancer. Doctors can freeze the actinic keratosis spots off with liquid nitrogen or use a special tool to burn off actinic keratosis spots. Doctors can also prescribe a medicated cream or gel to apply to actinic keratosis areas. The 3 most common treatments are 5-fluorouracil cream, imiquimod cream, and diclofenac gel. To be effective, these medicines must be applied to the actinic keratosis spots once or twice every day over several weeks. The most common side effects from these medicines are redness, tenderness, itching, burning, and skin irritation in areas where the medicine is applied.
- Providers must explain to the Oregon Health Authority why someone needs medicine for actinic keratosis before the Oregon Health Plan will pay for it. This process is called prior authorization.

Research Questions:
1. What is the evidence for the efficacy of self-administered topical 5-fluorouracil, imiquimod, diclofenac, and tirbanibulin and provider-administered aminolaevulinic acid in treating AK?
2. What is the comparative safety of topical 5-fluorouracil, imiquimod, diclofenac, tirbanibulin and aminolaevulinic acid in treating AK?
3. Are there specific subpopulations based on age, ethnicity, comorbidities, disease duration or severity for which one therapeutic agent is better tolerated or more effective than other available topical treatments when used to manage AK?

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Conclusions:

- Three systematic reviews[2-4] and 2 clinical guidelines[5,6] provide evidence for the safety and efficacy of topical drugs to treat AK. There is evidence to support the efficacy topical drugs for AK but insufficient evidence to directly compare treatments.[5,6] A summary of comparative randomized controlled trials (RCTs) is presented in **Table 2**. Overall, these studies are at high-risk of bias due to open-label study design and enrollment of small patient populations.
- A 2009 systematic review evaluated RCTs which compared the treatment of AK with 5% 5-fluorouracil cream compared to other treatments including imiquimod cream, cryotherapy, diclofenac 3% gel, facial resurfacing, photodynamic therapy (PDT), 5% 5-fluorouracil cream augmented with tretinoin, and 0.5% 5-fluorouracil cream.[2] This review provides low-quality evidence to indicate that about 50% of patients using 5% 5-fluorouracil cream for the treatment of AK lesions can expect complete clearance; overall, an 80% reduction in lesion count can be expected; and a 90% reduction in total lesion count is likely.[2] The duration of follow-up varied between studies; from 3 to 12 weeks.[2] Although few patients stop treatment as a result of adverse events, up to one-half may not be able to complete the full treatment course.[2] However, the quality of the studies providing this evidence is poor.[2] Evidence on alternative treatments studied head-to-head with topical 5-fluorouracil is limited.[2]
- A 2012 Cochrane review assessed the effects of topical, oral, mechanical, and chemical interventions for management of AK.[3] Most of the studies lacked descriptions of some methodological details, such as the generation of the randomization sequence or allocation concealment, and half of the studies had a high risk of reporting bias.[3] Low-quality evidence showed that the primary outcome, complete clearance of AK lesions, equally favored 4 topical treatments compared to vehicle or placebo: 3% diclofenac (risk ration [RR] 2.46, 95% confidence interval [CI] 1.66 to 3.66; 3 RCTs; n=420), 0.5% 5-fluorouracil (RR 8.86, 95% CI: 3.67 to 21.44; 3 RCTs; n=522), 5% imiquimod (RR 7.70, 95% CI 4.63 to 12.79; 9 RCTs; n=1871), and 0.025% to 0.05% ingenol gel (RR 4.50, 95% CI 2.61 to 7.74; 2 RCTs; n= 456).[3] Of note, ingenol gel is on longer commercially available in the United States. One RCT compared 0.5% and 5% 5-fluorouracil formulations and found comparable efficacy and safety between both agents.[3]
- A 2022 systematic review compared different therapeutic options for managing AK.[4] The treatments included imiquimod, 5-fluorouracil, diclofenac, PDT with aminolevulinic acid (ALA-PDT), and PDT with methyl-aminolevulinate (PDT-MAL).[4] The included studies were of low to moderate risk of bias.[4] Twenty-three studies investigated treatment with imiquimod as monotherapy, while two studies investigated imiquimod plus cryotherapy and one used imiquimod plus PDT-MAL.[4] Overall, the percent reduction in AKs was 67.5 ± 19.6% at 1–3 months, 64.0 ± 13.0% at 3–6 months and 68.0 ± 1.6% at 6–12 months after treatment with imiquimod.[4] Thirteen studies compared topical 5-fluorouracil as monotherapy, and several others investigated 5-fluorouracil in combination with another agent (salicylic acid, calcipotriol, cryotherapy, PDT-MAL, and PDT-ALA).[4] Overall, after treatment with 5-fluorouracil monotherapy, the number of AKs was reduced by 80.1% at 1–3 months, and 67.4% at 3–6 months.[4] Treatment success is ≥ 75% clearance of AK lesions. Four studies investigated the effectiveness of twice daily application of diclofenac sodium 3.0% gel in the treatment of AKs.[4] Percent clearance of AKs at 1–3 months post diclofenac treatment was 36.3 ± 9.5%, which was lower compared to 5-fluorouracil and imiquimod therapies.[4]
- In 2021, the American Academy of Dermatology (AAD) published guidelines to assist in clinical decision-making for the management of AK.[5] Topical agents, cryosurgery, and PDT are all recommended in the guidance.[5] Choice of treatment is based on a number of factors, including the site of the AKs, whether AKs are solitary, multiple, or within an affected field, and patient preferences and tolerability.[5] Specific recommendations for topical therapies and quality of evidence are as follows:
    - The AAD recommends field treatment with 5-fluorouracil cream or imiquimod cream (Strong Recommendation; Moderate-Quality Evidence).[5]
    - The AAD conditionally recommends the use of diclofenac gel (Low-Quality Evidence).[5]
    - The AAD conditionally recommends red light PDT with aminolevulinic acid over cryosurgery alone (Low-Quality Evidence).[5]
    - AAD conditionally recommends combination treatment cryosurgery with 5-fluorouracil or imiquimod over cryosurgery alone (based on Moderate- and Low-Quality Evidence, respectively).[5]

- In 2022 the AAD published a focused guideline update on management of AK.[6] The purpose of the focused update was to incorporate recently published evidence on the use of topical tirbanibulin to treat AK.[6] Tirbanibulin was approved for the topical, field-directed treatment of AK on the scalp or face by the Food and Drug Administration (FDA) in December 2020.[6] Two phase 3 trials were identified and analysis of this evidence resulted in one recommendation.[6] Although the AAD work group recognized that tirbanibulin cost may be prohibitive without adequate insurance coverage and other strongly recommended treatments for AK may be available for lower cost, they concluded that the use of tirbanibulin is likely acceptable to patients and providers and feasible to implement especially considering the abbreviated duration of tirbanibulin treatment compared with the duration of other available topically applied agents for the management of AK.[6]
    - AAD recommends field treatment with topical tirbanibulin (Strong Recommendation; High-Quality Evidence).[6]
- There is insufficient evidence to show that there are subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one topical treatment for AK is more effective or associated with fewer adverse events.

Recommendations:

- Based on review of evidence, designate at least one topical formulation of 5-FU and imiquimod which are indicated for treatment of basal cell carcinoma and genital warts, as preferred on the preferred drug list (PDL). Maintain diclofenac 3% gel as non-preferred and add tirbanibulin 1% ointment and aminolevulinic acid gel as non-preferred agents to the PDL and create a PDL class called "Topical Agents for Actinic Keratosis".
- Implement PA criteria for topical agents used in AK to provide a pathway to coverage for AK in people with the EPSDT benefit.
- Evaluate medication costs in executive session**.**

Background:

Actinic keratoses are rough scaly patches that arise on skin that is chronically exposed to ultraviolet (UV) radiation.[5] Patches range from pink, red, or brown and may present with tenderness, burning or itching, although most lesions are asymptomatic.[3] Actinic keratosis is the most frequently diagnosed premalignant skin disease in fair-skinned, Caucasian individuals.[7] Actinic keratosis is usually the initial lesion in a disease continuum that progresses to invasive, squamous cell carcinoma.[7] The real progression rate toward an invasive, squamous cell carcinoma, which has a metastatic risk of 0.5% to 3.3%, is unknown, varying from 0.025% to 20%.[8] The risk of progression in squamous cell carcinoma increases in patients with multiple AKs (more than five); for example it is 4-fold higher in patients with 6-20 AKs and 11-fold higher in those with more than 20 lesions.[9] However, this inability to predict which AK will transform into an invasive squamous cell carcinoma indicates that treatment of each visible AK is advisable.[8]

With a prevalence of 37.5% among white people 50 years of age or older, AK is one of the most frequent reasons for patients to visit a dermatologist.[7] Individual patients may have single or multiple lesions, but the average number of AKs per person is 6 to 8 when the patient first visits the dermatologist.[10] Actinic keratosis is more prevalent in males.[10] A meta-analysis of 60 observational studies reported an overall world-wide prevalence of AK of 14%, with an estimated incidence rate of 1.9 per 1000 person-years.[11] The highest prevalence of AK has been recorded in Australia, where it affects 40%–60% of white individuals aged ≥ 40 years.[12] Reported rates are lower in the United States, where studies have reported prevalence rates of 16% and 25%.[12] Prevalence may be as high as 55% in people 65-74 years of age with extensive sun exposure.[12] Increasing exposure to UV light during recreational pursuits and the decrease in the protective ozone layer are gradually increasing the incidence of AKs, even in individuals not exposed to sunlight through their occupations.[10]

Actinic keratoses are usually seen as multiple lesions in sun-exposed areas including the face, hands and forearms, neck, shoulders, and scalp in people with premature baldness.[10] Individuals who live in areas with high exposure to UV radiation with fair skin, particularly those with freckles, light-colored eyes (blue or green), and blonde or red hair, are most at risk.[10] Occasionally, AKs may also result from exposure to X-rays and to repeated UV light from artificial sources.[10]

Immunocompromised patients are also known to be at increased risk of AK, including organ transplant recipients taking immunosuppressive medications.[12] In patients with diffuse signs of skin photocarcinogenesis, AKs may be multiple and may be difficult to manage therapeutically, especially in people who, for professional or lifestyle reasons, are chronically photoexposed.[10] In these cases, lesions are usually widespread and tend to recur.[10]

Diagnosis of AK is based upon provider visual inspection and examination. A skin biopsy may be performed to exclude malignancy if any suspicious features (i.e., large size, rapid growth, ulceration, bleeding) are present. There are several treatments that are highly effective for AK, and cure rates are high.[10] Sun protection is recommended for all patients with AK including broad spectrum sunscreen, avoidance of high peak sun hours, and sun protective clothing. Nonpharmacologic treatments include curettage, liquid nitrogen cryosurgery, dermabrasion, PDT, and radiotherapy.[10] Self-administered topical medical treatments include 5-fluorouracil cream, imiquimod cream, diclofenac 3% gel, and tirbanibulin 1% ointment (see **Table 1**). The topical photosensitizer, aminolaevulinic acid, is applied prior to PDT and must be administered by a health care provider.[13] Cryosurgery (liquid nitrogen) should be considered the treatment of choice for patients with only a few lesions (1-6 lesions) or isolated lesions, or for patients who are noncompliant with topical agents.[9] Complete response rate for individual lesions to cryotherapy is around 98%, and the result depends on the duration of the freezing.[9]

Treatment can be directed either at individual lesions or to larger areas of the skin where several visible and less visible lesions occur (field-directed treatment).[14] The use of topical agents to promote reversal of neoplastic transformation in surrounding tissue may provide a field effect on subclinical disease and may contribute to the prevention of additional lesions in adjacent areas.[8] Clearance rates with topical medications are dependent upon patient adherence.[9] Duration of therapy varies, depending on the topical product that is prescribed (see **Table 1**). Adverse reactions including skin swelling, redness, burning and itching may make it difficult for patients to adhere to the prescribed topical regimen. Outcomes used to evaluate AK treatment efficacy include treatment success (≥ 75% reduction in the number of AK lesions from baseline), mean reduction in the number of AK lesions, change in lesion area, and proportion of patients with complete (100%) AK lesion clearance.[3] Frequency of adverse events, tolerability and impact on patient satisfaction have also been evaluated in comparative studies.[3]

In a study of Medicare claims data, 81.9% of people with a diagnosis of AK received treatment.[15] The most common treatment type was non-pharmacologic curettage or cryosurgery.[15] Only 1.5% of people had claims billed for PDT and 2.9% had claims for topical medications.[15] In the Oregon Medicaid fee-for-service (FFS) population, 1,302 people had a diagnosis of AK from 4/1/2023 to 3/31/2024. Because 5-fluorouracil and imiquimod creams have funded FDA-indications for treatment of basal cell carcinoma and genital warts, there is utilization of these products in the Oregon Medicaid population. In the fourth quarter of 2024 (September to December) there were 11 claims for imiquimod cream and no utilization of 5-fluorouracil cream in the Oregon Health Plan (OHP) fee-for-service (FFS) population.

A summary of relevant drug information is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings, and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Topical Drugs for Treatment of Actinic Keratosis and Other Indications

Generic Drug Name (BRAND NAME)	Strength/ Formulation	FDA-Approved Indications	Patient or Health Care Provider Administered	AK Dosing Parameters
5-fluorouracil (CARAC, EFUDEX)[16]	0.5% cream 4% cream	• Actinic Keratosis in adults	Patient	0.5% and 4% cream: Apply once daily to lesions for 4 weeks.

	5% cream 2% solution 5% solution	• Basal Cell Carcinoma in adults (5% cream and solution only)		5% cream, 2% solution and 5% solution: Apply twice daily to lesions for 2-4 weeks.
Imiquimod (ZYCLARA)[17]	2.5% cream 3.75% cream 5% cream	• Actinic Keratosis in adults • Basal Cell Carcinoma in adults (5% cream only) • Genital and Perianal Warts approved in children and adolescents ≥ 12 years (3.75% and 5% cream only)	Patient	2.5% and 3.75% cream: Apply once daily at bedtime for 2-week cycles (2 weeks on treatment, 2 weeks off, 2 weeks on) over 6 weeks. May repeat cycle up to 2 times. Leave on for 8 hours, then remove with soap and water. 5% cream: Apply to lesions to an involved area ≤ 25 cm^2 twice weekly for 16 weeks. Leave on for 8 hours, then remove with soap and water.
Diclofenac Sodium (SOLARAZE)[18]	3% gel	• Actinic Keratosis in adults	Patient	Apply to lesions twice daily for 60-90 days.
Tirbanibulin (KLISYRI)[19]	1% ointment	• Actinic Keratosis in adults	Patient	Apply once daily up to 100 cm^2 area for 5 days.
Aminolevulinic acid (AMELUZ, LEVULAN)[13]	10% gel (red and blue light) 20% solution (red light)	• Actinic Keratosis prior to PDT in adults	Health Care Provider	Apply prior to blue-light or red-light PDT. May treat lesions that have not completely resolved 3 months after the initial treatment.
Abbreviations: FDA = Food and Drug Administration; PDT = photodynamic therapy				

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), Scottish Intercollegiate Guidelines Network (SIGN), and Oregon Mental Health Clinical Advisory Group (MHCAG) 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:

Effectiveness Of 5-Fluorouracil Treatment for Actinic Keratosis

A 2009 systematic review evaluated RCTs which compared the treatment of AK with 5-fluorouracil versus placebo or another treatment.[2] Literature was searched through January 2008 and 13 RCTs met inclusion critiera.[2] Eight studies compared 5-fluorouracil 5% cream with other treatments including imiquimod cream, cryotherapy, diclofenac sodium 3% gel, facial resurfacing, PDT, 5-fluorouracil 5% cream augmented with tretinoin, and 5-fluorouracil 0.5% cream.[2] One study compared different dosing regimens of 5-fluorouracil 5% cream (twice daily for 3 weeks versus twice daily for 1 day per week for 12 weeks).[2] Three studies compared 5-fluorouracil 0.5% cream with placebo, and one study compared 5-fluorouracil 0.5% with aminolevulinic acid-PDT, activated with either blue light or pulsed laser light.[2]

Several different outcome measures were used to determine the efficacy of treatment, including absolute and proportional changes in lesion counts per patient, changes in total lesion count, change in lesion area, tolerability, and patient preferences.[2] Nine studies reported the proportion of patients achieving 100% clinical clearance of the lesions.[2] The duration of follow-up varied between studies.[2] As the complete healing of lesions treated with 5-fluorouracil 5% cream may not be evident for up to 2 months following the cessation of active treatment, 8 weeks post-treatment was considered to be the minimum time period to evaluate short-term benefit.[2] The assessment in 7 studies was short, with outcomes being assessed 4 weeks after the cessation of treatment.[2] Three studies assessed outcomes at around 8 weeks, and long-term assessment data were reported in 4 studies, at 6 months and 12 months post-treatment.[2]

The majority of studies were poorly reported, with only 5 studies providing any detail about randomization methods and only 2 of these adequately describing allocation concealment.[2] Only one study was double-blind, and four were single-blind (outcome assessment only).[2] Although most studies claimed to undertake intention-to-treat analysis, only 5 included all randomized patients in the analysis.[2] Insufficient baseline data were provided in 2 studies, preventing the comparison of treatment groups.[2] Eight studies did not report fully on their pre-specified outcomes; commonly, studies reported percentages without giving either the denominator or numerator, or did not provide standard deviations or ranges for the data when reporting means or medians.[2] In summary, most of the included studies were at moderate to high risk of bias, and therefore the results should be interpreted with caution and few, if any, generalizations could be made.[2]

Treatment with 5-fluorouracil 5% cream resulted in an average reduction of 79.5% (range, 59.2%–100%) in the mean number of lesions, from an average of 24.0 at baseline (range, 10.3–61.8) to 4.0 (range, 0–8.8) at follow-up.[2] In comparison, treatment with 5-fluorouracil 0.5% cream resulted in an average reduction of 86.1% (range, 77.9%–91.7%) in the mean number of lesions, from an average of 13.9 lesions at baseline to 3.9 lesions at follow-up.[2] The average number of lesions was reduced by 94.5% (range, 92.9–96.6%) when treated by laser resurfacing, and 28.0% (range, 21.6–34.4%) when treated with placebo.[2] Clearance of. $\geq$ 75% of lesions from baseline is considered treatment success.[2]

Of the 8 studies that reported a reduction in the mean or median number of lesions per patient, only 3 provided sufficient data to enable assessment of the weighted mean difference (WMD) between agents.[2] There was no statistically significant difference in the WMD of 5-fluorouracil 5% cream compared with 5-fluorouracil 5% augmented with tretinoin (WMD, –0.8; 95% CI, 0.8 to 2.4), resurfacing with carbon dioxide laser compared to placebo (WMD, –3.3; 95% CI, –9.9 to 3.3) or 30% trichloroacetic acid peel compared to placebo (WMD, –1.1, 95% CI –6.0 to 3.8).[2] Treatment with 5-fluorouracil 0.5% cream for 1 week resulted in a statistically significant greater reduction in the mean number of lesions per patient than did placebo (WMD, 4.8; 95% CI, 3.1 to 6.5).[2]

Treatment with 5-fluorouracil 5% cream cleared 93.8% (606/646) of lesions at 24 weeks, and 98.0% (124/126) of lesions at 4 weeks, compared with 65.9% (323/490) of lesions cleared with imiquimod and 89% (111/125) of lesions cleared with diclofenac gel.[2] Across the studies, an average of 49.0% (range, 0%–96%)

of patients treated with 5-fluorouracil 5% cream and 34.8% (range, 14.9–57.8%) of patients treated with 5-fluorouracil 0.5% cream were reported as achieving clearance of 100% of lesions.[2] In comparison, no patients reported 100% clearance treated with acid peel or aminolevulinic acid-PDT activated with red light.[2] One hundred percent clearance of AK lesions was reported In 4.3% of patients using placebo, in 37.5% of patients treated with carbon dioxide laser resurfacing, in 50% of patients treated with aminolevulinic acid-PDT activated by blue light, in 54.5% of patients treated with imiquimod, and in 68% of patients treated with cryotherapy.[2]

Treatment with 5-fluorouracil is associated with application site reactions, and most studies assessed the severity of these reactions, although the methods varied between studies making data synthesis difficult.[2] Cosmetic outcome was assessed in only one study, and at 3 months there was no difference between the groups treated with 5-fluorouracil 5% cream, cryotherapy, or imiquimod cream; however, at 12 months, 4% of patients treated with 5-fluorouracil 5% or cryotherapy and 81% of patients treated with imiquimod showed a positive cosmetic outcome (based on scarring, atrophy, and induration).[2] This is a very large difference, but it is unclear whether investigators were blind to the treatment groups, introducing a high risk of bias in these results.[2]

Only two studies assessed patient preferences for treatment.[2] In the study comparing 0.5% and 5% 5-fluorouracil, 85% (17/20) of patients preferred 5-fluorouracil 0.5% with the remaining 3 patients preferring 5-fluorouracil 5%.[2] The study comparing diclofenac gel and 5-fluorouracil 5% reported that 79% of patients were very or completely satisfied with diclofenac, compared with 68% with this level of satisfaction with 5-fluorouracil 5% cream.[2] However, the patients were not blind to the treatment in either of these studies, limiting the validity of this assessment.[2] Only 3 studies reported the number of patients withdrawing from the study as a result of adverse events: 1.9% (4/213) of patients using 5-fluorouracil 0.5% and 5.9% (1/17) of patients using 5-fluorouracil 5% cream.[2]

In summary, this systematic review provides low-quality evidence to indicate that about 50% of patients using 5-fluorouracil 5% for the treatment of AK lesions can expect complete clearance; overall, an 80% reduction in lesion count can be expected; and a 90% reduction in total lesion count is likely.[2] Although few patients stop treatment as a result of adverse events, up to one-half may not be able to complete the full treatment course.[2] Evidence on alternative treatments studied head-to-head with 5-fluorouracil is limited.[2]

Cochrane: Interventions For Actinic Keratoses

A 2012 Cochrane review assessed the effects of topical, oral, mechanical, and chemical interventions for AK.[3] Literature was searched through March 2011 for RCTs that compared treatment of AK with either placebo, vehicle, or active therapy.[3] Eighty-three RCTs met inclusion criteria, with a total of 10,036 participants.[3] The RCTs covered 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions, including PDT.[3] Sixty RCTs investigated topical treatments applied to a skin area by the participants: adapalene gel, aretinoid methyl sulfone, betulin-based oleogel, calcipotriol, colchicine, diclofenac, 2-(difluoromethyl)-dl-ornithine (DFMO), 5-fluorouracil, imiquimod, ingenol mebutate, isotretinoin, masoprocol, nicotinamide, resiquimod, sunscreen, vitamin E, and tretinoin.[14] One RCT evaluated oral etretinate.[3] Clinical staff administered 2 mechanical treatments (carbon dioxide and laser resurfacing) on a skin area (2 RCTs), and they administered 3 chemical treatments: cryotherapy on individual lesions, PDT on individual lesions or a skin area, and trichloroacetic acid peel on a skin area (37 RCTs).[3] Lesions were located on the head only (i.e. face, forehead, temples, cheeks, scalp, ear, lips, and neck) in 59 RCTs, on only non-head locations (i.e., upper and lower extremities, legs, arms, elbow, forearms, hands, dorsa of hands, shoulder, décolleté, chest, trunk, and back) in 9 RCTs and on both head and non-head locations in 22 RCTs.[3]

Most of the studies lacked descriptions of some methodological details, such as the generation of the randomization sequence or allocation concealment, and half of the studies had a high risk of reporting bias.[3] Study comparison was difficult because of the multiple parameters used to report efficacy and safety outcomes, as well as statistical limitations.[3] No data was identified on the possible reduction of squamous cell carcinoma.[3]

The primary outcome, complete clearance of AK lesions, favored 4 field-directed treatments compared to vehicle or placebo: 3% diclofenac (RR 2.46, 95% CI 1.66 to 3.66; 3 RCTs; n=420), 0.5% 5-fluorouracil (RR 8.86, 95% CI: 3.67 to 21.44; 3 RCTs; n=522), 5% imiquimod (RR 7.70, 95% CI 4.63 to 12.79; 9 RCTs; n=1871), and 0.025% to 0.05% ingenol gel (RR 4.50, 95% CI 2.61 to 7.74; 2 RCTs; n= 456).[3] Of note, ingenol gel is on longer commercially available in the United States. The medication was withdrawn by LEO Pharma in 2020 from worldwide markets due to an increased risk of squamous cell carcinoma and other nonmelanoma skin malignancies associated with the drug's use when compared to other treatment options of AK.[14] One RCT compared 0.5% and 5% 5-fluorouracil and found comparable efficacy and safety between both agents.[3]

Lesion clearance was also favored with PDT compared to placebo-PDT with the following photosensitizers: aminolevulinic acid (blue light: RR 6.22, 95% CI 2.88 to 13.43; 1 study with 243 participants, aminolevulinic acid (red light: RR 5.94, 95% CI 3.35 to 10.54; 3 studies with 422 participants).[3] Aminolevulinic acid-PDT was also favored compared to cryotherapy (RR 1.31, 95% CI 1.05 to 1.64).[3]

A significant number of participants withdrew because of adverse events with 144 participants affected out of 1000 taking 3% diclofenac in 2.5% hyaluronic acid; compared to 40 participants affected out of 1000 taking 2.5% hyaluronic acid alone; and 56 participants affected out of 1000 taking 5% imiquimod compared to 21 participants affected out of 1000 taking placebo.[3] In general, 5-fluorouracil treatment did not lead to withdrawal because of adverse events; however, substantial skin irritation was associated with this intervention.[3]

The authors concluded that for individual lesions, photodynamic therapy appears more effective in lesion clearance than cryotherapy (low-quality evidence).[3] For field directed therapy, topical diclofenac, 5-fluorouracil, and imiquimod, low-quality evidence shows topical agents had similar efficacy in complete clearance of AK lesions, but their associated adverse events were different.[3] More comparative evidence is needed to determine the best therapeutic approach in managing AK.[3]

Treatment Of Actinic Keratosis

A 2022 systematic review compared different therapeutic options for managing AK.[4] Literature was searched through December 2019 and 80 RCTs (n=6,748) met inclusion criteria.[4] The most commonly studied modalities were imiquimod (n=23 studies), 5-fluorouracil (n=13), ALA-PDT (n=19 studies), and PDT-MAL (n=17 studies).[4] Among all included studies, the proportion of male to female patients was 3.5:1, and the mean age was 69 years.[4] The included studies were of low to moderate risk of bias.[4] Homogeneity in the primary outcome by I^2 was > 50% and, therefore, meta-analysis was not possible.[4]

The percent clearance of AKs after treatment with all types of PDT was 67.0 ± 16.2% at 1–3 months, 76.1 ± 10.8% at 3–6 months, and 59.8 ± 9.7% at 6–12 months.[4] Subgroup analysis revealed that PDT-ALA had mean lesion reduction rates of 66.2 ± 17.0% at 1–3 months, 75.2 ± 9.9% at 3–6 months, and 64.2 ± 6.2% at 6–12 months; whereas PDT-MAL had lesion reduction of 72.2 ± 10.6%, 77.7 ± 12.8%, and 51.1% at 1–3, 3–6, and 6–12 months, respectively. PDT-ALA and PDT-MAL were not significantly different at 1–3 months and 3–6 months, but PDT-ALA was significantly more effective than PDT-MAL at 1 year.[4] All participants who were treated with PDT (100%) experienced erythema.[4] A fair percent (47.6%) experienced severe pain, which was higher than with other treatment modalities.

Twenty-three studies investigated treatment with imiquimod as monotherapy, while two studies investigated imiquimod plus cryotherapy and one used imiquimod plus PDT-MAL.[4] The most common application methods were 3 applications of 5% imiquimod per week for 4–6 weeks, or daily application of 3.75% imiquimod alternating 2 weeks on and 2 weeks off. Overall, the percent reduction in AKs was 67.5 ± 19.6% at 1–3 months, 64.0 ± 13.0% at 3–6 months and 68.0 ± 1.6% at 6–12 months after treatment with imiquimod. Compared to other treatments included in this analysis, imiquimod was non-inferior to any other treatment and superior only to diclofenac.[4] Commonly reported side effects included erythema (53.3%), stinging/itching (41.6%), and crusting (33.5%).[4]

Thirteen studies compared topical 5-fluorouracil as monotherapy, and several others investigated 5-fluorouracil in combination with another agent (salicylic acid, calcipotriol, cryotherapy, PDT-MAL, and PDT-ALA).[4] Most studies of 5-fluorouracil monotherapy implemented the standard twice daily application of 5% 5-fluorouracil for 3 weeks, whereas shorter application durations were implemented in combination therapy studies.[4] Two studies investigated lower strength (0.5%) 5-fluorouracil, while the remainder used the standard 5% concentration.[4] Overall, after treatment with 5-fluorouracil monotherapy, the number of AKs was reduced by 80.1% at 1–3 months, and 67.4% at 3–6 months.[4] Relative to the efficacy of other treatments included in this analysis, 5-fluorouracil was superior compared only to diclofenac at both 1–3 months and 3–6 months.[4] Only one included study evaluated the long-term effectiveness of 5-fluorouracil at 12 months and found that long-term percent clearance rates were comparable to 1–3 months and 3–6 months time points.[4] Overall, the recurrence rate of AKs at one year post-treatment with 5-fluorouracil monotherapy was 27%.[4] A vast majority of patients included in this analysis (90.7%) reported discomfort with 5-fluorouracil application, which is a significant disadvantage of this treatment method compared to other modalities.[4]

Four studies investigated the effectiveness of twice daily application of diclofenac sodium 3.0% gel in the treatment of AKs.[4] Percent clearance of AKs at 1–3 months post-treatment was 36.3 ± 9.5%, which was lower compared to most other treatment modalities.[4] Only one study included in the analysis reported sustained clearance of 45% at 6 months.[4] In summary, based on the results of this analysis, all treatments except for diclofenac were non-inferior to each other in the treatment of AKs.[4]

After review, 8 systematic reviews were excluded due to poor quality (e.g., network meta-analyses),[20-25] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[26,27] or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

American Academy Of Dermatology Guidelines Of Care For The Management Of Actinic Keratosis

In 2021, the AAD published guidelines to assist in clinical decision-making for the management of AK.[5] Topical agents, cryosurgery, and PDT are all recommended.[5] Choice of treatment is based on a number of factors, including the site of the AKs, whether AKs are solitary, multiple, or within an affected field, and patient preferences and tolerability.[5] Lesion-directed treatments are used to manage few or isolated AKs.

Treating individual AKs in the office setting with physical modalities such as liquid nitrogen cryosurgery or destructive modalities such as curettage offers the patient a treatment that is completed within a single visit and requires only that the patient participate in post-procedural skincare.[5] Cryosurgery is recommended for solitary AK lesions.[5]

Field directed treatments, such as topical agents or PDT, can be used to manage multiple AKs and keratinocyte changes in a contiguous area and may provide benefits in reducing the risk of developing new AKs, limiting AK recurrence, and mitigating subclinical damage.[5] Topical agents can be used focally or in broad areas and are advantageous when AKs occur in areas of high density or areas with indistinct clinical borders.[5] The recommended topical agents all have the potential for generating local skin reactions.[5] As skin reactions can result in the termination of treatment without reaching the desired therapeutic outcome, the clinician should work with the patient to tailor an individual treatment program that achieves the desired results.[5] A few small studies directly compared the efficacy and safety of topical medications to treat AK.[5] This limited evidence was considered by the AAD Work Group to be insufficient to form recommendations on the comparative efficacy and safety of topical therapies for AK (see **Table 2**).[5]

AAD topical treatment recommendations for patients with AK and quality of evidence:

- The AAD recommends field treatment with 5-fluorouracil cream or imiquimod cream (Strong Recommendation; Moderate-Quality Evidence).[5]
- The AAD conditionally recommends the use of diclofenac gel (Low-Quality Evidence).[5]
- The AAD conditionally recommends red light PDT with aminolevulinic acid over cryosurgery alone (Low-Quality Evidence).[5]
- AAD conditionally recommends combination treatment cryosurgery with 5-fluorouracil or imiquimod over cryosurgery alone (based on Moderate- and Low-Quality Evidence, respectively).[5]

American Academy of Dermatology Focused Update: Management of Actinic Keratosis

In 2022 the AAD published a focused guideline update on management of AK.[6] The purpose of the focused update was to incorporate recently published evidence on the use of topical tirbanibulin to treat AK.[6] A first-in-class microtubule inhibitor, tirbanibulin, was approved for the topical, field-directed treatment of AK on the scalp or face by the FDA in December 2020.[6] Two trials were identified and analysis of this evidence resulted in one recommendation.[6] Two phase 3 randomized, double-blinded, parallel-group, placebo-controlled trials (n=702) compared a standard regimen of topical tirbanibulin 1% or a placebo vehicle applied once daily to a 25 cm^2 treatment field containing 4 to 8 AKs on the face or scalp for 5 consecutive days.[28] The primary outcome was the percentage of patients with a complete (100%) reduction in the number of lesions in the application area at day 57.[28] The secondary outcome was the percentage of patients with a partial (≥75%) reduction in the number of lesions within the application area at day 57.[28] The incidence of recurrence was evaluated at 1 year.[28]

On day 57, the participants treated with tirbanibulin experienced higher rates of complete clearance of AKs in the treatment area (pooled clearance rate 49.3%) than those treated with the vehicle (pooled clearance rate, 8.6%; RR, 6.14; 95% CI, 2.73 to 13.80; P<0.0001).[6] The participants treated with tirbanibulin also experienced significantly higher rates of partial clearance (≥75% reduction in the number of treated AKs) than those treated with the vehicle (pooled partial clearance rate, (72.2% vs. RR, 3.99; 95% CI, 3.16 to 5.04; P<0.00001).[6] At 12 months, the estimated percentage of previously cleared participants with recurrent lesions in the treatment area was 47% and the estimate of those with recurrent or new lesions in the treatment area was 73%.[6] The most common local reactions to tirbanibulin were erythema in 91% of the patients and flaking or scaling in 82% of patients.[28] The most common adverse events reported through day 57 of the phase III trials were application site pruritus (reported in 9.1% of tirbanibulin-treated participants vs 6.0% of vehicle-treated participants) and pain (reported in 9.9% of tirbanibulin-treated participants vs 3.2% of vehicle-treated participants).[6]

Trials comparing tirbanibulin with conventional treatments with longer follow-up are needed to determine the effects of tirbanibulin therapy on AK.[28] Although the AAD work group recognized that tirbanibulin cost may be prohibitive without adequate insurance coverage and other strongly recommended treatments for AK may be available for lower cost, they concluded that the use of tirbanibulin is likely acceptable to patients and providers and feasible to implement especially considering the abbreviated duration of tirbanibulin treatment compared with the duration of other available topically applied agents for the management of AK.[6]

Recommendation:

- AAD recommends field treatment with topical tirbanibulin (Strong Recommendation; High-Quality Evidence).[6]

Randomized Controlled Trials:

A total of 101 citations were manually reviewed from the initial literature search. After further review, 95 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 6 trials are summarized in **Table 2** below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Krawtchenko, et al[29] (2007) Single-center, open-label trial Patients randomized to 1 of 3 active treatment arms	1. 5-fluorouracil 5% cream applied twice a day over 4 weeks 2. Imiquimod 5% cream applied for 8 hours 3 times a week over 4 weeks (for 1 or 2 treatment courses) 3. Cryosurgery (liquid nitrogen spray) applied 20 to 40 sec for each lesion and repeated in 2 weeks for insufficiently cleared lesions.	Caucasian patients with ≥ 5 typical, visible AK lesions at head, neck, and chest. 1. n=24 2. n=26 3. n=25 Total enrollment: 75 patients Male = 62 Female = 13 Mean age =74 years Mean number of AK lesions: 8	Complete clearance of AK lesions 6 weeks after last cryosurgery, 4 weeks after last 5-fluorouracil application, and 8 weeks after last application of imiquimod and at 12-month follow-up.	<u>Total clearance 4 to 8 weeks after last application:</u> 1. n=23 (96%) 2. n=22 (85%) 3. n=17 (68%) 1 vs 3 : p=0.03 2 vs 3: p=0.03 () <u>Total clearance 12 months after last application:</u> 1. n=13 (57%) 2. n=19 (86%) 3. n=7 (41%) 1 vs 3 : p=0.01 2 vs 3: p=0.01	1. Unclear if patients and investigators were blinded to treatment assignment. 2. Unclear how many patients received additional treatments with imiquimod or cryosurgery. 3. Small patient population, study not powered to detect significant differences between treatment arms. 4. 59% of patients had received previous treatment - type of treatment not reported. Could introduce bias in terms of treatment response to active comparators in this trial. 5. Statistical analysis only completed for imiquimod compared to 5FU or cryosurgery.
Jansen, et al[7] (2019) MC, Single-Blind, Phase IV RCT	1. 5-fluorouracil 5% cream applied twice daily for 4 weeks 2. Imiquimod 5% cream applied 3 times a week for 4 weeks 3. Methyl aminolevulinate-PDT for one session 4. Ingenol gel 0.015% applied once a day for 3 days total*	Adults with ≥ 5 AK lesions on the head, involving one continuous area of 25 to 100 cm^2 1.155 2.156 3.156 4.157 Total enrollment: 624 patients, 90% were male, mean age 75 years	Proportion of patients with a reduction ≥ 75% in the number of AK lesions from baseline to 12 months after the end of treatment.	<u>Treatment success at 12 months:</u> 1. n=108 (82.4%) 2. n=76 (71.0%) 3. n=57 (49.6%) 4. n=42 (42.9%) <u>Probability of treatment success 12 months after end of treatment:</u> 1. 74.7%; 95% CI 66.8 to 81.0 2. 53.9%; 95% CI 45.4 to 61.6 3. 37.7%; 95% CI 30.0 to 45.3 4. 28.9%; 95% CI 21.8 to 36.3 <u>Treatment failure after one treatment cycle:</u>	1. Single-blind study. Investigator who determined treatment outcome was blinded to treatment assignment. 2. Protocol included retreatment if patient had initial treatment failure at 3 months. More than one-third of patient population had initial treatment failure and received 2 courses of treatment. 3. All treatment arms included pretreatment curettage, which is not always the standard of care.

	*removed from market in 2020			1. 14.8% (n=23/155) 2. 7.2% (n=58/156) 3. 34.6% (n=54/156) 4. 47.8% (n=75/157) <u>Percentage of patients who were retreated:</u> 1. 83% (n=19/23) 2. 76% (n=44/58) 3. 76% (n=41/54) 4. 80% (n=60/75) <u>HR for treatment failure compared to 5-fluorouracil:</u> 1 vs. 2 HR = 2.03; 95% CI 1.36 to 3.04; p<0.001 1 vs 3 HR = 2.73; 95% CI 1.87 to 3.99; p<0.001 1 vs 4 HR = 3.33; 95% CI 2.39 to 4.85; p<0.001	4. Of the 10 authors, 5 reported potential conflicts of interest, including the blinded investigator.
Akarsu, et al[30] (2011) Single center, open-label, evaluator-blinded study	1. Diclofenac 3% gel applied twice daily for 12 weeks 2. Imiquimod 5% cream applied twice a week for 16 weeks 3. Base cream applied twice daily for 12 weeks	Adults with 1 AK lesion. 1. 21 2. 20 3. 20 Baseline TTS score 1. 3.85 $\pm$ 0.37 2. 3.95 $\pm$ 0.22 3. 3.80 $\pm$ 0.41 Baseline PGII scores not reported Total of 61 patients: 37 men 31 women	Treatment efficacy as assessed by investigator assessed by 5-point TTS and self-reported 7-point PGII scores Higher TTS scores = worse total skin thickness score 0 = complete clearance 1 = lesion visible but not palpable 2 = lesion visible and palpable 3 = lesion raised with visible scaling 4 = lesion hyperkeratotic and > 1 mm in thickness	<u>Change from baseline in TTS score at 24 weeks:</u> <u>TTS score:</u> 1. 2.00 2. 1.15 3. 3.40 2 vs 3: MD = 1.4 95% CI 0.52 to 2.27 1 vs 3: MD = 2.25 95% CI 1.36 to 3.13 1 vs 2:	1. Not clear if TTS has been validated in other trials. 2. MCID not reported for either score (TTS or PGII). 3. Small patient population, not clear if study was powered to detect differences between treatment arms.

		Mean age: 65.8 years	MCID not available Higher PGII scores = more improvement 0 = significantly worse 1 = slightly worse 2 = no change 3 = slightly improved 4 = moderately improved 5 = significantly improved 6 = completely improved MCID not available	MD = 0.85 95% CI 0.36 to 1.66 P=0.034 <u>Change from baseline in PGII score at 24 weeks:</u> 1. 4.40 2. 4.43 3. 2.70 2 vs. 3 MD = -1.72 95% CI -2.88 to -0.57 1 vs 3 MD = -1.70 95% CI -2.86 to -0.53 1 vs 2 MD = 0.02 95% CI -0.99 to 1.05 NS	
Kose, et al[31] (2007) Single center, open-label study	1. Diclofenac 3% gel applied once a day for 12 weeks 2. Imiquimod 5% cream applied 3 times a week for 12 weeks	Adults with ≥ 3 AK lesions on the face and scalp 1. n=24 2. n=25 Total of 49 patients Male = 29 Female = 21 Average age = 56.4 years	Global improvement (7-point) IGII and PGII scores were used to assess efficacy. Higher scores on both scales indicate improvement.	<u>Percent improvement on the IGII score at the end of therapy:</u> Moderate Improvement 1. 36% 2. 5% P value NR Significant Improvement 1. 52% 2. 73% P value NR Complete Improvement 1. 12% 2. 22% p> 0.05	1. One of the clinical efficacy metrics was patient self-reported (PGII) which may be subject to bias. 2. Open-label study design introduces bias in investigator assessment and patient response. 3. Small patient population, not clear if study was powered to detect differences between treatment arms. 4. Results reported as percentages, specific patient data not reported 5. Statistical analysis only completed for assessment of complete improvement.

				Percent improvement on the PGII score at the end of therapy: Moderate Improvement 1. 27% 2. 12% P value NR Significant Improvement 1. 45% 2. 65% P value NR Complete Improvement 1. 28% 2. 23% p> 0.05	
Tanghetti et al[32] (2015) Randomized 1:1:1 to one of three treatment arms. Single-blind (investigator)	1. 5-fluorouracil 5% cream for 6-7 days followed by aminolevulinic acid 20% followed by PDT x1 application 2. 5-fluorouracil 5% cream applied twice daily for 6-7 days 3. Aminolevulinic acid 20% followed by PDT x 1	Total enrollment: 30 patients 1. 10 2. 10 3. 10	AK counts at 1- and 3-months post treatment Mean Baseline AK counts 1. 23.0 2. 25.9 3. 38.9	Mean AK counts 1 month after treatment: 1. 2.8 2. 3.5 3. 5.8 p-values not reported Mean AK counts 3 months after treatment: 1. 2.3 2. 4.2 3. 8.2 p-values not reported	1.Baseline AK counts were not equal across all 3 treatment arms. Baseline aminolevulinic acid group had more lesions than the other 2 groups. 2. Inclusion and exclusion criteria not reported. 3. Statistical analysis not reported. 4. Small patient population, not clear if study was powered to detect differences between treatment arms.
Segatto et al[33] (2013) Randomized, parallel group study	1. Diclofenac 3% gel applied twice daily for 12 weeks 2. 5-fluorouracil 5% cream applied twice daily for 4 weeks	Adults with $\geq$ 5 AK lesions on the face, hands, and scalp 1. n=15 2. n=13 Total enrollment: 28 patients Male = 13 Female = 15	Average number of lesions 8 weeks after treatment. Baseline number of AK lesions 1. 13.6 $\pm$ 4.5 2. 17.4 $\pm$ 6.69	Average number of lesions after 8 weeks of treatment: 1. 6.6 $\pm$ 2.94 (MD before and after treatment: 7; p<0.001) 2. 3.15 $\pm$ 2.15 (MD before and after treatment: 14.25; p<0.001) 1 vs 2 change in number of lesions (7 vs. 14.25; p<0.001)	1. Assessment investigator was blinded to treatment assignment. 2. Small patient population, not clear if study was powered to detect differences between treatment arms. 3. Number of baseline AK lesions was not balanced between groups.

		Mean age = 72 years Average number of AK lesions = 15			
Abbreviations: 5-fluorouracil = 5-fluorouracil; AK = Actinic Keratosis; CI = confidence interval; HR = hazard ratio; IGII= Investigator Global Improvement Index; MC = multi-center; MCID = minimal clinically important difference; MD = mean difference; PDT = photodynamic therapy; PGII = Patient Global Improvement Index; PDT = photodynamic therapy; RCT = randomized controlled trial; TTS = Total Thickness Score					

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Appendix 1: PDL Status

GENERIC NAME	BRAND NAME	FORM	PDL STATUS
diclofenac sodium	DICLOFENAC SODIUM	GEL (GRAM)	N
aminolevulinic acid HCl	AMELUZ	GEL (GRAM)	
aminolevulinic acid HCl	LEVULAN	SOL W/APPL	
fluorouracil	FLUOROURACIL	CREAM (G)	
fluorouracil	EFUDEX	CREAM (G)	
fluorouracil	FLUOROURACIL	SOLUTION	
imiquimod	IMIQUIMOD	CREAM PACK	
imiquimod	ZYCLARA	CREAM PACK	
imiquimod	IMIQUIMOD	CRM MD PMP	
imiquimod	ZYCLARA	CRM MD PMP	

Appendix 2: Specific Drug Information

Table 3. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
5-fluorouracil[16]	Pyrimidine antimetabolite that interferes with DNA synthesis to prevent cell proliferation.	6% of topical dose is systemically absorbed. Tmax: ~1 hour	N/A	• Cmax: 1.03 hours • AUC: 22.39 ng/hr/mL
Imiquimod[17]	Immune response modifier: toll-like receptor 7 agonist that activates immune cells and cytokines. Unknown mechanism of action in AK.	Tmax: 9-12 hours	Renal Excretion: < 3%	• Half-life: 20 to 24.1 hours
Diclofenac Sodium[18]	Unknown in the treatment of AK.	Tmax: 4.5 hours	Primarily Renal Excretion	• Half-life: 79 hours
Tirbanibulin[19]	Microtubule inhibitor, unknown mechanism of action in AK.	Tmax: ~6 hours	Hepatic Metabolism by CYP3A4 and CYP2C8	N/A

			Excretion has not been fully characterized in humans	
Aminolaevulinic acid[13]	Porphyrin precursor, which optimizes photosensitization prior to illumination with red or blue light photodynamic therapy.	Tmax: 2 hours	N/A	N/A
Abbreviations: AK = Actinic Keratosis; AUC = area under the curve; Cmax = maximum plasma concentration; hr = hours; mL = milliliters; N/A = Not Available; Tmax = time to peak absorption				

Table 4. Use in Specific Populations

	Fluorouracil[16]	Imiquimod[17]	Diclofenac[18]	Tirbanibulin[19]	Aminolaevulinic acid[13]
Contraindicated in pregnancy	X				
Contraindicated in patients with dihydropyridine dehydrogenase (DPD) deficiency	X				
Contraindicated in pregnancy after 30 weeks of gestation			X		
Safe to use in pregnancy		Unknown		Unknown	Unknown

Drug Safety:

Diclofenac Topical Gel: Black Boxed Warning for the risk of serious cardiovascular and gastrointestinal events.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.[18]
- Diclofenac gel is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.[18]
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.[18]

Table 5. Summary of Warnings and Precautions.

Warning/Precaution	**5-Fluorouracil[16]**	**Imiquimod[17]**	**Diclofenac[18]**	**Tirbanibulin[19]**	**Aminolaevulinic acid[13]**
Hypersensitivity	X		X		
Local Skin Reactions	X	X	X	X	
Photosensitivity	X	X	X		X

Systemic Reactions (Flu-like signs and symptoms)		X			
Use on damaged skin (eczema, infected lesions, burns or wounds)			X		
History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs			X		
Hepatotoxicity			X		
Severe Heart Failure			X		
Porphyria					X

Appendix 3: Abstracts of Randomized Clinical Trials

A Randomized Study of Topical 5% Imiquimod Vs. Topical 5-Fluorouracil Vs. Cryosurgery In Immunocompetent Patients With Actinic Keratoses: A Comparison Of Clinical And Histological Outcomes Including 1-Year Follow-Up[29]

Background: Actinic keratoses (AK) frequently occur on sun-exposed skin and are considered as in situ squamous cell carcinoma. To date, no treatment algorithm exists for first- or second-line therapies due to the lack of comparative studies.

Objective: This study compared the initial and 12-month clinical clearance, histological clearance, and cosmetic outcomes of topically applied 5% imiquimod (IMIQ) cream, 5% 5-fluorouracil (5-fluorouracil) ointment and cryosurgery for the treatment of AK.

Patients/methods: Patients were randomized to one of the following three treatment groups: one or two courses of cryosurgery (20-40 s per lesion), topical 5-fluorouracil (twice daily for 4 weeks), or one or two courses of topical imiquimod (three times per week for 4 weeks each).

Results: Sixty-eight per cent (17/25) of patients treated with cryosurgery, 96% (23/24) of patients treated with 5-fluorouracil, and 85% (22/26) of patients treated with IMIQ achieved initial clinical clearance, $p = 0.03$. The histological clearance rate for cryosurgery was 32% (8/25), 67% (16/24) for 5-fluorouracil, and 73% (19/26) in the IMIQ group, $p = 0.03$. The 12-month follow-up showed a high rate of recurrent and new lesions in the 5-fluorouracil and cryosurgery arms. The sustained clearance rate of initially cleared individual lesions was 28% (7/25) for cryosurgery, 54% (13/24) for 5-fluorouracil and 73% (19/26) for IMIQ ($p < 0.01$). Sustained clearance of the total treatment field was 4% (1/25), 33% (8/24), and 73% (19/26) of patients after cryosurgery, 5-fluorouracil, and IMIQ, respectively ($p < 0.01$). The patients in the IMIQ group were judged to have the best cosmetic outcomes ($p = 0.0001$).

Conclusion: Imiquimod treatment of AK resulted in superior sustained clearance and cosmetic outcomes compared with cryosurgery and 5-fluorouracil. It should be considered as a first line therapy for sustained treatment of AK.

Randomized Trial of Four Treatment Approaches for Actinic Keratosis[7]

Background: Actinic keratosis is the most frequent premalignant skin disease in the white population. In current guidelines, no clear recommendations are made about which treatment is preferred.

Methods: We investigated the effectiveness of four frequently used field-directed treatments (for multiple lesions in a continuous area). Patients with a clinical diagnosis of five or more actinic keratosis lesions on the head, involving one continuous area of 25 to 100 cm^2, were enrolled at four Dutch hospitals. Patients were randomly assigned to treatment with 5% fluorouracil cream, 5% imiquimod cream, methyl aminolevulinate photodynamic therapy (MAL-PDT), or 0.015%

ingenol mebutate gel. The primary outcome was the proportion of patients with a reduction of 75% or more in the number of actinic keratosis lesions from baseline to 12 months after the end of treatment. Both a modified intention-to-treat analysis and a per-protocol analysis were performed.
Results: A total of 624 patients were included from November 2014 through March 2017. At 12 months after the end of treatment, the cumulative probability of remaining free from treatment failure was significantly higher among patients who received fluorouracil (74.7%; 95% confidence interval [CI], 66.8 to 81.0) than among those who received imiquimod (53.9%; 95% CI, 45.4 to 61.6), MAL-PDT (37.7%; 95% CI, 30.0 to 45.3), or ingenol mebutate (28.9%; 95% CI, 21.8 to 36.3). As compared with fluorouracil, the hazard ratio for treatment failure was 2.03 (95% CI, 1.36 to 3.04) with imiquimod, 2.73 (95% CI, 1.87 to 3.99) with MAL-PDT, and 3.33 (95% CI, 2.29 to 4.85) with ingenol mebutate (P≤0.001 for all comparisons). No unexpected toxic effects were documented.
Conclusions: At 12 months after the end of treatment in patients with multiple actinic keratosis lesions on the head, 5% fluorouracil cream was the most effective of four field-directed treatments. (Funded by the Netherlands Organization for Health Research and Development; ClinicalTrials.gov number, NCT02281682.).

Comparison Of Topical 3% Diclofenac Sodium Gel And 5% Imiquimod Cream For The Treatment Of Actinic Keratoses[30]
Background. There is a wide spectrum of treatments available for actinic keratosis (AK). Topical diclofenac sodium and imiquimod are two topical treatments, which are noninvasive, easily applied, well-tolerated and effective.
Aim. To compare the effects of topical 3% diclofenac sodium plus hyaluranon (DFS) gel, 5% imiquimod (IMQ) cream, and base cream (BC) in patients with AK.
Methods. In total, 61 patients, diagnosed clinically and histopathologically as having AK, were randomized into three treatment groups to receive topical treatment with either DFS (twice daily for 12 weeks), IMQ (twice per week for 16 weeks) or BC (twice daily for 12 weeks). Patients were evaluated clinically at 0, 4, 8, 12, 16, 20 and 24 weeks. Treatment efficacy was assessed by Total Thickness Score (TTS) and Patient Global Improvement Index (PGII).
Results. Complete clearance rates for DFS, IMQ and BC at the end of the treatment and at the end of the total follow-up period were 19.1%, 20% and 0%, and 14.3%, 45% and 0%, respectively. Although the average TTS value of the DFS group at week 24 was significantly higher than that of the IMQ group, the PGII values were not significantly different.
Conclusions. Although DFS and IMQ each had considerable efficacy in the treatment of AK, the efficacy of DFS seemed to decrease after cessation of treatment.

Comparison Of the Efficacy And Tolerability Of 3% Diclofenac Sodium Gel And 5% Imiquimod Cream In The Treatment Of Actinic Keratosis[31]
Background: Topical diclofenac and imiquimod have been reported to be effective in the treatment of actinic keratosis, but a study to compare these two drugs has not been reported yet.
Objective: To compare the efficacy and safety of topical 3% diclofenac gel plus hyaluronic acid and 5% imiquimod cream in the treatment of actinic keratosis.
Methods: Forty-nine patients with actinic keratosis were enrolled in this randomized comparative open-label study. Twenty-four patients applied 3% diclofenac gel once a daily to their lesions, while the other 25 patients were treated with a 5% imiquimod cream three times a week for 12 weeks. Patients were examined before treatment and every month of the treatment. Assessments were made by investigators according to the Investigator and the Patient Global Improvement Indices (IGII) and (PGII).
Results: According to the IGII results, a complete response was observed in 12% of the diclofenac group and 22% of the imiquimod group. For the PGII scores, a complete response was observed in 28% of the diclofenac group and 23% of the imiquimod group. There were no significant differences between the two groups (p>0.05). Both treatments were well tolerated, with most adverse events related to skin.
Conclusion: The two drugs were found to be equally effective and safe in the treatment of actinic keratosis but complete remission was very low. Therefore, topical treatments with these two drugs were not seen to be completely effective, and combined therapies and further studies are needed.

A Controlled Comparison Study of Topical Fluorouracil 5% Cream Pre-Treatment of Aminolevulinic Acid/Photodynamic Therapy for Actinic Keratosis[32]

Introduction: Topical Fluorouracil 5% cream (5-fluorouracil) and 20% aminolevulinic acid (ALA)/ photodynamic therapy (PDT) are both FDA approved for the treatment of Actinic Keratosis (AK). We have studied the use of these 2 agents alone and in a sequential manner. We have also used a 5-fluorouracil re-challenge 3 months after treatment to highlight the efficacy of these treatments.

Methods: This was an investigator-blinded randomized study in which 30 patients were randomized 1:1:1 into the following groups: Group 1 patients pretreated for 6-7 days with 5-fluorouracil, ALA applied with incubation of 2 hours, ALA removed with wet gauze, illuminated treated areas with 10 J/cm(2) with Blu-U device; Group 2 patients treated with 5-fluorouracil BID for 6-7 days and no ALA/PDT; Group 3 patients received no pretreatment, ALA applied with incubation of 2 hours, ALA removed with wet gauze, illuminated treated areas with 10 J.cm2 with Blu-U device. Patients were seen at screening/baseline, treatment for ALA/PDT, 24 hours post treatment, 1 week post treatment and 3 months post treatment. All subjects were then given a re-challenge course of 5-fluorouracil for 6 days and reassessed.

Results: AK counts in all groups were dramatically decreased and similar at 1- and 3-months post treatment. The re-challenge brought a significant difference with many subclinical lesions in the area of activity in the ALA and 5-fluorouracil alone groups.

Conclusions: All three arms appeared equal in treating visible AKs. These data strongly suggests a synergistic role of 5-fluorouracil with ALA/PDT over ALA/PDT or 5-fluorouracil alone in treating the subclinical lesions demonstrated on a 5-fluorouracil re-challenge. Treatment of these subclinical lesions should result in a longer remission. The data also suggests that a 5-fluorouracil re-challenge could be a clinical tool to judge the efficacy of treatment for AK if these subclinical lesions are proven to be an AK precursor.

Comparative Study of Actinic Keratosis Treatment With 3% Diclofenac Sodium And 5% 5-Fluorouracil[33]

BACKGROUND: Actinic keratosis is a frequent lesion which occurs in sunlight exposed areas. Diclofenac sodium and 5-Fluorouracil are effective, non-invasive and easy-to-apply topical treatment options.

OBJECTIVES: To assess and compare the effectiveness of 3% diclofenac sodium associated with 2.5% hyaluronic acid and of 5% 5-Fluorouracil for the treatment of actinic keratosis, as well as the patient's degree of satisfaction and tolerability.

METHODS: 28 patients with a clinical diagnosis of actinic keratosis were randomized to receive diclofenac sodium or 5-Fluorouracil and were clinically assessed before and after treatment as well as 8 weeks after the end of treatment. Modified versions of the Investigator and Patient Global Improvement Scores were used.

RESULTS: The average number of lesions in the diclofenac sodium group before and after treatment was 13.6 and 6.6 ($p<0,001$), respectively, while it was 17.4 and 3.15 ($p<0.001$) in the 5-Fluorouracil group. There was a significant reduction in the number of lesions in the 5-Fluorouracil group in relation to the diclofenac sodium group ($p<0.001$). To the non-blinded physician, there was a higher satisfactory therapeutic response in the 5-Fluorouracil group ($p<0.001$); to the blinded physician, there was a higher satisfactory response in this same group, although not statistically significant ($p=0.09$). There was a high degree of satisfaction in both groups (73% in the diclofenac sodium group and 77% in the 5-Fluorouracil group; $p=0.827$). Regarding adverse effects, the diclofenac sodium group presented a higher degree of satisfaction (93.3% vs 38.4%; $p=0.008$). Erythema, edema, crusts and itching were significantly higher in the 5-Fluorouracil group.

CONCLUSION: We concluded that 5-Fluorouracil was more effective; however, it showed lower tolerability than diclofenac sodium

Appendix 4: Medline Search Strategy
Ovid MEDLINE(R) ALL <1946 to March 05, 2025>

1	exp Keratosis, Actinic/	2675
2	5 fluorouracil.mp. or Fluorouracil/	59928
3	Imiquimod/	3597
4	Diclofenac/	9202
5	tirbanibulin.mp.	108
6	Aminolevulinic Acid/	6889
7	2 or 3 or 4 or 5 or 6	79299
8	Administration, Topical/	41448
9	7 and 8	1900
10	1 and 9	107
11	limit 10 to (english language and humans)	101

Appendix 5: Key Inclusion Criteria

Population	Adults with actinic keratosis
Intervention	Topical 5-fluorouracil, imiquimod, diclofenac, tirbanibulin, and aminolaevulinic acid
Comparator	Other topical agents or placebo
Outcomes	Clearance of actinic keratoses
Timing	2 to 6 months after treatment
Setting	Outpatient application, except for aminolaevulinic acid which is provider administered prior to photodynamic therapy

Topical Therapies for Actinic Keratosis

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature. Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 3 months

Requires PA:

- Non-preferred agents for pharmacy claims
- Aminolevulinic ointment for provider administered claims

Covered Alternatives:

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

Table 1. Topical Medications FDA-Approved in Actinic Keratosis and Other Indications

Generic Drug Name (BRAND NAME)	Strength/ Formulation	FDA-Approved Indications in Adults	Patient or Health Care Provider Administered	Dosing Guidance
5-fluorouracil (TOLAK, EFUDEX)	0.5% cream 4% cream 5% cream 2% solution 5% solution	• Actinic Keratosis • Basal Cell Carcinoma (5% cream or solution)	Patient	Maximum duration of therapy: 2 months Actinic Keratosis: • Fluorouracil 0.5% and 4% cream: Apply once daily up to 4 weeks. • Fluorouracil 1% cream: Apply twice daily for an average of 2-6 weeks. • Fluorouracil 5% cream: Apply twice daily for an average of 2-4 weeks. • Fluorouracil 2% and 5% solution: Apply twice daily for an average of 2-4 weeks. Basal Cell Carcinoma: • Fluorouracil 5% cream or solution: Apply twice daily for an average of 2-4 weeks.

Imiquimod (ALDARA, ZYCLARA)[1]	2.5% cream 3.75% cream 5% cream	• Actinic Keratosis in adults (2.5%, 3.75%, and 5% cream) • Basal Cell Carcinoma in adults (5% cream only) • Genital and Perianal Warts (3.75% cream & 5% cream) approved in children and adolescents ≥ 12 years)	Patient	Actinic Keratosis: • Imiquimod 2.5% and 3.75% cream: Apply at bedtime (remove in 8 hours) x 2 weeks, off for 2 weeks then repeat x 2 weeks. Apply up to 0.5 grams per application. • Imiquimod 5% cream: Apply once daily before bedtime 2 times per week for 16 weeks. Apply no more than 1 packet per application. Basal Cell Carcinoma: • Imiquimod 5% cream: Apply once daily before bedtime 5 times per week for 6 weeks. Amount of cream used is based on target tumor diameter. Genital Warts: • Imiquimod 3.75% cream: Apply once daily (remove in 8 hours) up to 8 weeks. Apply up to 0.25 grams per application. • Imiquimod 5% cream: Apply once daily before bedtime 3 times per week until total clearance or for a maximum of 16 weeks.
Diclofenac Sodium (SOLARAZE)	3% gel	• Actinic Keratosis	Patient	• Apply twice daily for 60 to 90 days.
Tirbanibulin (KLISYRI)	1% ointment	• Actinic Keratosis	Patient	• Apply once daily (max one single dose packet) x 5 consecutive days.
Aminolevulinic acid (AMELUZ, LEVULAN)	10% gel (red or blue light) 20% solution (red light)	• Actinic Keratosis prior to photodynamic therapy	Health Care Provider	• 10% gel: Apply a maximum of 6 grams (3 tubes) at one time. Retreat lesions that have not completely resolved 3 months after the initial treatment. • 20% gel: Apply one treatment and may repeat after 8 weeks.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication (see **Table 1**)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Has the patient tried a preferred agent and do they have a contraindication, intolerance, or failure with this therapy?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP. If eligible for EPSDT review: Go to #5.
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)	**Yes:** Approve for up to 4 months based on dosing parameters in Table 1.	**No:** Pass to RPh. Deny; medical necessity.

P&T/DUR Review: 6/25 (DM)
Implementation: TBD

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Prior Authorization Update: Tesamorelin (EGRIFTA), injection

Plain Language Summary:

- Lipodystrophy is a condition that changes the way body makes, uses and stores fat. People with human immunodeficiency virus (HIV) who take certain medicines may be more commonly affected. Treatments for HIV that contain zidovudine or stavudine can cause lipodystrophy, especially after long-term use.
- Fat loss occurs in the arms, legs or face while the stomach, back of the neck and chest can gain fat. For people with lipodystrophy, these changes in body shape can be very upsetting and can affect quality of life.
- Several treatments can prevent or improve body shape changes in people with HIV including:
    - Changing HIV medicines
    - Exercising and changing their diet
    - Taking tesamorelin, a medicine that reduces excess stomach fat in people with lipodystrophy associated with HIV medicines.
- Providers who prescribe tesamorelin to a person enrolled in the Oregon Health Plan (OHP) must receive approval from the Oregon Health Authority before OHP will pay for it. This process is called prior authorization (PA).

Purpose of Update: Treatment of HIV-associated lipodystrophy is currently not funded by the Health Evidence Review Commission (HERC) Prioritized List of Health Services.[1] This PA update will evaluate recently published evidence to support revisions of PA criteria and establish specific medical necessity and appropriateness criteria for patients with the Early Periodic Screening Diagnostic and Treatment Benefit.

Background:

Tesamorelin, a growth hormone releasing factor (GRF) analog indicated for reduction of excess abdominal fat in patients with HIV and lipodystrophy, was first reviewed by the Pharmacy and Therapeutics (P & T) committee at the April 2012 meeting.[2] The committee approved PA criteria to limit the use of tesamorelin in OHP-funded conditions. At the September 2015 P & T meeting the PA criteria were re-evaluated and no changes to the PA criteria were recommended at that time (**Appendix 1**). In the third quarter of 2024 there were 9 OHP fee-for-service members with a diagnosis of HIV-associated lipodystrophy. In the first quarter of 2025, there were no pharmacy claims for stavudine or zidovudine.

Lipodystrophy refers to the abnormal distribution of adipose tissue.[3] Human immunodeficiency virus (HIV)-associated lipodystrophy is an undesirable adverse effect of antiretroviral therapy (ART) that occurs due to the redistribution of adipose tissue.[4] HIV-associated lipodystrophy can manifest as two distinct phenotypes: fat accumulation (lipohypertrophy) or fat loss (lipoatrophy).[4] In some patients, the 2 manifestations may coexist as well. The production of

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inflammatory cytokines such as interleukins are provoked, which results in adipose cell destruction.[3] In addition, insulin signaling function and glucose transport can be impaired.[3] Lipodystrophy can be inherited or acquired, although inherited lipodystrophic syndromes are very rare.[3] The most prevalent type of lipodystrophy is an acquired form that occurs in individuals with HIV who are receiving highly active antiretroviral therapy (HAART). Up to 40–70% of patients on HAART are reported to have HIV-associated lipodystrophy syndrome (HALS).[3,5]

Lipoatrophy occurs on the face, buttocks, arms, and legs.[4] In contrast, lipohypertrophy occurs in the truncal areas and manifests as abdominal obesity, mammary hypertrophy, accumulation of fat on the neck, or lipomas.[4] These body shape changes, especially facial lipoatrophy, have been linked to depression, decreased self-esteem, sexual dysfunction, and social isolation and can greatly affect the patient's quality of life and adherence to ART.[4] Lipodystrophy also contributes to morbidity via the development of insulin resistance, hyperlipidemia, and endothelial dysfunction, which can increase the risk of cardiovascular disease.[4] Risk factors for HALS include older age, greater severity of HIV-infection, increased viral load, low count of CD4-positive T lymphocytes and coinfection with hepatitis C virus.[3] Modifying the ART regimen so that stavudine or zidovudine is replaced with a different medication, namely tenofovir or abacavir, is the primary medical approach to managing lipodystrophy.[6] This can result in modest gains in limb fat.[6] Tenofovir and abacavir are first-line nucleoside reverse transcriptase inhibitors (NRTIs) because of their efficacy, safety, and convenience, whereas stavudine and zidovudine are associated with many adverse events and inferior virologic potency.[6]

In HIV-associated lipodystrophy, patients have blunted growth hormone (GH) secretion in proportion to the extent of abdominal fat accumulation.[7] Since GH increases lipolysis and suppresses de novo lipogenesis, low GH secretion has been theorized to potentiate abdominal fat accumulation and hepatic steatosis in this patient population.[7] Based on this hypothesis, the GRF analog, tesamorelin was developed as a strategy to restore physiologic GH pulsatility in patients with HIV-associated lipodystrophy.[8]

Two phase 3 clinical randomized controlled trials (RCTs) evaluated the efficacy of tesamorelin compared to placebo over 26 weeks in patients with ART-associated lipodystrophy (n=806).[9] Both RCTs enrolled patients in a 26-week extension phase to evaluate long-term safety.[9] In a pooled analysis of both RCTs, tesamorelin was shown to statistically significantly reduce visceral adipose fat (VAT) compared with placebo (-15.4 vs. -0.6%; $p<0.001$).[9] Secondary efficacy endpoints from the extension phases indicated that the decrease in VAT was not maintained after treatment discontinuation. [9] There was limited reduction in body mass index and waist circumference after 26 weeks of treatment with tesamorelin.[9] This evidence was presented to the P & T Committee at the 2012 meeting.[2]

Adverse events observed with tesamorelin included injection site reactions, arthralgias, limb pain, rash, myalgias, and peripheral edema.[10] Though GH is known to increase insulin resistance, physiology studies have shown no worsening of glycemic control with tesamorelin.[10] However, in a small number of patients, glucose levels may increase, and thus optimization of glycemic control before initiation of therapy and periodic blood glucose monitoring while on treatment may be warranted.[11] Patients receiving tesamorelin should undergo routine assessment of IGF-1; a dose reduction may rarely be needed to maintain levels within the normal range.[11] In addition, patients on tesamorelin should undergo age-appropriate cancer screening before and while on therapy given theoretical concerns that GH may potentiate cancer growth, though tesamorelin specifically has not been shown to increase cancer risk.[11] Tesamorelin is the only medication approved in the United States to treat abdominal fat accumulation in HIV.[11] Tesamorelin has not been studied in the context of other lipodystrophy syndromes characterized by increased visceral adiposity and is not currently approved outside the context of HIV.[11]

Recommendations:

- Revise PA criteria for tesamorelin to define medical necessity and appropriateness for patients with the Early Periodic Screening Diagnostic and Treatment Benefit.
- Maintain tesamorelin as nonpreferred on the Prioritized Drug List (PDL).

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11. EGRIFTA (tesamorelin) Subcutanous Injection Prescribing Information. Montreal, Quebec, Canada; Theratechnologies Inc. 02/2024.

Appendix 1: Proposed Prior Authorization Criteria

Tesamorelin (Egrifta®)

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.
- ~~Restrict use to OHP-funded diagnoses in adults.~~ Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 months

Requires PA:

- Tesamorelin (Egrifta and Egrifta SV®) subcutaneous injection

Covered Alternatives:

- No preferred alternatives

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the indicated treatment for reduction of excess abdominal fat in HIV-infected patients with lipodystrophy (ICD10 E881)?	**Yes:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3.	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is there documentation that lipodystrophy has not sufficiently improved or cannot be managed by switching HIV antiretroviral therapy and lifestyle changes (e.g., diet and exercise)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~3.~~4. Is there documentation that the condition is of sufficient severity that it impacts the patient's mental or physical health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical necessity.

P&T/DUR Review: *6/25 (DM); 9/15 (AG); 4/12*
Implementation: *TBD; 10/15; 7/12*

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Drug Class Review: Targeted Drugs for Dry Eye Disease

Date of Review: June 2025 **End Date of Literature Search:** 02/26/2025

Purpose for Class Review:
The purpose of this review is to evaluate the evidence related to the treatment of dry eye, which is currently unfunded. A medical necessity pathway for coverage for Early and Periodic Screening, Diagnostic, and Treatment (EPSTD) patients will be created, which can be expanded to additional populations in 2027 when the Oregon Health Plan (OHP) prioritized list is retired.

Plain Language Summary:
- Dry eye disease is a common eye condition associated with eye pain and trouble seeing. Dry eye is currently not a funded treatment for Oregon Health Plan members. Prescription dry eye therapies are available for patients who qualify through the Early and Periodic Screening, Diagnostic, and Treatment (EPSTD) program.
- Artificial tears, also known as lubricants, are available without a prescription. Artificial tears are recommended to help the initial symptoms of dry eye.
- If artificial tears fail to provide relief of symptoms, prescription products are available to treat the symptoms associated with dry eye. Prescription dry eye drops are cyclosporine, loteprednol, lifitegrast and perfluorohexyloctane. Varenicline nasal spray is a prescription used to improve dry eye symptoms.
- Randomized controlled trials, systematic reviews, and meta-analyses provide evidence that Food and Drug Administration (FDA) approved products for dry are more effective than placebo (an inactive product) for improving dry eye symptoms.
- Guidelines recommend treating dry eye disease with artificial tears as an initial option and using prescription products if symptoms of dry eye continue.
- The Drug Use Research and Management Group recommends that artificial tears be used for patients with dry eye. If bothersome symptoms persist, and the member qualifies under EPSDT, then prescription products for dry eye should be covered after going through the prior authorization process.

Research Questions:
1. What is the new comparative evidence for efficacy and effectiveness for certain drugs used for dry eye disease for outcomes such as symptom improvement?
2. What is the evidence for safety associated with certain drugs used for dry eye (e.g., burning or pain at instillation site)?
3. Are there subpopulations in which certain dry eye treatments are associated with more benefit or more harm?

Conclusions:
- In this review there were 2 new systematic reviews and meta-analyses, 2 new guidelines, and 7 randomized controlled trials (RCTs) identified.
- A Cochrane review found topical steroids to have lower scores (which is favored) in patient reported symptom scores (measured by the Ocular Surface Disease Index [OSDI] or Visual Analog Scale, 0-100 points) than artificial tears (AT) in patients with dry eye moderate evidence (standard mean difference [SMD] -0.29; 95% confidence interval [CI], -0.42 to -0.16; moderate evidence). A change of 0.2 is representative of a small difference which may not be

clinically significant.[1] Tear film break up time (TBUT) was longer with steroids compared to AT based on low quality of evidence. The TBUT is used to measure the time the tear film on the eye surface remains stable before breaking up, shorter lengths of time are indicative of dry eye (10 seconds or less). The change in TBUT was considered clinically meaningful (mean difference [MD] 7.0 sec; 95% CI, 0.06 to 1.34) with a minimal clinically significant change of 5 sec with steroids compared to AT.[1] Low-quality evidence found greater reductions in patient reported symptoms in those treated with steroids compared to cyclosporin (CSA) (standard mean difference [SMD] -0.33; 95% CI, -0.51 to -0.15).[1]

- The use of CSA, in combination with AT, was more effective for reducing the signs and symptoms of dry eye at 6 months compared to AT alone based on a Cochrane review (low-quality evidence).[2] The evidence on tear production and stability was inconsistent.[2]
- The American Academy of Ophthalmology (AAO) guidance on the treatment of dry eye disease recommends ocular lubricants (i.e., artificial tears) first-line for dry eye (high-quality evidence).[3] Prescription products are considered second-line with no preference of one therapy over another.
- The National Institute for Health and Care Excellence (NICE) recommends the use of CSA as an option for adult patients with dry eye and severe keratitis that does not improve with the use of AT.[4]
- Seven randomized clinical trials compared the efficacy and safety of the following dry eye therapies compared to vehicle or saline: lifitigrast[5–7], CSA[8], perfluorohexyloctane[9,10] and varenicline[11]. Active treatments were more effective at reporting patient symptom compared to control.
- There was insufficient evidence to suggest that there are certain subpopulations who would benefit more or less from certain therapies for dry eye.
- There is also a pathway for coverage for the treatment of vernal keratoconjunctivitis as CSA products are used for this indication.

Recommendations:

- Create a PDL class for prescription drugs used for dry eye. Make all prescription products for the treatment of dry eye and vernal keratoconjunctivitis nonpreferred based on the evidence.
- No changes in coverage for over-the-counter artificial tear products.
- Implement prior authorization (PA) criteria to provide a pathway for coverage for therapies for vernal keratoconjunctivitis and for dry eye therapies for patients with comorbidities which allow for funding of dry eye or who qualify under EPSTD (**Appendix 6**).
- Evaluate costs in executive session.

Background:

Dry eye syndrome, also known as dry eye disease or keratoconjuctivitis, is a common eye ailment diagnosed upon clinical examination. It occurs in 5% to 50% of the population, depending on study population and diagnostic criteria.[2] A recent systematic review and meta-analysis reports an incidence of 3.5% in those 18 years and older and 7.8% in adults 68 years and older.[12] Common symptoms of dry eye are discomfort and visual disability, such as blurred vision and inability to read or drive. Burning, photophobia and dryness may also be present.[2] Dry eye is the result of the inability of the lacrimal functional unit (lacrimal glands, ocular surface and lids, and the sensory and motor nerves) to maintain a stable precorneal tear layer.[2] Ocular inflammation is thought to be a key component of dry eye.[1] Causes of dry eye can be due to aging, inflammation, cataract or refractive surgery, diabetes, Sjögren's syndrome, thyroid eye disease, or secondary to ocular diseases such as glaucoma.[2] The most common risk factor is age and it is more common in women compared to men.[2] Additional risk factors are contact lens wear, screen time, androgen deficiency and medication use (i.e., diuretics, anxiolytics, nonsteroidal anti-inflammatory drugs [NSAIDs], antipsychotics, inhaled steroids and antidepressants).[13]

There is no one test used to diagnose dry eye and clinical examination is the standard of care for diagnosis.[3] Types of dry eye include aqueous-deficient dry eye, evaporative dry eye, and mixed mechanism of both types. Tear supplements and tear stimulants for tear preservation are recommended for aqueous-deficient

dry eye.[1] There is a lack of evidence to recommend punctal plugs or autologous serum eye drops.[1] The treatment of evaporated dry eye treatment is guided by underlying cause, with the use of topical steroids and cyclosporine recommended for ocular surface inflammation.[1]

Therapies to treat dry eye consists of procedural and pharmacotherapy. Long-term treatment is often necessary, as most treatments are for symptomatic improvements compared to curative.[3] Clinical assessment of treatment efficacy is most often determined by symptom improvement in response to therapy. Over the counter ocular lubricants (i.e., artificial tears) can be helpful in the management of dry eye, and are available in liquid, gel and ointment formulations. Non-preserved tear substitutes are recommended if patients require administration of 4 times a day or more, as excessive exposure to preservatives can cause toxic conjuctivitis.[14] Persistent symptoms may require additional treatment. Prescription drugs FDA-approved for the treatment of dry eye include topical products: loteprednol, lifitegrast, cyclosporine, and perfluorohexyloctane (**Table 1).** Varenicline nasal spray is the only nasal treatment approved for dry eye. Approved treatments for dry eye have different mechanisms and there is no guidance on comparative efficacy of prescription products.[13] Cyclosporine is an immunomodulatory therapy that prevents activation and function of T lymphocytes.[2] In some cases, topical CSA may lead to long-term remission in symptoms.[3] Topical steroids are often used for the short-term (up to 1 month) treatment of dry eye. Topical steroids have a rapid onset of action making them a pre-treatment option before using long-term treatments such as CSA.[1] Topical lifitegrast is an integrin antagonist that has evidence of improving signs and symptoms of dry eye in patients with mild to severe symptoms. Safety of use beyond 12 months is uknown.[3] Intranasal varenicline, a nicotinic acetylcholine receptor agonist, stimulates natural tear production. Perfluorohexyloctane is a tear substitute drop demonstrating improvement in the signs and symptoms of dry eye. Topical products take between 1-3 months after initiation to alleviate symptoms; however, CSA treatment effects may take longer.[15]

For patients with severe dry eye, such as those with Sjögren's syndrome, a cholinergic agonist may be appropriate. Drugs approved for this indication include the cholinergic agonists, pilocarpine and cevimeline. Adverse effects include excessive sweating and ocular irritation.[3] For patients with blepharitis, including meibomian gland dysfunction, the use of oral tetracycline or doxycycline for 2-4 weeks or oral azithromycin for 5 days may be effective for the treatment of dry eye.[14]

Patients with vernal keratoconjunctivitis (VK) may also be prescribed CSA products, in which topical doses with concentrations of 0.1% or greater may be an effective treatment for this condition.[16] The brand name CSA product, VERKAZIA, is specifically approved for VK. Vernal keratoconjunctivitis is inflammation of conjunctiva usually occurring in children and young adults, ages 5-25 years, in hot, dry climates such as Middle East, Mediterranean basin, North and West Africa, parts of India, Central America and South America.[16] Other medications besides topical CSA for VK include mast cell stabilizers, antihistamines, NSAIDs, and topical corticosteroids (short-term).[16] There are no direct comparison studies evaluating treatments for VK.

The most common adverse reactions associated with the use of prescription dry eye products include instillation site pain and blurred vision. Patients prescribed corticosteroids should be monitored for adverse events such as increased intraocular pressure and cataract formation.[3]

Important outcomes in the treatment of dry eye are general symptom improvement, including relief of eye discomfort, dryness, and visual impairment. There is not a gold standard for symptom assessment. The OSDI is a validated questionnaire used for evaluation of dry eye symptoms. It includes 12 questions to determine the severity of dry eye.[13] Total score ranges from 0-100 points with higher scores indicating greater disability. The minimal clinically important difference (MCID) for OSDI is 4.5 to 7.3 units for mild to moderate dry eye and 7.3-13.4 units for severe dry eye.[17] The Dry Eye Questionnaire-5 (DEQ-5) focuses on degree of eye discomfort, dryness and wateriness by rating severity on a 0 (never) to 4 (constantly) scale. A score of 6 or more is considered positive for the diagnosis of dry eye.[18] The Visual Analog Scale (VAS) is also used to rank severity of symptoms, with a change in symptom severity score of at least 30% considered a clinically significant change. The Schirmer tear test measures the rate of tear production in the eye and is used in the diagnosis of dry eye.

Fluorescein staining scores can also assist in the diagnosis of dry eye by highlighting areas of damage on the ocular surface. The National Eye Institute Grading Scale is often used.[19] Scores are graded from 0 to 3, with a 0 indicating no staining and 3 indicating severe eye staining. A score higher than 0 is abnormal.

There was only one claim for loteprednol in Q3 of 2024 quarter most likely for an indication other than dry eye. Dry eye currently falls below the funding line so there is no utilization for the other products.

A summary of relevant drug information is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. FDA-approved Drugs for Dry Eye Disease Indications and Dosing.

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Loteprednol 0.25% suspension (EYSUVIS)[20]	• Indicated for the short-term (up to 2 weeks) treatment of the signs and symptoms of dry eye disease	• Topical	1-2 drops into each eye four times daily
Lifitegrast 5% solution (XIIDRA)[21]	• For the treatment of the signs and symptoms of dry eye disease	• Topical	One drop twice daily in each eye approximately 12 hours apart.
Cyclosporine 0.05% emulsion (RESTASIS)[22]	• To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.	• Topical	One drop twice a day in each eye approximately 12 hours apart.
Cyclosporine 0.09% solution (CEQUA)[23]	• To increase tear production in patients with keratoconjunctivitis sicca (dry eye)	• Topical	One drop twice daily approximately 12 hours apart into each eye. Discard the vial immediately after using in both eyes.
Cyclosporine 0.1% emulsion (VERKAZIA)[24]	• For the treatment of vernal keratoconjunctivitis (seasonal eye irritation) in children and adults	• Topical	One drop, 4 times daily (morning, noon, afternoon and evening) in each affected eye
Cyclosporine 0.1% solution (VEVYE)[25]	• For the treatment of the signs and symptoms of dry eye disease	• Topical	One drop twice a day in each eye approximately 12 hours apart
Varenicline nasal spray (TYRVAYA)[26]	• For the treatment of the signs and symptoms of dry eye disease	• Nasal	One spray in each nostril twice daily approximately 12 hours apart
Perfluorohexyloctane solution (MIEBO)[27]	• For the treatment of the signs and symptoms of dry eye disease	• Topical	One drop four times a day

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, Canada's Drug Agency (CDA-AMA), Scottish Intercollegiate Guidelines Network (SIGN), and Oregon Mental Health Clinical Advisory Group (MHCAG) 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 – Topical Corticosteroids for Dry Eye
A Cochrane systematic review and meta-analysis evaluated treatment of dry eye.[1] The literature was searched up to August of 2021. Randomized controlled trials of ophthalmic topical steroids (as monotherapy or in combination with tobramycin) were compared to no treatment, AT, inert vehicles , AT plus tobramycin or CSA. Topical steroids used in the studies were clobetasone, difluprednate, loteprednol etabonate, fluorometholone, methylprednisolone and corticosteroid. There were 22 RCTs identified for inclusion. All but one trial included adults 18 years and older.[1] Females accounted for 79% of the population.[1] Most trials were small, enrolling 40-158 participants. Topical steroid use ranged from 1 week to 3 months.[1] Five trials included patients with Sjögren's syndrome. Almost half of the trials were at high risk of bias due to selective outcome reporting.

Topical steroids, with or without tobramycin, were compared to eye lubricants (e.g., hyaluronate, soothe emollient or polyvinylpyrrolidone), vehicle, no treatment or AT in 15 studies. There was moderate strength of evidence that the change in patient-reported symptom scores were lower in those treated with topical steroids compared to AT (SMD -0.29; 95% CI, -0.42 to -0.16).[1] Tear film break up time was longer in the steroid treated group compared to AT, suggesting benefit with steroids (MD 0.70; 95% CI, 0.06 to 1.34) (low quality of evidence).[1] Lower fluorescein corneal staining scores were present in those treated with steroids compared to AT (SMD -0.40; 95% CI, -0.62 to -0.18) (moderate quality of evidence). Steroids, compared to AT, were associated with elevated intraocular pressure but evidence was considered very low.

Steroids (e.g., fluorometholone, loteprednol, or methylprednisolone) alone, or in combination with CSA, were compared to CSA. Symptom scores were lower in patients treated with steroids compared to CSA (SMD -0.33; 95% CI, -0.51 to -0.15) based on low quality evidence.[1] Changes of 0.2 were considered small; therefore, unlikely to be clinically significant. A moderate change would be 0.5 in symptom scores. Changes in TBUT were longer in those treated with steroids compared to CSA based on low quality evidence (MD 0.37 sec; 95% CI, -0.13 to 0.87); however, changes were not statistically significant.[1] Changes in fluorescein corneal staining scores were higher in the steroid group suggesting that treatment with CSA was favored (SMD 0.05; 95% CI, -0.25 to 0.35; p>0.05) (low quality of evidence).[1] There was very low evidence of increased intraocular pressure in those treated with steroids compared to CSA (relative risk [RR] 1.45; 95% CI, 0.25 to 8.33; p>0.05).[1]

Overall, topical steroids provide small to moderate relief of symptoms of dry eye compared to lubricants or CSA. Additional research is needed to determine the effects on tear film quality and quantity.

Cochrane – Topical Cyclosporine for Dry Eye Syndrome

In 2019 a systematic review and meta-analysis was conducted by Cochrane on the treatment of dry eye with topical CSA.[2] Thirty trials enrolling 4,009 patients were identified for inclusion. Trials lasted 6 weeks to 12 months. Trials studied the use of CSA compared to AT and CSA plus AT versus CSA alone. Concentrations of CSA were 0.05%, 0.1%, 1% and 2%.[2] A meta-analysis of all trial results was not possible due to lack of details results reporting.

A majority of trials (n=18) studied CSA 0.05% in combination with AT compared to a placebo vehicle and AT or AT monotherapy. All results for dry eye outcomes were based on low quality of evidence.[2] Symptom improvement at 6 months was reported by one, small (n=56) RCT and found CSA to be superior to comparator (MD -4.80; 95% CI, -6.41 to -3.19).[2] Ocular surface dye staining results at 6 months was not conclusive with 2 trials reporting results with inconsistent findings. Aqueous tear production (measured by Schirmer test scores) found CSA to be superior to comparators in one analysis (RR 3.50; 95% CI, 2.09 to 5.85) and improved, but not statistically so, in another analysis (RR 0.98; 95% CI, 0.83 to 1.17) (7 studies total).[2] Tear film stability at 6 months, measured by TBUT, was improved in those treated with CSA versus comparator with results ranging from 0.90 to 4.00. Conjunctival goblet cell density was higher in those treated with CSA compared to control with a MD of 22.5 cells per unit (95% CI, 16.3 to 28.8).[2] CSA was consistently associated with burning and stinging upon administration.

Additional comparisons studying different concentrations of CSA generally favored CSA over control; however, calculations on the differences were not able to be calculated due to lack of result reporting.

After review, one systematic review was 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).[28]

Guidelines:

High Quality Guidelines:

American Academy of Ophthalmology – Dry Eye Syndrome Preferred Practice Patterns Guideline

The AAO updated previous guidance on the treatment of dry eye with a 2023 guideline.[3] Literature was searched on March 3, 2022 and June 7, 2023. Studies are rated using the SIGN scale from I++ to III (See **Appendix 1** for details). Recommendations are defined by GRADE as strong or discretionary.[3]

Ocular lubricants are offered as a Step 1 treatment for dry eye (I+, Good, Strong).[3] Non-preserved ocular lubricants can be tried as Step 2 therapy if ocular lubricants are inadequate. In Step 2 the following prescription drugs can be used to manage dry eye[3]:

- Topical antibiotic or antibiotic/steroid combination applied to the lid margin for anterior blepharitis.
- Topical corticosteroids (limited duration)
- Topical secretagogues
- Topical nonglucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics (used for meibomianitis and blepharitis)

If the above fail to control symptoms, then Step 3 recommends oral secretagogues, autologous/allogenic serum eye drops (I+, Moderate, Discretionary) and therapeutic contact lens as options (e.g., soft bandage lens and rigid scleral lenses).[3] In Step 4 for those without adequate relief from Steps 1-3 can consider:

topical corticosteroids for longer duration, amniotic membrane grafts, surgical punctal occlusion, or other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation).[3]

Limitations to the guideline include the lack of grading of all recommendations provided. Only select recommendations provided an evidence grade and strength of recommendation.

NICE – Cyclosporin for Treating Dry Eye

2015 NICE guidance focused on the use of CSA for people with dry eye that have not improved with AT.[4] Cyclosporin is recommended as an option for adults with dry eye with severe keratitis that has not improved with AT treatment.

Patients with Sjögren's syndrome and severe dry eye received the most benefit of CSA, with AT.[4] There was a lack of comparative evidence studying CSA compared to the established standard of care, corticosteroid and AT treatment. Eye pain, eye irritation, lacrimation, ocular hyperemia and eyelid erythema were noted common adverse reactions. There is no evidence of differences between CSA formulations due to lack of comparative data.[4]

Excluded Publications:

After review, 1 guideline was excluded due to poor quality.

The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS II) Management and Therapy Report was excluded due to poor quality, rigor of development and systematic approach.[29]

Randomized Controlled Trials:

A total of 125 citations were manually reviewed from the initial literature search. After further review, 118 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 7 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Akpek, et al[8] ESSENCE-2 DB, MC, PC Phase 3, RCT	1. Water-free CSA 0.1% solution (VEVYE) twice daily Vs. 2. Vehicle twice daily Trial duration = 29 days	Patients with moderate to severe dry eye N=834	Change from baseline in total corneal fluorescein staining (tCFS; score 0-15 National Eye Institute Scale*) and eye dryness score (0-100 VAS; higher score indicates higher discomfort).	Change in tCFS: 1. -4.0 grades 2. -3.6 grades change -0.4 (95% CI, -0.8 to 0; p=0.03) Dryness score: 1. -12.2 2. -13.6 Change 1.4 (95% CI, -1.8 to 4.6 p=0.38)	Patients had to be using AT and dryness score of 50 or more for inclusion. Eye with highest baseline tCFS was designated the study eye. *Cyclosporine was more effective than placebo for tCFS scores but not for dryness scores.*

Holland, et al[7] OPUS-3 DB, MC, PC Phase 3, RCT	1. Lifitegrast 5.0% solution twice daily Vs. 2. Vehicle twice daily Trial duration = 12 weeks	Patients with artificial tear use within the previous 30 days, corneal staining score of ≥2.0 (0-4 scale), STS >1 to <10 mm and eye dryness score of ≥40 (0-100 VAS) N=711	Change in eye dryness score (VAS in study eye) from baseline to day 84	Change in VAS: 1. -37 2. -29 TE 7.16 (95% CI, 3.04 to 11.28; P<0.0007)	Patients were an average of 58.7 years and 75.5% were female. Cataracts were present in 33.9% of patients. Fifty-eight percent of patients had a mean ICSS of 2.46 and mean eye dryness score of 68 at baseline indicating more severe dry eye. *Lifitegrast was more effective than placebo for changes in VAS.*
Sheppard, et al[9] MOJAVE DB, MC, PC (saline), Phase 3, RCT	1. Perfluorohexyloctane solution 1 drop 4 times daily Vs. 2. Hypotonic saline 0.6% 4 times daily Trial duration = 8 weeks	Adult patients with self-reported history of dry eye disease in both eyes that was verified by dry eye testing N=620	Change from baseline in tCFS (score 0-15 National Eye Institute Scale*) and eye dryness score (0-100 VAS; higher score indicates higher discomfort).	Change in tCFS: 1. -2.3 grades 2. -1.1 grades MC -1.2 (95% CI, -1.7 to -0.8; p<0.001) Dryness score: 1. -29.4 2. -19.2 MD-10.2 (95% CI, -14.4 to -6.1 p<0.001)	Patients were mostly white females with a mean age of 54 years. Eye dryness at baseline was a mean of 64 suggestive of severe dry eyes. Hypotonic saline has been used in the treatment of dry eye. *Perfluorohexyloctane was more effective than placebo for tCFS scores and for dryness scores.*
Sheppard, et al[5] OPUS-1 DB, MC, PC Phase 3, RCT	1. Lifitegrast 5.0% solution twice daily Vs. 2. Vehicle twice daily Trial duration = 84 days	Patients with bilateral dry eye disease N=588	Mean change from baseline ICSS at day 84 and mean change from baseline in the VR-OSDI†	Change in ICSS: 1. 0.16 2. -0.9 P=0.0007 Change in VR-OSDI was not significant (numerical results were not provided) P=0.7894	Fifty percent of patients had cataracts and 43% were using artificial tears. Lack of study details makes interpretation of results difficult. *Lifitegrast was more effective than placebo for changes in ICSS but not for changes in VR-OSDI.*

Tauber, et al[10] GOBI DB, MC, PC (saline), Phase 3, RCT	1. Perfluorohexyloctane solution 1 drop 4 times daily Vs. 2. Hypotonic saline 0.6% 4 times daily Trial duration = 8 weeks	Adult patients with self-reported history of dry eye disease in both eyes that was verified by dry eye testing N=599	Change from baseline in (tCFS; score 0-15 National Eye Institute Scale*) and eye dryness score (0-100 VAS; higher score indicates higher discomfort).	Change in tCFS: 1. -2.0 grades 2. -1.0 grades LSMD -0.97 (95% CI, -1.4 to -0.55; p<0.001) Dryness score: 1. -27.4 2. -19.7 LSMD -7.6 (95% CI, -11.8 to -3.4 p<0.001)	Patients were mostly white females with a mean age of 61 years. Eye dryness at baseline was a mean of 67 suggestive of severe dry eyes. Hypotonic saline has been used in the treatment of dry eye. *Perfluorohexyloctane was more effective than placebo for tCFS scores and for dryness scores.*
Tauber, et al[6] OPUS-2 DB, MC, PC Phase 3, RCT	1. Lifitegrast 5.0% solution twice daily Vs. 2. Vehicle twice daily Trial duration = 84 days	Patients with artificial tear use within the previous 30 days, inferior corneal staining score of ≥0.5 (0-4 scale), STS >1 to <10 mm and eye dryness score of >40 (0-100 VAS) N=718	Change in eye dryness score (VAS in both eyes) and change in ICSS in study eye	Change in VAS: 1. -35.30 2. -22.75 TE 12.61 (95% CI, 8.51 to 16.70; P<0.0001) Change in ICSS: 1. -0.71 2. -0.73 TE 0.03 (95% CI, -0.10 to 0.17; P=0.6186)	Cataracts were present in 35% of patients. Over 70% were female. Fifty-eight percent of patients had inferior corneal staining score or > 1.5 and eye dryness score of ≥60 at baseline indicating more severe dry eye. *Lifitegrast was more effective than placebo for changes in VAS but not for changes in ICSS.*
Wirta, et al ONSET-2 DB, MC, PC Phase 3, RCT	1. Varenicline 0.03 mg solution 1 spray twice daily intranasally 2. Varenicline 0.06 mg solution 1 spray twice daily intranasally Vs.	Adults 22 years and older with a diagnosis of dry eye disease, artificial tear use, ocular surface index score of 23 or more and STS	Percentage of patients achieving a 10-mm improvement or more in STS at week 4	1. 47.3% 2. 49.2% 3. 27.8% 1. vs. 3. OR 2.6 (95% CI, 1.7 to 3.8; p<0.0001; ARR 19.5/NNT 5) 2. vs. 3. OR 2.5 (95% CI, 1.7 to 3.6; p<0.0001; ARR 21.4/NNT 5)	Patients were an average of 58 years old and mostly White (83%) with moderate to severe dry eye. *Varenicline was more effective than placebo for the percent of patients with a clinically meaningful increase in STS (defined as an increase of at least 10 mm from baseline)*

	3. Vehicle 1 spray twice daily intranasally Trial duration = 4 weeks	of 10 mm or less N=758			
Key: * National Eye Institute Scale: scale ranges from 0 (no staining) to 3 (heavy staining) for 5 areas of the cornea. †The VR-OSDI measures ocular surface disease by accessing dry eye symptoms. Abbreviations: ARR – absolute risk reduction; AT – artificial tears; CI - confidence interval; CSA – cyclosporine; DB - double-blind; ICSS - inferior corneal fluorescein staining score; LSMD – least square mean difference; MC – multi-center; MD – mean difference; NNT – number needed to treat; OR - odds ratio; PC – placebo-controlled; RCT – randomized controlled trial; STS - Schirmer test score; TE – treatment effect; tCFS - total corneal fluorescein staining; VAS – visual analog score; VR-OSDI- Visual-Related function subscale score of the Ocular Surface Disease Index.					

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Appendix 1:

Evidence Grading for the Scottish Intercollegiate Guideline Network[3]:
I++: High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++: High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
II+: Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-: Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III: Nonanalytic studies (e.g., case reports, case series)

Appendix 2: Specific Drug Information

Table 3. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Cyclosporine ophthalmic solution 0.09% (CEQUA)[23]	Calcineurin inhibitor immunosuppressant agent thought to act as a partial immunomodulator when applied topically	Not detectable	NA	NA
Cyclosporine ophthalmic emulsion 0.05% (RESTASIS)[22]				
Cyclosporine ophthalmic solution 0.1% (VEVYE)[25]				
Lifitegrast ophthalmic solution 5% (XIIDRA)[21]	Lymphocyte function-associated antigen-1 (LFA-1) antagonist	Trough plasma concentrations ranged from 0.55 ng/mL to 3.74 ng/mL	NA	NA
Loteprednol ophthalmic solution 0.25% (EYESUVIS)[20]	Corticosteroid inhibition of inflammatory response thought to inhibit prostaglandin production	Below limit of quantitation in plasma	NA	NA
Perfluorohexyloctane ophthalmic solution (MIEBO)[27]	Semifluorinated alkane which creates a monolayer at the air-liquid interface of the tear film which reduces evaporation	Low systemic blood levels after topical administration	Not metabolized by liver microsomes in vitro	NA
Varenicline solution (TYRVAYA)[26]	Cholinergic agonist resulting in increased production of basal tear film	Systemic exposure following intranasal administration was approximately 7.5% of 1 mg oral dose of varenicline	Minimal metabolism with 92% excreted unchanged in the urine	Half-life = 19 hours ± 10 hours

Abbreviations: NA = not applicable

Use in Specific Populations:

Drug Safety:

Common adverse events are dependent upon class of drug, with the exception of preservatives. When preservatives are added to any product, they can cause eye irritation if used often. The most common adverse event for perfluorohexyloctane solution is blurred vision. This solution is preservative free. Varenicline is most associated with sneezing and cough. Instillation site reactions (e.g., pain and burning) are the most common side effect for CSA products. The most common adverse reaction occurring with lifitegrast are instillation-site irritation and decreased visual acuity. Loteprednol is associated with instillation site pain as the most common adverse reaction.

There are no warnings/precautions or contraindications for drugs used for dry eye unless described in **Table 4** below.

Table 4. Summary of Warnings and Precautions.

Warning/Precaution	Loteprednol suspension	Cyclosporine drops (RESTASIS)	Cyclosporine drops (VEVYE)	Lifitegrast solution
Delayed healing and corneal perforation	X			
Increase intraocular pressure	X			
Cataracts	X			
Bacterial infections	X			
Viral infections	X			
Fungal infections	X			
Do not touch vial tip to eye		X		
Contraindications	In patients with viral diseases of the cornea and conjunctiva and mycobacterial infection of the eye and fungal diseases of ocular structures	Hypersensitivity	None	Hypersensitivity

Appendix 3: Study Abstracts

Efficacy and Safety of a Water-Free Topical Cyclosporine, 0.1%, Solution for the Treatment of Moderate to Severe Dry Eye Disease: The ESSENCE-2 Randomized Clinical Trial

Esen K Akpek , David L Wirta , Johnathon E Downing, Joseph Tauber, John D Sheppard, Joseph B Ciolino, Alice S Meides, Sonja Krösser

Importance: Dry eye disease (DED) is a common public health problem with significant impact on vision-related quality of life and well-being of patients. Medications with rapid onset of action and a good tolerability profile remain an unmet need.
Objective: To assess efficacy, safety, and tolerability of a water-free cyclosporine ophthalmic solution, 0.1% (CyclASol [Novaliq GmbH]), applied twice daily in DED compared with vehicle.
Design, setting, and participants: CyclASol for the Treatment of Signs and Symptoms of Dry Eye Disease (ESSENCE-2) was a phase 3, multicenter, randomized, double-masked, vehicle-controlled clinical study conducted from December 5, 2020, to October 8, 2021. Following a 14-day run-in period with an artificial tear administered 2 times per day, eligible participants were randomly assigned 1:1 to the treatment groups. Patients with moderate to severe DED were included in the study.
Interventions: Cyclosporine solution vs vehicle administered 2 times per day for 29 days.
Main outcomes and measures: The primary end points were changes from baseline in total corneal fluorescein staining (tCFS; 0-15 National Eye Institute scale) and in dryness score (0-100 visual analog scale) at day 29. Conjunctival staining, central corneal fluorescein staining, and tCFS responders were also assessed.
Results: A total of 834 study participants were randomly assigned to cyclosporine (423 [50.7%]) or vehicle (411 [49.3%]) groups at 27 sites. Participants had a mean (SD) age of 57.1 (15.8) years, and 609 (73.0%) were female individuals. The majority of participants self-identified in the following race categories: 79 Asian (9.5 %), 108 Black (12.9%), and 635 White (76.1%). Participants treated with cyclosporine solution had greater improvement in tCFS (-4.0 grades) than the vehicle group (-3.6 grades) at day 29 (change [Δ] = -0.4; 95% CI, -0.8 to 0; P = .03). The dryness score showed treatment benefits from baseline in both groups: -12.2 points for cyclosporine and -13.6 points for vehicle (Δ = 1.4; 95% CI, -1.8 to 4.6; P = .38). In the cyclosporine group, 293 participants (71.6%) achieved clinically meaningful reductions of 3 grades or higher in tCFS vs 236 (59.7%) in the vehicle group (Δ = 12.6%; 95% CI, 6.0%-19.3%; P < .001). These responders showed greater improvement in symptoms at day 29 including dryness (Δ = -4.6; 95% CI, -8.0 to -1.2; P = .007) and blurred vision (Δ = -3.5; 95% CI, -6.6 to -4.0; P = .03) compared with nonresponders.
Conclusions and relevance: The ESSENCE-2 trial confirmed that treatment with a water-free cyclosporine solution, 0.1%, results in early therapeutic effects on the ocular surface compared with vehicle. The responder analyses suggest that the effect is clinically meaningful in 71.6% of participants in the cyclosporine group.

Lifitegrast for the Treatment of Dry Eye Disease: Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3)

Edward J Holland, Jodi Luchs, Paul M Karpecki, Kelly K Nichols, Mitchell A Jackson, Kenneth Sall, Joseph Tauber, Monica Roy, Aparna Raychaudhuri, Amir Shojaei

Purpose: Lifitegrast is a lymphocyte function-associated antigen-1 antagonist developed to reduce inflammation in dry eye disease (DED). We report the results of OPUS-3 (NCT02284516), a phase III study evaluating the efficacy and safety of lifitegrast versus placebo in participants with DED.
Design: Twelve-week, phase III, randomized, double-masked, multicenter, placebo-controlled study.
Participants: Adults aged ≥18 years with Schirmer tear test (without anesthesia) ≥1 and ≤10 mm, corneal fluorescein staining score ≥2.0 (0-4 scale), eye dryness score (EDS) ≥40 (0-100 visual analogue scale [VAS]), and history of artificial tear use within 30 days of study entry.
Methods: After a 14-day placebo run-in, participants were randomized 1:1 to lifitegrast ophthalmic solution 5.0% or placebo twice daily for 84 days.

Main outcome measures: The primary efficacy end point was change from baseline to day 84 in EDS. Key secondary efficacy end points were change from baseline to days 42 and 14 in EDS. Other secondary efficacy end points included additional VAS items (burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, pain), ocular discomfort score (ODS), and safety/tolerability of lifitegrast versus placebo.
Results: In the study, 711 participants were randomized: placebo, 356; lifitegrast, 355 (intention-to-treat [ITT] population). At day 84, lifitegrast-treated participants experienced significantly greater improvement from baseline in EDS versus those receiving placebo (treatment effect [TE], 7.16; 95% confidence interval [CI], 3.04-11.28; P = 0.0007). Mean changes from baseline in EDS also significantly favored lifitegrast on days 42 (TE, 9.32; 95% CI, 5.44-13.20; P < 0.0001) and 14 (TE, 7.85; 95% CI, 4.33-11.37; P < 0.0001). No statistically significant differences were observed in ODS between treatment groups at days 84, 42, or 14. A greater improvement was observed in lifitegrast-treated participants at day 42 in itching (nominal P = 0.0318), foreign body sensation (nominal P = 0.0418), and eye discomfort (P = 0.0048) versus participants receiving placebo. Most treatment-emergent adverse events were mild to moderate in severity; no serious ocular adverse events were reported.
Conclusions: Lifitegrast significantly improved symptoms of eye dryness, as measured by EDS, versus placebo in participants with DED. Improvement in EDS was observed as early as day 14. Lifitegrast appeared well tolerated.

NOV03 for Signs and Symptoms of Dry Eye Disease Associated With Meibomian Gland Dysfunction: The Randomized Phase 3 MOJAVE Study
John D Sheppard, Fred Kurata, Alice T Epitropoulos, Sonja Krösser, Jason L Vittitow; MOJAVE Study Group

Purpose: To evaluate the efficacy and safety of NOV03 (perfluorohexyloctane) ophthalmic drop for the treatment of signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD).
Design: Randomized, double-masked, controlled trial.
Methods: Patients ≥18 years of age with a history of DED and signs of MGD were randomly assigned 1:1 to treatment with NOV03 or hypotonic saline (0.6%) 4 times daily for 8 weeks. The primary sign and symptom endpoints were change from baseline to week 8 in total corneal fluorescein staining (tCFS; National Eye Institute scale) and eye dryness score (0-100 visual analog scale), respectively.
Results: A total of 620 patients (NOV03, n = 311; saline, n = 309) were randomized and treated. Least-squares (LS) mean change from baseline to week 8 was statistically significantly greater for NOV03 compared with saline for both tCFS (-2.3 vs -1.1; LS mean treatment difference, -1.2 [95% confidence interval -1.7 to -0.8]; P < .001) and visual analog scale dryness score (-29.4 vs -19.2; LS mean treatment difference, -10.2 [95% CI -14.4 to -6.1]; P < .001), with statistically significant between-group differences observed as early as week 2. The incidence of ocular adverse events was similar for NOV03 (12.9%) and saline (12.3%). There were no serious adverse events and no adverse events leading to treatment discontinuation.
Conclusions: In this randomized controlled trial of patients with DED associated with MGD, NOV03 significantly reduced both signs and symptoms of DED compared with hypotonic saline control. NOV03 was well tolerated, with an adverse event profile similar to that of saline.

Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study
John D Sheppard, Gail L Torkildsen, John D Lonsdale, Francis A D'Ambrosio Jr, Eugene B McLaurin, Richard A Eiferman, Kathryn S Kennedy, Charles P Semba; OPUS-1 Study Group

Purpose: To assess the efficacy and safety of lifitegrast ophthalmic solution 5.0% compared with placebo in subjects with dry eye disease.
Design: Prospective, randomized, double-masked, placebo-controlled, parallel arm, multicenter clinical trial.
Participants: A total of 588 adult subjects with dry eye disease.

Methods: Eligible subjects were randomized 1:1 to receive topically administered lifitegrast (5.0%) or placebo (vehicle) twice daily for 84 days after a 14-day open-label placebo run-in period. After enrollment (day 0), subjects were evaluated at days 14, 42, and 84. Key objective (fluorescein and lissamine staining scores [Ora scales]) and subjective (Ocular Surface Disease Index [OSDI], 7-item visual analog scale, and ocular discomfort score [Ora scale]) measures were assessed at all visits.
Main outcome measures: The primary objective efficacy measure (sign) was mean change from baseline inferior corneal staining score (ICSS) at day 84. The co-primary subjective efficacy measure (symptom) was the mean change from baseline in the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI). Supportive measures included corneal fluorescein scores (superior, central, total region) and conjunctival lissamine scores (nasal, temporal, total region) and symptom scores at day 84.
Results: The study met the primary objective efficacy ICSS end point in demonstrating superiority of lifitegrast compared with placebo (P = 0.0007). Lifitegrast significantly reduced corneal fluorescein staining (superior, P = 0.0392; total cornea, P = 0.0148) and conjunctival lissamine staining (nasal, P = 0.0039; total conjunctiva, P = 0.0086) at day 84 versus placebo. Significant (P < 0.05) improvements in nasal and total lissamine scores were observed at day 14 and maintained through day 84. The study did not meet the co-primary subjective VR-OSDI measure (P = 0.7894). However, significant improvements were observed at day 84 in ocular discomfort (P = 0.0273) and eye dryness (P = 0.0291), the most common and severe symptoms reported at baseline in both groups. There were no unanticipated or serious ocular adverse events (AEs). The most frequent reported ocular AEs were transient intermittent instillation site symptoms (irritation, discomfort) primarily on the initial lifitegrast dose at day 0.
Conclusions: Lifitegrast ophthalmic solution 5.0% significantly reduced corneal fluorescein and conjunctival lissamine staining and improved symptoms of ocular discomfort and eye dryness compared with placebo when administered twice daily over 84 days.

NOV03 for Dry Eye Disease Associated with Meibomian Gland Dysfunction: Results of the Randomized Phase 3 GOBI Study
Joseph Tauber, Gregg J Berdy, David L Wirta, Sonja Krösser, Jason L Vittitow; GOBI Study Group

Purpose: To evaluate the efficacy and safety of NOV03 (perfluorohexyloctane) ophthalmic drop in patients with dry eye disease (DED) associated with meibomian gland dysfunction (MGD).
Design: Eight-week, phase 3, multicenter, randomized, double-masked, saline-controlled study.
Participants: Adults ≥ 18 years with a history of DED for ≥ 6 months, tear film breakup time of ≤ 5 seconds, Schirmer I test (without anesthesia) score ≥ 5 mm, MGD score ≥ 3 (0-15 scale), and total corneal fluorescein staining (tCFS) score ≥ 4 and ≤ 11 (0-15 National Eye Institute [NEI] scale).
Methods: Patients were randomized 1:1 to NOV03 or hypotonic (0.6%) saline 4 times daily.
Main outcome measures: The primary sign and symptom end points were change from baseline in tCFS and eye dryness score (0-100 visual analog scale [VAS]) at week 8. Key secondary end points were change from baseline in eye dryness score at week 2, tCFS at week 2, eye burning or stinging score (0-100 VAS) at week 8, and central corneal fluorescein staining (cCFS; 0-3 NEI scale) at week 8.
Results: Of the 599 patients randomized, 597 were treated (NOV03, n = 303; saline, n = 294). At week 8, improvement from baseline was significantly greater (P < 0.001) with NOV03 versus saline for tCFS (least square [LS] mean treatment difference, -0.97; 95% confidence interval [CI]: -1.40, -0.55) and VAS dryness score (-7.6; 95% CI: -11.8, -3.4). Improvement from baseline also significantly (P < 0.01) favored NOV03 on all key secondary end points: LS mean treatment difference (95% CI) was -4.7 (-8.2, -1.2) for VAS dryness score at week 2, -0.6 (-0.9, -0.2) for tCFS at week 2, -5.5 (-9.5, -1.6) for VAS burning or stinging score at week 8, and -0.2 (-0.4, -0.1) for cCFS at week 8. Most ocular adverse events (AEs) were mild in severity; no serious ocular AEs occurred. One patient discontinued NOV03 because of an AE (eye irritation).
Conclusions: In patients with DED associated with MGD, NOV03 demonstrated statistically significant and clinically meaningful improvements versus hypotonic saline in signs and symptoms of DED and was well tolerated.

Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study
Joseph Tauber, Paul Karpecki, Robert Latkany, Jodi Luchs, Joseph Martel, Kenneth Sall, Aparna Raychaudhuri, Valerie Smith, Charles P Semba; OPUS-2 Investigators

Purpose: Lifitegrast is an integrin antagonist that decreases T-cell-mediated inflammation associated with dry eye disease (DED). We report the results of OPUS-2, a phase III study evaluating the efficacy and safety of lifitegrast compared with placebo for the treatment of DED.
Design: A 12-week, multicenter, randomized, prospective, double-masked, placebo-controlled clinical trial.
Participants: Adults aged ≥18 years with use of artificial tears within 30 days, inferior corneal staining score ≥0.5 (0-4 scale), Schirmer tear test (without anesthesia) ≥1 and ≤10 mm, and eye dryness score ≥40 (0-100 visual analogue scale [VAS]).
Methods: Subjects were randomized 1:1 after 14-day placebo run-in to lifitegrast ophthalmic solution 5.0% or placebo twice daily for 84 days.
Main outcome measures: Co-primary efficacy end points were change, from baseline to day 84, in eye dryness score (VAS, both eyes) and inferior corneal fluorescein staining score in the designated study eye. Secondary end points were change, from baseline to day 84, in ocular discomfort score (0-4 scale) in study eye, eye discomfort score (VAS), total corneal staining score in the study eye, and nasal conjunctival lissamine green staining score (0-4 scale) in the study eye. Treatment-emergent adverse events (TEAEs) were recorded.
Results: A total of 718 subjects were randomized: placebo, n = 360; lifitegrast, n = 358 (intent-to-treat population). Lifitegrast-treated subjects experienced greater improvement in eye dryness than placebo-treated subjects (treatment effect, 12.61; 95% confidence interval [CI], 8.51-16.70; P < 0.0001). There was no between-group difference in inferior corneal staining (treatment effect, 0.03; 95% CI, -0.10 to 0.17; P = 0.6186). There was nominally significant improvement of secondary symptom end points among lifitegrast-treated subjects: ocular discomfort (nominal P = 0.0005) and eye discomfort (nominal, P < 0.0001). There were no between-group differences on secondary signs: total corneal staining and nasal lissamine staining. More lifitegrast-treated subjects (33.7%) than placebo-treated subjects (16.4%) experienced ocular TEAEs; no ocular TEAEs were serious.
Conclusions: Lifitegrast met the co-primary symptom end point (eye dryness) but not the co-primary sign end point (inferior corneal staining). Secondary end point findings were consistent with this pattern. Most ocular TEAEs were mild to moderate; there were no unexpected TEAEs. Lifitegrast warrants further consideration as a treatment for DED.

Efficacy and Safety of OC-01 (Varenicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease: The ONSET-2 Phase 3 Randomized Trial
David Wirta, Patrick Vollmer, James Paauw, Kuei-Hsun Chiu, Eugenia Henry, Kristen Striffler, Jeffrey Nau; ONSET-2 Study Group Collaborators

Purpose: To evaluate the efficacy and safety of OC-01 (varenicline solution) nasal spray for treatment of patients with dry eye disease.
Design: Randomized, multicenter, double-masked, vehicle-controlled, phase 3 study.
Participants: Adults 22 years of age or older with a diagnosis of dry eye disease, artificial tear use, Ocular Surface Disease Index score of 23 or more, and Schirmer test score (STS) of 10 mm or less. Eligibility was not restricted by eye dryness score (EDS).
Methods: Patients (N = 758) were randomized in a 1:1:1 ratio to twice-daily treatment with 50-µl intranasal spray in each nostril of OC-01 0.03 mg (n = 260), OC-01 0.06 mg (n = 246), or vehicle (control; n = 252) for 4 weeks (ClinicalTrials.gov identifier, NCT04036292).
Main outcome measures: The primary efficacy end point was the percentage of patients achieving a 10-mm improvement or more in STS at week 4. Secondary end points included change from baseline to week 4 in STS and EDS in a controlled adverse environment (CAE) chamber and in the clinic. Treatment-emergent adverse events (TEAEs) were assessed.

Results: A statistically significantly greater percentage of patients achieved the primary end point in both OC-01 treatment groups compared with the vehicle group (OC-01 0.03 mg, 47.3%; OC-01 0.06 mg, 49.2%; vehicle, 27.8%; P < 0.0001 for both doses). Change from baseline in STS at week 4 was statistically significantly greater for patients receiving OC-01 than vehicle (P < 0.0001 for both doses). Eye dryness score assessed at week 4 improved with OC-01 treatment compared with vehicle, although the difference was not significant for EDS measured in the CAE chamber and showed (nominal) significance in the clinic. Overall, 86.5% of patients (654/756) reported at least 1 TEAE during the treatment period; most were mild, nonocular (sneezing, cough, throat irritation, and instillation site irritation) and were reported by fewer patients in the vehicle group than in the OC-01 treatment groups (OC-01 0.03 mg, 97.3%; OC-01 0.06 mg, 99.2%; vehicle, 57%).
Conclusions: OC-01 nasal spray was well tolerated and showed a clinically meaningful effect on signs and symptoms of dry eye disease.
Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 26, 2025
Search Strategy:

#	Searches	Results
1	Loteprednol.mp. or Loteprednol Etabonate/	285
2	Lifitegrast.mp.	132
3	varenicline.mp. or Varenicline/	2488
4	perfluorohexyloctane.mp.	109
5	cyclosporine solution.mp.	18
6	1 or 2 or 3 or 4 or 5	3015
7	limit 6 to (english language and humans and yr="2015 -Current")	1130
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	125

Appendix 5: Key Inclusion Criteria

Population	Patients with dry eye disease
Intervention	Prescription drugs for the treatment of dry eye
Comparator	Vehicle or active comparator
Outcomes	Symptomatic improvement of dry eye disease
Setting	Outpatient

Targeted Drugs for Dry Eye Disease

Goal(s):

- Allow for coverage of approved prescription therapies for dry eye disease and vernal keratoconjunctivitis when they are funded in 2027.
- Allow case-by-case review for members covered under the EPSDT program.
- Over-the-counter artificial tears do not require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred prescription drugs for dry eye and vernal keratoconjunctivitis

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a prescription dry eye product or product for vernal keratoconjunctivitis?	**Yes**: Go to Renewal Criteria below	**No:** Go to #4
4. Is the request for a patient with dry eye?	**Yes:** Go to #5	**No:** Go to #10
5. Is the diagnosis funded by OHP?	**Yes:** Go to #8	**No:** Go to #6

Approval Criteria		
6. Does the patient have dry eye resulting in blurred vision or other visual impairment as a result of a chronic eye condition or medical condition (e.g., Sjögren's syndrome, lupus, cataracts, etc.)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; If eligible for EPSDT review go to #7
7. If the member is eligible for EPSDT review, 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 #8	**No:** Pass to RPh. Deny; medical necessity
8. Has the patient tried artificial tears/ocular lubricants for at least 4 weeks without improvement in symptoms?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of artificial tears
9. Is there documentation of baseline dry eye symptoms based on the Ocular Surface Disease Index (OSDI) or visual analog score (VAS)?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; recommend baseline assessment of dry eye symptoms
10. Does the patient have a diagnosis vernal keratoconjunctivitis?	**Yes:** Go to #11	**No:** Pass to RPh. Deny
11. Is the diagnosis funded by OHP?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; If eligible for EPSDT review go to #12.
12. If the member is eligible for EPSDT review, 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 #13	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
13. Is the medication being prescribed by an optometrist or ophthalmologist?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; recommend referral to optometrist or ophthalmologist.
14. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for a maximum of 12 months.

Renewal Criteria		
1. Is the request for a renewal of a previously approved dry eye disease medication?	**Yes**: Go to #2	**No:** Go to Approval Criteria above
2. Is the request for a patient with dry eye?	**Yes**: Go to #3	**No**: Go to #4
3. Is there documentation of improvement from baseline dry eye symptom scores (e.g., OSDI change of 4.5 units or more or VAS reduction of 30% or more) as assessed by the prescribing provider?	**Yes**: Approve for a maximum of 12 months	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for a patient with vernal keratoconjunctivitis and the provider reports improvement in symptoms (this is a rare disease without validated tools for symptom assessment)?	**Yes**: Approve for a maximum of 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/25 (KS)
Implementation: TBD

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Prior Authorization Update: Esketamine Monotherapy

Plain Language Summary:

- Esketamine is a medicine that people take to improve symptoms of depression (such as sadness, low mood, loss of interest) when at least 2 other medicines have not improved these symptoms. It is a spray that is inhaled in the nose and must be given during a clinic visit. After taking esketamine, providers monitor for side effects of the medicine for at least 2 hours in the clinic.
- Esketamine has mostly been studied in combination with other antidepressant medicines. However, a recent study showed that esketamine improved depression symptoms when it is prescribed to people who were not taking other antidepressant medicines.
- The Oregon Health Authority currently requires providers to document that someone has tried at least 2 other antidepressants and are currently taking another antidepressant before they will pay for esketamine.
- We recommend that the Oregon Health Authority be allowed to pay for esketamine for people who are not currently taking other antidepressants but continue to require documentation that that people have previously tried at least 2 other antidepressants.

Conclusions:

- Esketamine recently received approval from the Food and Drug Administration (FDA) for monotherapy in people with treatment-resistant depression. The randomized controlled trial (RCT) used for FDA approval enrolled people with moderate to severe depression symptoms (with an average Montgomery-Åsberg Depression Rating Scale [MADRS] of 37 at baseline).[1] The RCT is currently unpublished and risk of bias cannot be fully assessed.
- Depression symptoms (evaluated by MADRS) improved an average of -11.4 and -13.0 points from baseline for esketamine 56 mg and 84 mg compared to -6.3 points with placebo (least square mean difference [LSMD] -5.1; 95 % CI -7.9 to -2.3 and LSMD -6.8; 95% CI -9.5 to -4.1).[1] The MADRS score is a 10 item scale with a total score from 0 to 60 points with larger scores indicating more severe depression. In clinical trials, scores of less than 10 or 12 have been used to indicate remission, improvement of more than 50% from baseline indicate response to treatment, and improvements as small as 2 points may be clinically relevant.[2,3]

Recommendations:

- Update PA criteria to permit monotherapy with esketamine in people with treatment-resistant depression.

Background

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 for an adequate dose and duration.[4] It is not uncommon for first-line treatments to fail to manage depressive symptoms. It is estimated that for major depressive disorder, about one-thirds of patients have an inadequate response to initial therapy and one-third of patients have inadequate response to 2 therapies.[4] There is little evidence to guide next steps in therapy after an initial treatment failure.[4] Common treatment options used in clinical practice include a

trial of a different first-line antidepressant from the same class, use of an antidepressant from a different class, and augmentation of current therapy with a second agent. The Oregon Mental Health Clinical Advisory Group evaluated evidence of medications for treatment-resistant depression in December 2021. The following therapies are listed as evidence-supported options to augment antidepressant therapy for people with treatment-resistant depression:[5]

- Antidepressants: bupropion, mirtazapine
- Antipsychotics such as aripiprazole, brexpiprazole, quetiapine, olanzapine, risperidone, ziprasidone, and cariprazine.
- Esketamine
- Lithium
- Modafinil

This review evaluates new evidence for esketamine when used as monotherapy for treatment-resistant depression. Evidence related to the efficacy and safety of medications for treatment-resistant depression have previously been reviewed by the P&T committee. Evidence of benefit for esketamine is mixed depending on the population and outcome studied. Initial approval was based on 4 placebo-controlled phase 3 RCTs in adults with moderate to severe major depressive disorder (MDD) who had failed to have benefit with at least 2 alternative antidepressants for the current depressive episode. Two studies demonstrated improvement in depressive symptoms compared to placebo when esketamine was added to an oral antidepressant.[6,7] Two studies did not meet their primary endpoint for improvement of depression symtpoms,[7,8] and esketamine did not improve depression symptoms compared to placebo in a RCT of older adults (≥ 65 years of age) with MDD.[8] Data was supported by an open-label, non-comparative study evaluating esketamine use for up to 1 year.[9] In 2 additional RCTs, esketamine improved depression symptoms but not symptoms of suicide in hospitalized patients with MDD at high risk for suicide.[10,11] One RCT directly compared esketamine to quetiapine in adults with treatment-resistant depression (on background therapy with selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]).[12] Esketamine improved remission rates compared to quetiapine extended release (ER) at 8 weeks with an absolute risk reduction (ARR) of 9.5% and number needed to treat (NNT) of 11.[12]

New Indication:

In January 2025, esketamine received FDA-approval as monotherapy for treatment-resistant depression based on results of one placebo-controlled RCT (NCT04599855).[1,13] Efficacy and safety data from this trial are summarized in **Tables 1 and 2**. After 28 days, esketamine improved depression symptoms (evaluated with the MADRS) compared to placebo. The MADRS score is a 10 item scale with a total score from 0 to 60 points with larger scores indicating more severe depression. In clinical trials, scores of less than 10 or 12 indicate remission, improvement of more than 50% from baseline indicate response to treatment, and worsening of scores to 22 or more define relapse.[2] However, the scale is also non-linear, and improvements of 2 points have been documented as clinically relevant.[3] People enrolled in the study had an average baseline MADRS score of 37 indicating moderate to severe depression symptoms. The average improvement from baseline was -11.4 points and -13.0 points for esketamine 56 mg and 84 mg compared to -6.3 points with placebo (LSMD -5.1; 95 % CI -7.9 to -2.3 and LSMD -6.8; 95% CI -9.5 to -4.1).[1] As this trial is currently unpublished, the risk of bias and applicability cannot be fully assessed. About 20% of randomized patients were not included in final analysis and details about included patients and how missing data was handled are not currently available. The most common adverse events associated with esketamine were dissociation, nausea/vomiting, dizziness, headache, and anxiety. These events may have contributed to unblinding of treatment groups and increased risk for performance or detection bias.

Table 1. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.NCT04599855[1,13] DB, PC, MC, RCT	1. Esketamine intranasal twice weekly 56 mg 2. Esketamine intranasal twice weekly 84 mg 3. Placebo 1:1:2 Duration: 4 weeks Participants could enroll in an open label, extension period up to 16 weeks	Demographics: - Median age 46 years - 61% female - Non-Hispanic: 89.9% - Race 87% White 7% Black - Average MADRS: 37 Key Inclusion Criteria: - Adults ≥ 18 years of age - MDD without psychotic features - Symptom duration ≥ 2 years - Treatment-resistant depression (i.e., ≤25% improvement to ≥2 antidepressants of adequate dose and duration in the current depressive episode) - Inventory of Depressive Symptomology-Clinician score ≥ 34 (30 items) - Medically stable (e.g, no abnormal vital signs, labs, electrocardiogram, physical or medical history of clinical significance) - Stable dose of thyroid hormone or normal TSH/free T4) Key Exclusion Criteria: - Prior nonresponse to ≥ 7 treatments of electroconvulsive therapy in the current depressive episode - Vagal nerve stimulation or deep brain stimulation in the current depressive episode - History of seizures	ITT: 1. 106 2. 121 3. 250 PP: 1. 86 2. 95 3. 197 Attrition: 1. 5 2. 14 3. 12 Open label enrollment 1. 99 2. 106 3. 237	Primary Endpoint: Change from baseline in MADRS at 28 days (PP) 1. LSM -11.4 (SE 1.2) 2. LSM -13.0 (SE 1.2) 3. LSM -6.3 (SE 0.8) 1 vs. 3: -5.1 (95% CI -7.9 to -2.3) 2 vs. 3: -6.8 (95% CI -9.5 to -4.1) Secondary Endpoint: Change from baseline in MADRS at 2 days 1. LSM -13.9 (SD 10.15) 2. LSM -13.0 (SD 9.68) 3. LSM -9.7 (SD 10.27) 1 vs. 3: -3.8 (95% CI -6.29 to -1.22) 2 vs. 3: -3.4 (95% CI -5.89 to -1.00)	NA	Discontinuation due to AE 1. 1 (1%) 2. 5 (4%) 3. 2 (1%) Serious AE: 1. 1 (1%) 2. 2 (1%) 3. 3 (1%) Non-serious AE: 1. 69 (66%) 2. 80 (66%) 3. 73 (29%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: No details available. Study is unpublished and risk of bias cannot be fully assessed. Performance Bias: Matched placebo. Potential for unblinding due to adverse events. The most common adverse events included nausea, dizziness, headache, and disassociation. Detection Bias: Matched placebo. Potential for unblinding due to adverse events. Attrition Bias: Unclear how missing data was handled. Primary analysis was not based on the ITT population. Reporting Bias: Study is unpublished and risk of bias cannot be fully assessed. Other Bias: Study is unpublished and risk of bias cannot be fully assessed. **Applicability**: Patient: Included patients had treatment-resistant MDD for the current depressive episode based on ≤ 25% improvement after 2 alternative antidepressants. Average baseline MADRS score is indicative of moderate-severe depression. Intervention: Dosing of esketamine was consistent with FDA-labeled induction dose for treatment-resistant depression. During the open-label continuation study period, the dose was reduced to one does every week or every other week. Comparator: Placebo Outcomes: MADRS is an established outcome assessment used in clinical trials of depression. Setting: 54 locations in the United States

Abbreviations: AE = adverse events; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; ITT = intention to treat; LSM = least square mean; MADRS = Montgomery-Åsberg Depression Rating Scale; MC = multicenter; MDD = major depressive disorder; NA = not applicable; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TSH = thyroid stimulating hormone

Table 2. Common adverse events occurring in >5% of people with treatment-resistant depression and at a greater rate with esketamine monotherapy compared to placebo

	Esketamine (56 and 84 mg) (n=226)	Placebo (n=250)
Dissociation*	28%	4%
Nausea	25%	8%
Dizziness	22%	7%
Headache	19%	9%
Anxiety	10%	4%
Vomiting	7%	<1%
Feeling drunk	7%	<1%
Lethargy	7%	5%
Sedation	6%	2%

*includes dissociation, depersonalization/derealization disorder, derealization, diplopia, photophobia, vision blurred, feeling hot, paresthesia, and tinnitus

Esketamine labeling includes a box warning for sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behaviors.[1] The Risk Evaluation and Mitigation Strategies (REMS) program is intended to monitor and manage risk for these adverse events. Other warnings and precautions include risk cognitive impairment, increased blood pressure, impaired ability to drive or operate machinery, ulcerative or interstitial cystitis, and embryo-fetal toxicity.[1]

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Esketamine (Spravato)

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

Length of Authorization:
- Up to 6 months

Requires PA:
- Esketamine (pharmacy and physician administered claims).

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~6. Is the patient currently on a therapeutic dose of an oral antidepressant (Average minimum effective dose for antidepressants can be found at: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf)~~	~~**Yes:** Go to #7~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Esketamine is indicated for use with an oral antidepressant.~~
6. ~~Does the patient have~~Is there prescriber attestation or documentation of treatment-resistant depression ~~(failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)~~ based on all the following criteria: a. Diagnosis of unipolar major depressive disorder b. Patient has tried at least 2 different antidepressants in which: i. There has been inadequate response after at least 6 weeks of treatment at an average minimum therapeutic dose or greater; or ii. The patient has not been able to continue treatment for at least 6 weeks due to intolerable side effects. Minimum therapeutic doses can be found here: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf	**Yes:** Go to #~~10~~9	**No:** Go to #~~7~~8
7. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**Yes:** Go to #~~8~~9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.

Approval Criteria		
8. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #9~~10~~	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 28 days for induction (either 56 mg and/or 84 mg for titration) not to exceed 24 units total to be covered within the approved time window. The approved time window typically spans 60 days to accommodate scheduling visits.

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~~3~~
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days) ~~Go to #3~~	**No**: Pass to RPh. Deny; medical appropriateness.
~~Has the patient been adherent to oral antidepressant therapy?~~	~~**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~

Renewal Criteria		
3. 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 24 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 6/24(KS);2/24; 12/23 (KS); 2/23, 10/21; 2/21; 7/19
Implementation:7/1/24; 1/1/22; 3/1/21; 8/19/19

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Drug Use Evaluation: Esketamine

Plain Language Summary:

- Esketamine is a medicine that people take to improve symptoms of depression (such as sadness, low mood, or loss of interest) when at least 2 other medicines have not improved these symptoms. It is a spray that is inhaled in the nose and must be given during a clinic visit. After taking esketamine, providers monitor for side effects of the medicine for at least 2 hours in the clinic.
- The Oregon Health Authority currently requires providers to document that someone has tried at least 2 other antidepressants and are currently taking another antidepressant before they will pay for esketamine. In an evaluation of claims data, most members did not appear to have recently tried 2 antidepressants for a long enough time or at a dose that might help symptoms based on claims data even though the provider documented trial of at least 2 antidepressants in their chart notes.
- About 73% of people who started esketamine had paid claims beyond a 45-day period indicating that these members likely had documented benefit from therapy.
- We recommend that the Oregon Health Authority be allowed to pay for esketamine for people who are not currently taking other antidepressants but continue to require documentation that that people have previously tried at least 2 other antidepressants.

Research Questions:

Population 1: Initial therapy

1. For people prescribed esketamine, what proportion of people have a diagnosis of treatment-resistant depression that can be identified based on claims data (e.g., two 6-week trials of an antidepressant with adequate dose)?
2. What provider specialties initiate esketamine in Oregon Medicaid patients?
3. For people with an initial denied claim for esketamine, how many had a subsequent paid claim in the following 3 months?

Population 2: Continuation of therapy

4. For people who start esketamine, how many continue treatment beyond the induction period?
5. For member with ≤ 45 days of treatment, how many had a PA request submitted for continued therapy?
6. What were the documented reasons for lack of continued therapy?

Conclusions:

- In an analysis of Oregon Medicaid utilization of esketamine, about 56% of members prescribed esketamine (n=129) had an initial denied claim. In members with an initial denial, 74% had a subsequent paid claim in the following 3 months indicating that treatment-resistant depression or acute suicidal ideation was documented in the chart notes upon submission of a prior authorization (PA) request.

Author: Sarah Servid, PharmD June 2025

- In people prescribed esketamine, 61% of members had claims for at least 2 antidepressants in the 12 months before starting esketamine. However, only 29% of patients were classified as having treatment-resistant depression based on available claims data. Treatment-resistant depression was defined as at least 6-weeks of 2 or more different antidepressants with adequate dose in the 12 months prior to initiation of esketamine. We did not distinguish between antidepressants given separately, at different times and antidepressants that were administered concomitantly.
- Esketamine was prescribed most commonly by psychiatrists (34%) and psychiatric mental health nurse practitioners (48%) who were practicing in urban areas of Oregon (92%).
- Of 226 patients who started esketamine treatment, 73% of members had paid claims beyond a 45-day period indicating that they stayed on treatment beyond the 1 month induction period.
- About 18% of people (n=40) had paid claims for less than 45 days (mean 18 days) and did not have any subsequent denied claims. This may indicate that esketamine was voluntarily discontinued for these members.
- About 10% of members (n=22) had less than 45 days of therapy and had a subsequent denied claim for esketamine indicating PA was required. Of these members, 59% (n=13) had a subsequent approved PA, 18% (n=4) had a denied PA, and 23% of members did not have a PA request for ongoing therapy.
- All 4 members who had a denied PA for ongoing therapy documented no improvement in depression symptoms. Denials were also based on off-label maintenance doses (twice weekly dosing instead of every week or every other week) and lack of adherence to concomitant oral antidepressant therapy.

Mental Health Clinical Advisory Group Recommendations

The Mental Health Clinical Advisory Group discussed what level of documentation should be required to verify treatment-resistant depression. After consideration of evidence and Medicaid utilization of esketamine, the lived experiences of people with depression, other guideline recommendations, and overall treatment success rate after trial of 2 other antidepressants, the Mental Health Clinical Advisory Group suggested incorporating intolerance to oral antidepressants and provider attestation of previous antidepressant trials into the prior authorization criteria.

Recommendations:

- Update current PA criteria to clarify documentation required to support diagnosis of treatment-resistant depression.

Background

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 for an adequate dose and duration.[1] It is not uncommon for first-line treatments to fail to manage depressive symptoms. It is estimated that for major depressive disorder, about one-thirds of patients have an inadequate response to initial therapy and one-third of patients have inadequate response to 2 therapies.[1] There is little evidence to guide next steps in therapy after an initial treatment failure.[1] Common treatment options used in clinical practice include a trial of a different first-line antidepressant from the same class, use of an antidepressant from a different class, and augmentation of current therapy with a second agent. The Oregon Mental Health Clinical Advisory Group evaluated evidence of medications for treatment-resistant depression in December 2021. The following therapies are listed as evidence-supported options to augment antidepressant therapy for people with treatment-resistant depression:[2]

- Antidepressants: bupropion, mirtazapine
- Antipsychotics such as aripiprazole, brexpiprazole, quetiapine, olanzapine, risperidone, ziprasidone, and cariprazine.
- Esketamine
- Lithium
- Modafinil

This review evaluates data on esketamine utilization in the Oregon Medicaid population. Esketamine was initially approved for treatment-resistant major depressive disorder in March 2019 and the Oregon Fee-for-service Medicaid program began paying for pharmacy claims in July 2019. Evidence for esketamine has been previously reviewed by the P&T committee.

When billed through the pharmacy benefit, esketamine is carved-out of Coordinated Care Organization (CCO) budgets and the fee-for-service (FFS) program is the primary payer. If billed through the medical benefit, esketamine payment is the responsibility of the CCO for CCO-enrolled members. This evaluation will focus on claims paid through the pharmacy benefit. Even when paid through the pharmacy benefit, esketamine is required to be administered in a healthcare setting and requires at least 2 hours of monitoring after administration for adverse effects.[3] Treatment is initiated at 2 doses per week for the first 4 weeks, then reduced to a maintenance dose of 1 dose weekly or every 2 weeks.[3]

In the fee-for-service program, PA is required for esketamine initiation and for continuation beyond 1 month. Current clinical PA criteria require documentation of treatment-resistant depression, referral for non-pharmacologic treatment, and use in conjunction with an oral antidepressant. Renewal criteria require documentation of symptom improvement and adherence to oral antidepressant treatment (See **Appendix 2**). Dose is limited based on FDA-approved induction and maintenance doses.

The goals of this analysis are to evaluate:

1) whether diagnoses of treatment-resistant depression can be identified based on claims in people who request treatment for esketamine and
2) how many people continue therapy beyond the induction period (i.e., 1st month of treatment)

Methods:

Population 1: Initial therapy

The index event (IE) was defined as the first paid or denied FFS pharmacy claim for esketamine. If members had a paid and denied claim on the same date, then the IE was classified as paid.

Time periods for review:

- The claims evaluation window was from 7/1/2019 to 12/31/2024
- The baseline period was defined as the 12 months before the IE (exclusive of the IE)
- The follow-up period was defined as the 3 months following the IE (inclusive of the IE)

Inclusion criteria:

- At least one paid or denied FFS pharmacy claim for esketamine (defined based on HICL Sequence number [HSN]: 041003) during the claim evaluation window. Denied claims were included if they were associated with an error code indicating PA was required but not associated with claims indicating errors in billing (**Appendix 1; Table A1**).

Exclusion criteria:

- Patients with non-Medicaid primary insurance coverage (TPL) effective during the baseline or follow-up period.
- Less than 75% of days Medicaid eligibility during the baseline or follow-up period.
- Claims for benefit plans indicating Medicare or limited rug benefit during the baseline or follow-up period (**Table 1**). Claims data for these members may be incomplete.

Table 1. Members excluded from the initial treatment population

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

Definitions and Outcomes:

- Oral antidepressant utilization during the baseline period was categorized based on mechanism and dose. Treatment-resistant depression was defined as claims for 2 distinct oral antidepressants (based on HSN) prescribed for a duration of at least 6 consecutive weeks with no more than a 2 week gap in therapy and with a minimum daily dose in **Appendix 1; Table A3**. We did not distinguish between antidepressants given separately, at different times and antidepressants that were administered concomitantly.
- Provider type was defined based on primary taxonomy for common mental health providers (**Appendix 1, Table A4**) and location (county). Location was categorized as urban, rural or frontier according to the 2024 Oregon Office of Rural Health data (**Appendix 1; Table A5**).
- For members with an initial denied claim, paid claims for esketamine were identified in the follow-up period.

<u>Population 2: Continuation of therapy</u>

The index event (IE) was defined as the first paid FFS pharmacy claim for esketamine.

Time periods for review:

- The claims evaluation window was from 7/1/2019 to 12/31/2024
- The follow-up period was defined as the 3 months following the IE

Inclusion criteria:

- At least one paid FFS pharmacy claim for esketamine (defined based on HSN: 041003) during the claim evaluation window.

Exclusion criteria:

- Patients with non-Medicaid primary insurance coverage (TPL) effective during the follow up period.
- Less than 75% of days OHP eligibility during the follow-up period.
- Claims for benefit plans indicating Medicare or limited rug benefit during the follow up period (**Table 2**). Claims data for these members may be incomplete.

Table 2. Members excluded from the continuation of therapy population

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

Definitions and Outcomes:

- Duration of therapy (defined as time from first to last claim in the follow-up period)
- Duration of therapy was categorized based on 2 variables: 1) duration of more or less than 45 days and 2) presence or absence of denied claims in the follow-up period. If scheduled exactly as described in clinical trials the induction period will last 28 days. In reality, dispensing and scheduling visits may lengthen the induction period so a 45 day period was evaluated. Presence of denied claims in the follow-up period may indicate delays related to prior authorization requirements for ongoing therapy.
- PA submissions in the follow up period (exclusive of the IE date) was also evaluated for members with ≤ 45 days of therapy. A manual review of denial letters was performed to identify reasons for denied PAs.

Results:

Population 1: Initial therapy

Of 306 members with pharmacy claims for esketamine from 7/1/2019 to 12/31/2024, 229 people (75% of the population) had potentially complete claims data in the 12 months before their first claim (**Table 3**). Included members were predominately female (68%) and enrolled in CCOs (99%). Most patients had a diagnosis of major depressive disorder in the 12 months before their first claim for esketamine (93%) and comorbid mental health conditions were common (**Table 4**).

Table 3. Attrition for initial treatment population

	Paid		Denied		Total	
Exclusion Criteria	#	%	#	%	#	%
Total patients identified	132		174		306	
- TPL in baseline period	113	85.6%	155	89.1%	268	87.6%
- Medicare or limited drug benefit in baseline period	112	84.8%	153	87.9%	265	86.6%
- Less than 75% of days Medicaid eligibility during the baseline period AND follow up periods	100	75.8%	129	74.1%	229	74.8%
Remaining patients	100	75.8%	129	74.1%	229	74.8%

Table 4. Baseline demographics

	Paid		Denied		Total	
	100	%	129	%	229	%
Age						
18-64	100	100.0%	129	100.0%	229	100.0%
Sex						
Male	30	30.0%	43	33.3%	73	31.9%
Female	70	70.0%	86	66.7%	156	68.1%
CCO enrollment at the time of the IE						
FFS	2	2.0%	1	0.8%	3	1.3%
CCO	98	98.0%	128	99.2%	226	98.7%
Diagnoses in the baseline period						
Major Depressive Disorder	97	97.0%	115	89.1%	212	92.6%
Anxiety	80	80.0%	98	76.0%	178	77.7%
Post-Traumatic Stress Disorder	63	63.0%	76	58.9%	139	60.7%
Substance use disorders	38	38.0%	55	42.6%	93	40.6%
Sleep disorders	40	40.0%	44	34.1%	84	36.7%
Suicidal ideation/attempt	23	23.0%	27	20.9%	50	21.8%
Bipolar	16	16.0%	23	17.8%	39	17.0%
Schizophrenia	1	1.0%	2	1.6%	3	1.3%

Upon analysis of oral antidepressants prescribed in the 12 months before starting esketamine, 47% were prescribed a SSRI, 38% were prescribed a SNRI, and 62% of people were prescribed an atypical antidepressant (such as mirtazapine, bupropion, trazodone, vilazodone, or vortioxetine). Tricyclic antidepressants were prescribed for less than 8% of patients. Overall, 61% of members had claims for at least 2 antidepressants in the 12 months before starting esketamine (**Table 5**). However, when evaluating the number of people prescribed 2 or more oral antidepressants for at least 6 weeks at a minimum therapeutic dose, only 29% of patients were classified as having treatment-resistant depression (**Table 6**).

Prior authorization (PA) is required before starting esketamine, and about 56% of patients (n=129) had an initial denied claim for esketamine. In members with an initial denied claim, 74% had a subsequent paid claim in the following 3 months indicating that treatment-resistant depression or acute suicidal ideation was documented in the chart notes upon submission of a PA. Subsequent paid claims were slightly more common in people who had claims for at least 2 adequate trials of antidepressants in the past year (82%) compared to people who did not have claims history indicating treatment-resistant depression (71%; **Table 7**).

Table 5. Baseline antidepressants

	Paid		Denied		Total	
	100	%	129	%	229	%
Oral antidepressant in baseline period						
Other	63	63.0%	78	60.5%	141	61.6%
SSRI	43	43.0%	64	49.6%	107	46.7%
SNRI	40	40.0%	48	37.2%	88	38.4%
TCA	7	7.0%	13	10.1%	20	8.7%
MAOI	0	0.0%	1	0.8%	1	0.4%
Number of unique antidepressants (by HSN) in the baseline period, excluding IE						
0	3	3.0%	13	10.1%	16	7.0%
1	33	33.0%	40	31.0%	73	31.9%
2	35	35.0%	41	31.8%	76	33.2%
3	19	19.0%	17	13.2%	36	15.7%
4	6	6.0%	12	9.3%	18	7.9%
5	2	2.0%	4	3.1%	6	2.6%
6	2	2.0%	2	1.6%	4	1.7%

Table 6. Treatment-resistant depression based on claims (2 adequate antidepressant trials)

	Paid		Denied		Total	
	100	%	129	%	229	%
Treatment-resistant depression	33	33.0%	33	25.6%	66	28.8%
No treatment-resistant depression	67	67.0%	96	74.4%	163	71.2%

Table 7. Follow-up in members with a denied IE

	With treatment-resistant depression		No treatment-resistant depression		Total	
	33	%	96	%	129	%
Subsequent paid claim for esketamine in following 3 months	27	81.8%	68	70.8%	95	73.6%
No subsequent paid claim for esketamine in following 3 months	6	18.2%	28	29.2%	34	26.3%

Esketamine was prescribed most commonly by psychiatrists (34%) and psychiatric mental health nurse practitioners (48%) and less frequently by general practitioners (**Table 8**). Most of prescribing providers practice in urban locations (92%) and the majority of prescriptions are written by providers in the Portland, Eugene, or Medford areas (**Table 9**).

Table 8. Provider taxonomy on the IE

	Paid		Denied		Total	
	100	%	129	%	229	%
Psychiatrist	38	38.0%	41	31.8%	79	34.5%
Psychiatric mental health nurse practitioner (PMHNP)	38	38.0%	72	55.8%	110	48.0%
Other prescriber taxonomies						
PHYSICIAN-INTERNAL MEDICINE	14	14.0%	8	6.2%	22	9.6%
NURSE PRACTITIONER - FAMILY	10	10.0%	3	2.3%	13	5.7%
NATUROPATH	0	0.0%	3	2.3%	3	1.3%
NURSE PRACTITIONER	0	0.0%	1	0.8%	1	0.4%
PHYSICIAN-FAMILY MEDICINE	0	0.0%	1	0.8%	1	0.4%

Table 9. Prescribing provider location

	Paid		Denied		Total	
	100	%	129	%	229	%
By Oregon Category						
Urban	93	93.0%	118	91.5%	211	92.1%
Unknown	6	6.0%	5	3.9%	11	4.8%
Rural	1	1.0%	6	4.7%	7	3.1%
Frontier	0	0.0%	0	0.0%	0	0.0%
By County						
Multnomah County, OR	37	37.0%	41	31.8%	78	34.1%
Washington County, OR	23	23.0%	21	16.3%	44	19.2%
Clackamas County, OR	23	23.0%	11	8.5%	34	14.8%
Lane County, OR	5	5.0%	29	22.5%	34	14.8%
Jackson County, OR	2	2.0%	19	14.7%	21	9.2%
Clark County, WA	4	4.0%	2	1.6%	6	2.6%
Marion County, OR	2	2.0%	0	0.0%	2	0.9%
Douglas County, OR	0	0.0%	2	1.6%	2	0.9%
Deschutes County, OR	1	1.0%	0	0.0%	1	0.4%
Douglas County, MN	1	1.0%	0	0.0%	1	0.4%

Josephine County, OR	1	1.0%	0	0.0%	1	0.4%
Boulder County, CO	1	1.0%	0	0.0%	1	0.4%
Polk County, OR	0	0.0%	1	0.8%	1	0.4%
Maricopa County, AZ	0	0.0%	1	0.8%	1	0.4%
Miami-Dade County, FL	0	0.0%	1	0.8%	1	0.4%
San Diego County, CA	0	0.0%	1	0.8%	1	0.4%

Population 2: Continuation of therapy

Duration of therapy was evaluated for members starting treatment with esketamine. Of 264 members with a paid claim for esketamine from 7/1/2019 to 12/31/2024, 226 members (85%) had potentially complete claims data in the 3 months following their first claim (**Table 10**).

About 73% of members had claims that spanned more than a 45 day period in the 3 months following their first claim (**Table 11**). The average time between the first and last claim in this population was 87 days. About 18% of people (n=40) had claims for less than 45 days and did not have any denied claims. This may indicate discontinuation of therapy, either voluntarily or based on individual patient circumstances. Of these 40 members, most did not request PA for ongoing therapy (63%; **Table 12**), with an average duration of 18 days between the first and last claim for this population (**Table 11**). About 10% of members (n=22) had less than 45 days of therapy and a subsequent denied claim for esketamine indicating PA was required. In people with only short-term therapy and a subsequent denied claim, 59% (n=13) had a PA request approved, 18% (n=4) had a PA request denied, and 23% did not submit a PA request for ongoing therapy (**Table 12**). Denials for ongoing therapy were based on lack of improved symptoms, incorrect maintenance doses (twice weekly doses instead of every week or every other week), and lack of adherence to concomitant oral antidepressant therapy.

Table 10. Attrition

	Paid	
Exclusion Criteria	#	%
Total patients identified	264	
- TPL in follow-up period	256	97.0%
- Medicare or limited drug benefit in follow-up period	253	95.8%
- Less than 75% of days Medicaid eligibility during the follow-up period	226	85.6%
Remaining patients	226	85.6%

Table 11. Duration of therapy and treatment discontinuation

	Members		Duration (days)			
	226	%	Mean	(min/max)	Median	(Interquartile Range)
Continuation beyond induction period (members with >45 days of treatment)	164	72.6%	87	(47-109)	91	(84-96)
Short-term treatment (≤ 45 days) and no denied claims indicating PA was required	40	17.7%	18	(1-42)	18	(8-27)
Short-term treatment (≤ 45 days) and denied claims indicating PA was required	22	9.7%	26	(3-38)	28	(22-32)

Table 12. PA status for members with ≤ 45 days of treatment

	With Denied Claims		Without Denied Claims	
	22	%	40	%
PA Request Approved	13	59.1%	14	35.0%
PA Request Denied	4	18.2%	1	2.5%
Not taking an oral antidepressant	2	9.1%	1	0.0%
Request for induction dosing during maintenance phase	2	9.1%	1	0.0%
No documentation of symptom improvement	4	18.2%	1	2.5%
No PA submitted	5	22.7%	25	62.5%

Discussion and Limitations:

This analysis identified 306 Oregon Medicaid members with paid or denied pharmacy claims for esketamine since it was approved by the FDA in 2019 for treatment-resistant depression. While this represents a small proportion of Oregon Medicaid members with claims for esketamine, it is a substantial cost for the FFS pharmacy program. In the first quarter of 2025, esketamine accounted for 2.2% of all FFS pharmacy costs (over $1.1 million paid to pharmacies) for only 136 members. Access is primarily limited to urban areas of the state likely because of in-clinic administration and monitoring requirements. While esketamine can be billed through the medical or pharmacy benefit, this analysis focused on only pharmacy claims. The proportion of people with medical billing for esketamine was not evaluated.

While many people starting esketamine had recent claims for an oral antidepressant, only 29% of members had recent claims for at least 2 adequately dosed trials of oral antidepressants in the past 12 months. We did not quantify the proportion of members who had sequential trials of antidepressants, and some of these members prescribed 2 or more antidepressants may have been receiving them at the same time (as combination therapy). However, many members with an initial denied claim had subsequent paid claims for esketamine which indicates that treatment-resistant depression or acute suicidal ideation was documented in chart notes. The discrepancy between what is documented in the provider chart notes and the lack of recent claims data raises questions about what level of documentation is needed to confirm diagnosis of treatment-resistant depression. There are a variety of reasons for why people may not have recent claims for antidepressants. Side effects to oral antidepressants may limit the dose or duration that people are willing to take them. Because an adequate trial of oral antidepressants is typically 6-8 weeks, lack of perceived benefit in the first few weeks of therapy may also lead to discontinuation of therapy before the full therapeutic effect can be observed. Use of sub-therapeutic doses may also contribute to lack of perceived benefit and lead to documentation of treatment failure. If people have previously tried an oral antidepressant and did not have benefit or experienced side effects to therapy, they may be unwilling to try a similar medication for their current symptoms. While we excluded members with potentially incomplete claims from this analysis, gaps in claims data may also lead to under-representation of a member experience with oral antidepressants.

This analysis used the time between the first and last paid claim in the follow up period to evaluate duration of therapy for esketamine. This method was chosen because of the variability in the days' supply submitted on pharmacy claims for esketamine. However, this definition does not evaluate the proportion of

covered days, adherence to a therapy, or number of esketamine doses prescribed during the follow-up period. Some members with intermittent utilization of esketamine in the follow-up period may be incorrectly categorized as having ongoing treatment if they stop and restart therapy. The current analysis is also limited by the relatively short follow-up period of 3 months. However, despite these limitations, a significant proportion of people (18%) who initially start treatment with esketamine do not appear to continue therapy. The reasons for treatment discontinuation are not apparent based on claims data. A small proportion of members for which we do have chart notes submitted with PA, document lack of improvement in depression symptoms indicating ongoing need for renewal criteria and documentation that providers are utilizing the FDA-approved maintenance doses.

References:

1. Gabriel FC, Stein AT, Melo DO, et al. Guidelines' recommendations for the treatment-resistant depression: A systematic review of their quality. *PLoS ONE.* 2023;18(2):e0281501.
2. Oregon Health Authority. Mental Health Clinical Advisory Group. Drug Augmentatino for Treatment-resistant Depression. December 2021. Available online at https://www.oregon.gov/oha/HPA/DSI-Pharmacy/SiteAssets/Lists/MHCAGRecs/EditForm/Drug%20Augmentation%20for%20Treatment-resistant%20Depression.pdf. Accessed April 28, 2025.
3. Spravato (esketamine) nasal spray [product information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. January 2025.

Appendix 1: Drug Coding

Table A1. Error Codes associated with denied claims

Error Code	Error Status Description	
3002	NDC REQUIRES PA	Include
3000	UNITS EXCEED AUTHORIZED UNITS ON PA MASTER FILE	Include
3023	Non-Pref Drug. Consider Options at www.orpdl.org	Include
503	DATE DISPENSED AFTER BILLING DATE	Exclude
576	CLAIM HAS THIRD-PARTY PAYMENT	Exclude
4999	THIS DRUG IS COVERED BY MEDICARE PART D	Exclude
2509	RECIPIENT COVERED BY MEDICARE	Exclude
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)	Exclude
513	RECIPIENT NAME AND NUMBER DISAGREE	Exclude
221	DAYS SUPPLY MISSING	Exclude
219	QUANTITY DISPENSED IS MISSING	Exclude
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE	Exclude
628	Other Coverage Reject Code Required for OCC 3	Exclude
4002	Non-Covered Drug	Exclude
4891	Not covered drug class	Exclude
4890	Non covered drug class	Exclude
205	PRESCRIBING PROVIDER ID MISSING	Exclude
643	INVALID OTHER COVERAGE CODE	Exclude
270	HEADER TOTAL BILLED AMOUNT INVALID	Exclude

505	THIRD PARTY PAYMENT AMOUNT MORE THAN CLAIM CHARGE	Exclude
268	BILLED AMOUNT MISSING	Exclude
238	RECIPIENT NAME IS MISSING	Exclude

Table A2. Comorbid mental health conditions

Mental Health Condition Description	ICD-10 codes
Major depressive disorder	F33x
Bipolar disorder	F31x
Schizophrenia and schizoaffective disorders	F20x, F25x
Sleep disorders	G47x
Anxiety disorders	F40x-F41x
Post-traumatic stress disorder	F431x
Substance use disorder	F10x-F19x
Suicidal ideation/attempt	R4585x; T1491x; Z9151

Table A3. Oral antidepressant categorization and minimum daily therapeutic doses

Drug Code (HSN)	Generic Name	Mechanism	Daily Dose (mg)
033510	selegiline	MAOI	6
001638	isocarboxazid	MAOI	40
001639	phenelzine sulfate	MAOI	15
001640	tranylcypromine sulfate	MAOI	30
049127	zuranolone	Other	50
009612	nefazodone HCl	Other	200
001652	trazodone HCl	Other	150
037597	vilazodone HCl	Other	20
040637	vortioxetine hydrobromide	Other	10
040202	desvenlafaxine	SNRI	50
035420	desvenlafaxine succinate	SNRI	50
026521	duloxetine HCl*	SNRI	60
040632	levomilnacipran HCl	SNRI	40
048091	venlafaxine besylate*	SNRI	75
008847	venlafaxine HCl*	SNRI	75
010321	citalopram hydrobromide*	SSRI	20
024022	escitalopram oxalate*	SSRI	10
001655	fluoxetine HCl*	SSRI	20

006338	fluvoxamine maleate	SSRI	50
007344	paroxetine HCl	SSRI	20
006324	sertraline HCl*	SSRI	100
001643	amitriptyline HCl*	TCA	50
001648	amoxapine	TCA	200
004744	clomipramine HCl	TCA	75
001645	desipramine HCl*	TCA	75
001650	doxepin HCl	TCA	75
001641	imipramine HCl	TCA	75
001642	imipramine pamoate	TCA	75
001651	maprotiline HCl	TCA	75
001644	nortriptyline HCl*	TCA	75
001646	protriptyline HCl	TCA	15
001649	trimipramine maleate	TCA	75
011505	mirtazapine*	Other	15
036156	bupropion HBr*	Other	300
001653	bupropion HCl*	Other	300
025800	olanzapine/fluoxetine HCl	Other	6/25
048220	dextromethorphan HBr/bupropion	Other	90/210

*Minimum doses were defined per MHCAG when available. Other minimum doses were defined according to Micromedex. Topical TCAs and bulk powders were excluded.

Table A4. Taxonomy codes for mental health providers

Taxonomy	Description	Category
2084A0401X	PSYCHIATRY & NEUROLOGY, ADDICTION MEDICINE	Psychiatrist
2084B0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-BARIATRIC MEDICINE	Psychiatrist
2084B0040X	BEHAVIORAL NEUROLOGY & NEUROPSYCHIATRY	Psychiatrist
2084D0003X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-DIAGNOSTIC NEUROIMAGING	Psychiatrist
2084E0001X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-EPILEPSY	Psychiatrist
2084F0202X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-FORENSIC PSYCHIATRY	Psychiatrist
2084H0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-HOSPICE AND PALLIATIVE MEDICINE	Psychiatrist
2084N0008X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROMUSCULAR MEDICINE	Psychiatrist
2084N0400X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY	Psychiatrist
2084N0402X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY WITH SPECIAL QUAL IN CHILD NEUROLO	Psychiatrist

2084N0600X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-CLINICAL NEUROPHYSIOLOGY	Psychiatrist
2084P0005X	PHYSICIAN-PSYCHIATRY&NERUOLOGY-NEURODEVELOPMENTAL DISABILITIES	Psychiatrist
2084P0015X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHOSOMATIC MEDICINE	Psychiatrist
2084P0800X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	Psychiatrist
2084P0802X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-ADDICTION PSYCHIATRY	Psychiatrist
2084P0804X	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	Psychiatrist
2084P0805X	PHYSICIAN-PSYCHIATRY&NEUROLGY-GERIATRIC PSYCHIATRY	Psychiatrist
2084P2900X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PAIN MEDICINE	Psychiatrist
2084S0010X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SPORTS MEDICINE	Psychiatrist
2084S0012X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SLEEP MEDICINE	Psychiatrist
2084V0102X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-VASCULAR NEUROLOGY	Psychiatrist
363LP0808X	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	PMHNP

Table A5. Provider location definitions by county and zip code

Zip Code	County	Designation	Zip Code	County	Designation	Zip Code	County	Designation
97814	BAKER	Frontier	97009	CLACKAMAS	Urban	97055	CLACKAMAS	Rural
97819	BAKER	Frontier	97011	CLACKAMAS	Rural	97067	CLACKAMAS	Rural
97905	BAKER	Frontier	97013	CLACKAMAS	Rural	97068	CLACKAMAS	Urban
97833	BAKER	Frontier	97015	CLACKAMAS	Urban	97070	CLACKAMAS	Urban
97834	BAKER	Frontier	97017	CLACKAMAS	Rural	97102	CLATSOP	Rural
97837	BAKER	Frontier	97089	CLACKAMAS	Urban	97103	CLATSOP	Rural
97907	BAKER	Frontier	97022	CLACKAMAS	Rural	97110	CLATSOP	Rural
97840	BAKER	Frontier	97023	CLACKAMAS	Rural	97121	CLATSOP	Rural
97870	BAKER	Frontier	97027	CLACKAMAS	Urban	97138	CLATSOP	Rural
97877	BAKER	Frontier	97028	CLACKAMAS	Rural	97145	CLATSOP	Rural
97884	BAKER	Frontier	97086	CLACKAMAS	Urban	97146	CLATSOP	Rural
97324	BENTON	Rural	97034	CLACKAMAS	Urban	97016	COLUMBIA	Rural
97330	BENTON	Urban	97035	CLACKAMAS	Urban	97018	COLUMBIA	Rural
97331	BENTON	Urban	97036	CLACKAMAS	Urban	97054	COLUMBIA	Rural
97333	BENTON	Urban	97222	CLACKAMAS	Urban	97048	COLUMBIA	Rural
97339	BENTON	Urban	97267	CLACKAMAS	Urban	97051	COLUMBIA	Rural
97456	BENTON	Rural	97038	CLACKAMAS	Rural	97056	COLUMBIA	Rural
97370	BENTON	Urban	97042	CLACKAMAS	Rural	97064	COLUMBIA	Rural
97004	CLACKAMAS	Rural	97045	CLACKAMAS	Urban	97053	COLUMBIA	Rural
			97049	CLACKAMAS	Rural	97407	COOS	Rural

97411	COOS	Rural
97414	COOS	Rural
97420	COOS	Rural
97423	COOS	Rural
97449	COOS	Rural
97458	COOS	Rural
97459	COOS	Rural
97466	COOS	Rural
97751	CROOK	Rural
97752	CROOK	Rural
97753	CROOK	Rural
97754	CROOK	Rural
97406	CURRY	Rural
97415	CURRY	Rural
97444	CURRY	Rural
97450	CURRY	Rural
97464	CURRY	Rural
97465	CURRY	Rural
97476	CURRY	Rural
97491	CURRY	Rural
97701	DESCHUTES	Urban
97702	DESCHUTES	Urban
97703	DESCHUTES	Urban
97707	DESCHUTES	Rural
97708	DESCHUTES	Urban
97709	DESCHUTES	Urban
97712	DESCHUTES	Rural
97739	DESCHUTES	Rural
97756	DESCHUTES	Rural
97759	DESCHUTES	Rural
97760	DESCHUTES	Rural
97410	DOUGLAS	Rural
97416	DOUGLAS	Rural
97417	DOUGLAS	Rural
97428	DOUGLAS	Rural
97429	DOUGLAS	Rural
97432	DOUGLAS	Rural
97435	DOUGLAS	Rural
97436	DOUGLAS	Rural
97441	DOUGLAS	Rural
97442	DOUGLAS	Rural
97443	DOUGLAS	Rural
97447	DOUGLAS	Rural
97457	DOUGLAS	Rural
97462	DOUGLAS	Rural
97467	DOUGLAS	Rural
97469	DOUGLAS	Rural
97470	DOUGLAS	Rural
97471	DOUGLAS	Rural
97473	DOUGLAS	Rural
97479	DOUGLAS	Rural
97481	DOUGLAS	Rural
97484	DOUGLAS	Rural
97486	DOUGLAS	Rural
97494	DOUGLAS	Rural
97495	DOUGLAS	Rural
97496	DOUGLAS	Rural
97499	DOUGLAS	Rural
97812	GILLIAM	Frontier
97823	GILLIAM	Frontier
97861	GILLIAM	Frontier
97817	GRANT	Frontier
97820	GRANT	Frontier
97825	GRANT	Frontier
97845	GRANT	Frontier
97848	GRANT	Frontier
97856	GRANT	Frontier
97864	GRANT	Frontier
97865	GRANT	Frontier
97869	GRANT	Frontier
97873	GRANT	Frontier
97720	HARNEY	Frontier
97732	HARNEY	Frontier
97722	HARNEY	Frontier
97904	HARNEY	Frontier
97710	HARNEY	Frontier
97736	HARNEY	Frontier
97738	HARNEY	Frontier
97721	HARNEY	Frontier
97758	HARNEY	Frontier
97014	HOOD RIVER	Rural
97031	HOOD RIVER	Rural
97041	HOOD RIVER	Rural
97520	JACKSON	Rural
97522	JACKSON	Rural
97502	JACKSON	Urban
97524	JACKSON	Rural
97525	JACKSON	Rural
97530	JACKSON	Rural
97501	JACKSON	Urban
97504	JACKSON	Urban
97535	JACKSON	Urban
97536	JACKSON	Rural
97537	JACKSON	Rural
97539	JACKSON	Rural
97540	JACKSON	Urban
97541	JACKSON	Rural
97503	JACKSON	Urban
97711	JEFFERSON	Rural
97730	JEFFERSON	Rural
97734	JEFFERSON	Rural
97741	JEFFERSON	Rural
97761	JEFFERSON	Rural
97523	JOSEPHINE	Rural
97526	JOSEPHINE	Rural

97527	JOSEPHINE	Rural
97528	JOSEPHINE	Rural
97531	JOSEPHINE	Rural
97532	JOSEPHINE	Rural
97533	JOSEPHINE	Rural
97534	JOSEPHINE	Rural
97538	JOSEPHINE	Rural
97543	JOSEPHINE	Rural
97544	JOSEPHINE	Rural
97497	JOSEPHINE	Rural
97621	KLAMATH	Rural
97622	KLAMATH	Rural
97623	KLAMATH	Rural
97731	KLAMATH	Rural
97624	KLAMATH	Rural
97604	KLAMATH	Rural
97733	KLAMATH	Rural
97425	KLAMATH	Rural
97625	KLAMATH	Rural
97626	KLAMATH	Rural
97737	KLAMATH	Rural
97627	KLAMATH	Rural
97601	KLAMATH	Rural
97602	KLAMATH	Rural
97603	KLAMATH	Rural
97632	KLAMATH	Rural
97633	KLAMATH	Rural
97634	KLAMATH	Rural
97639	KLAMATH	Rural
97620	LAKE	Frontier
97641	LAKE	Frontier
97735	LAKE	Frontier
97630	LAKE	Frontier
97635	LAKE	Frontier
97636	LAKE	Frontier
97637	LAKE	Frontier
97638	LAKE	Frontier
97640	LAKE	Frontier
97409	LANE	Urban
97412	LANE	Rural
97413	LANE	Rural
97419	LANE	Rural
97424	LANE	Rural
97426	LANE	Urban
97430	LANE	Rural
97431	LANE	Rural
97434	LANE	Rural
97437	LANE	Rural
97401	LANE	Urban
97402	LANE	Urban
97403	LANE	Urban
97404	LANE	Urban
97405	LANE	Urban
97408	LANE	Urban
97440	LANE	Urban
97438	LANE	Rural
97439	LANE	Rural
97448	LANE	Rural
97489	LANE	Rural
97451	LANE	Rural
97452	LANE	Rural
97453	LANE	Rural
97454	LANE	Rural
97461	LANE	Rural
97463	LANE	Rural
97455	LANE	Urban
97475	LANE	Urban
97477	LANE	Urban
97478	LANE	Urban
97480	LANE	Rural
97487	LANE	Rural
97488	LANE	Rural
97490	LANE	Rural
97492	LANE	Rural
97493	LANE	Rural
97326	LINCOLN	Rural
97341	LINCOLN	Rural
97343	LINCOLN	Rural
97388	LINCOLN	Rural
97367	LINCOLN	Rural
97357	LINCOLN	Rural
97364	LINCOLN	Rural
97365	LINCOLN	Rural
97368	LINCOLN	Rural
97369	LINCOLN	Rural
97372	LINCOLN	Rural
97376	LINCOLN	Rural
97380	LINCOLN	Rural
97366	LINCOLN	Rural
97390	LINCOLN	Rural
97391	LINCOLN	Rural
97394	LINCOLN	Rural
97498	LINCOLN	Rural
97321	LINN	Urban
97322	LINN	Urban
97327	LINN	Rural
97329	LINN	Rural
97335	LINN	Rural
97336	LINN	Rural
97345	LINN	Rural
97348	LINN	Rural
97446	LINN	Rural
97355	LINN	Rural
97358	LINN	Rural
97360	LINN	Rural

97374	LINN	Rural
97377	LINN	Rural
97386	LINN	Rural
97389	LINN	Urban
97901	MALHEUR	Frontier
97902	MALHEUR	Frontier
97903	MALHEUR	Frontier
97906	MALHEUR	Frontier
97908	MALHEUR	Frontier
97909	MALHEUR	Frontier
97910	MALHEUR	Frontier
97911	MALHEUR	Frontier
97913	MALHEUR	Frontier
97914	MALHEUR	Frontier
97917	MALHEUR	Frontier
97918	MALHEUR	Frontier
97920	MALHEUR	Frontier
97325	MARION	Rural
97002	MARION	Rural
97342	MARION	Rural
97020	MARION	Rural
97346	MARION	Rural
97026	MARION	Rural
97032	MARION	Rural
97350	MARION	Rural
97352	MARION	Urban
97303	MARION	Urban
97307	MARION	Urban
97359	MARION	Urban
97384	MARION	Rural
97362	MARION	Rural
97373	MARION	Rural
97137	MARION	Rural
97301	MARION	Urban
97302	MARION	Urban
97305	MARION	Urban
97306	MARION	Urban
97308	MARION	Urban
97309	MARION	Urban
97310	MARION	Urban
97312	MARION	Urban
97317	MARION	Urban
97375	MARION	Rural
97381	MARION	Rural
97383	MARION	Rural
97385	MARION	Rural
97392	MARION	Urban
97071	MARION	Rural
97818	MORROW	Frontier
97836	MORROW	Frontier
97843	MORROW	Frontier
97844	MORROW	Frontier
97839	MORROW	Frontier
97010	MULTNOMAH	Rural
97019	MULTNOMAH	Rural
97024	MULTNOMAH	Urban
97030	MULTNOMAH	Urban
97080	MULTNOMAH	Urban
97268	MULTNOMAH	Urban
97269	MULTNOMAH	Urban
97230	MULTNOMAH	Urban
97201	MULTNOMAH	Urban
97204	MULTNOMAH	Urban
97205	MULTNOMAH	Urban
97206	MULTNOMAH	Urban
97209	MULTNOMAH	Urban
97210	MULTNOMAH	Urban
97211	MULTNOMAH	Urban
97212	MULTNOMAH	Urban
97213	MULTNOMAH	Urban
97214	MULTNOMAH	Urban
97215	MULTNOMAH	Urban
97216	MULTNOMAH	Urban
97217	MULTNOMAH	Urban
97218	MULTNOMAH	Urban
97219	MULTNOMAH	Urban
97220	MULTNOMAH	Urban
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97227	MULTNOMAH	Urban
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97232	MULTNOMAH	Urban
97233	MULTNOMAH	Urban
97239	MULTNOMAH	Urban
97256	MULTNOMAH	Urban
97258	MULTNOMAH	Urban
97266	MULTNOMAH	Urban
97207	MULTNOMAH	Urban
97208	MULTNOMAH	Urban
97228	MULTNOMAH	Urban
97238	MULTNOMAH	Urban
97240	MULTNOMAH	Urban
97242	MULTNOMAH	Urban
97280	MULTNOMAH	Urban
97282	MULTNOMAH	Urban
97283	MULTNOMAH	Urban
97286	MULTNOMAH	Urban
97290	MULTNOMAH	Urban
97291	MULTNOMAH	Urban
97292	MULTNOMAH	Urban
97293	MULTNOMAH	Urban
97294	MULTNOMAH	Urban
97296	MULTNOMAH	Urban
97236	MULTNOMAH	Urban
97202	MULTNOMAH	Urban
97203	MULTNOMAH	Urban

97281	MULTNOMAH	Urban
97060	MULTNOMAH	Urban
97298	MULTNOMAH	Urban
97338	POLK	Rural
97344	POLK	Rural
97347	POLK	Rural
97351	POLK	Urban
97361	POLK	Rural
97371	POLK	Urban
97304	POLK	Urban
97029	SHERMAN	Frontier
97033	SHERMAN	Frontier
97039	SHERMAN	Frontier
97050	SHERMAN	Frontier
97065	SHERMAN	Frontier
97107	TILLAMOOK	Rural
97108	TILLAMOOK	Rural
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97118	TILLAMOOK	Rural
97122	TILLAMOOK	Rural
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97131	TILLAMOOK	Rural
97149	TILLAMOOK	Rural
97143	TILLAMOOK	Rural
97134	TILLAMOOK	Rural
97135	TILLAMOOK	Rural
97136	TILLAMOOK	Rural
97141	TILLAMOOK	Rural
97147	TILLAMOOK	Rural
97810	UMATILLA	Rural
97813	UMATILLA	Rural
97826	UMATILLA	Rural
97835	UMATILLA	Rural
97838	UMATILLA	Rural
97859	UMATILLA	Rural
97862	UMATILLA	Rural
97801	UMATILLA	Rural
97868	UMATILLA	Rural
97875	UMATILLA	Rural
97880	UMATILLA	Rural
97882	UMATILLA	Rural
97886	UMATILLA	Rural
97824	UNION	Rural
97827	UNION	Rural
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97885	WALLOWA	Frontier
97001	WASCO	Rural
97021	WASCO	Rural
97037	WASCO	Rural
97040	WASCO	Rural
97044	WASCO	Rural
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97006	WASHINGTON	Urban
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97077	WASHINGTON	Urban
97078	WASHINGTON	Urban
97076	WASHINGTON	Urban
97109	WASHINGTON	Rural
97225	WASHINGTON	Urban
97113	WASHINGTON	Urban
97116	WASHINGTON	Urban
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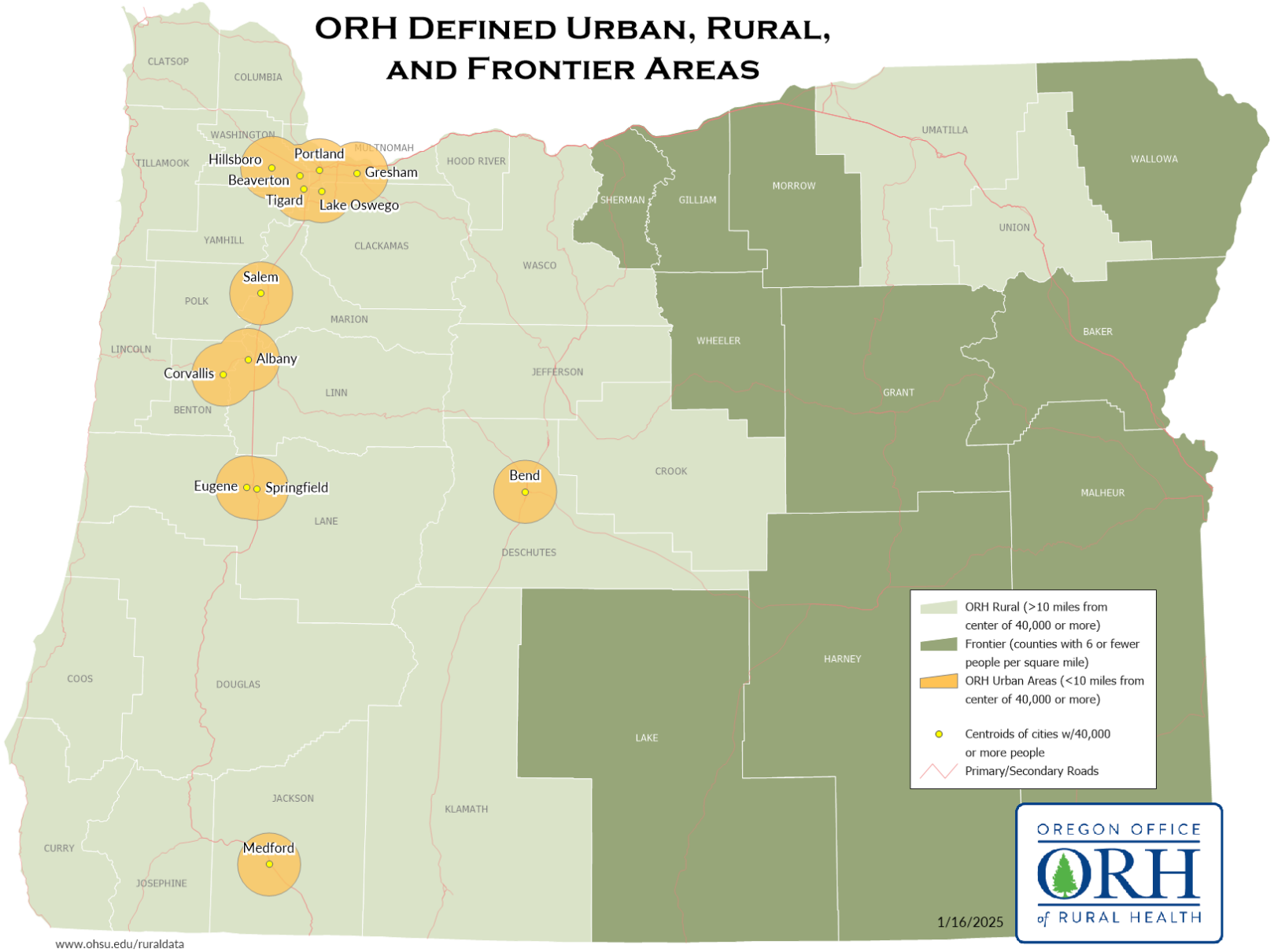
97133	WASHINGTON	Rural
97229	WASHINGTON	Urban
97140	WASHINGTON	Urban
97223	WASHINGTON	Urban
97224	WASHINGTON	Urban
97144	WASHINGTON	Rural
97062	WASHINGTON	Urban
97830	WHEELER	Frontier
97750	WHEELER	Frontier
97874	WHEELER	Frontier
97101	YAMHILL	Rural
97111	YAMHILL	Rural
97114	YAMHILL	Rural
97115	YAMHILL	Rural
97127	YAMHILL	Rural
97128	YAMHILL	Rural
97132	YAMHILL	Rural
97378	YAMHILL	Rural
97396	YAMHILL	Rural
97148	YAMHILL	Rural



Author: Servid

June 2025

Esketamine (Spravato)

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

Length of Authorization:
- Up to 6 months

Requires PA:
- Esketamine (pharmacy and physician administered claims).

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~6. Is the patient currently on a therapeutic dose of an oral antidepressant (Average minimum effective dose for antidepressants can be found at: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf)~~	~~**Yes:** Go to #7~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Esketamine is indicated for use with an oral antidepressant.~~
6. ~~Does the patient have~~Is there prescriber attestation or documentation of treatment-resistant depression ~~(failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)~~ based on all the following criteria: a. Diagnosis of unipolar major depressive disorder b. Patient has tried at least 2 different antidepressants in which: i. There has been inadequate response after at least 6 weeks of treatment at an average minimum therapeutic dose or greater; or ii. The patient has not been able to continue treatment for at least 6 weeks due to intolerable side effects. Minimum therapeutic doses can be found here: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf	**Yes:** Go to #~~10~~9	**No:** Go to #~~7~~8
7. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**Yes:** Go to #~~8~~9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.

Approval Criteria		
8. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #9~~10~~	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 28 days for induction (either 56 mg and/or 84 mg for titration) not to exceed 24 units total to be covered within the approved time window. The approved time window typically spans 60 days to accommodate scheduling visits.

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~~3~~
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days) ~~Go to #3~~	**No**: Pass to RPh. Deny; medical appropriateness.
~~Has the patient been adherent to oral antidepressant therapy?~~	~~**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~

Renewal Criteria		
3. 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 24 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 6/24(KS);2/24; 12/23 (KS); 2/23, 10/21; 2/21; 7/19
Implementation:7/1/24; 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: Suzetrigine (JOURNAVX) 50 mg tablet

Date of Review: June 2025
Generic Name: Suzetrigine

End Date of Literature Search: 04/13/2025
Brand Name (Manufacturer): Journavx™ (Vertex)

Dossier Received: yes

Plain Language Summary:

- Many patients experience pain due to different causes. Pain can last a short amount of time (acute) or last longer (chronic).
- The Food and Drug Administration recently approved suzetrigine for acute pain. Suzetrigine is not an opioid, such as hydrocodone, and evidence from short-term studies shows that it is probably not addictive. It works differently than acetaminophen or non-steroidal anti-inflammatory drugs (NSAID) such as ibuprofen to control pain.
- Based on 2 studies lasting 48 hours, suzetrigine may work better than a placebo to relieve moderate to severe pain after a surgery. There is no evidence that suzetrigine works better than low-dose hydrocodone/acetaminophen. Nearly all patients in these studies also took ibuprofen for breakthrough pain, and patients who received suzetrigine took ibuprofen at similar amounts as patients who took a placebo.
- One study allowed patients to take suzetrigine for up to 14 days (average 9.8 days). There were no major concerns for safety shown, but this study did not compare suzetrigine to another group and patients knew what they were taking.
- Suzetrigine is not studied or approved by the Food and Drug Administration for chronic pain. It has not been compared to a non-steroidal anti-inflammatory drug or taken simultaneously with an opioid. Suzetrigine is being studied for nerve pain from diabetes.
- We recommend requests for suzetrigine follow labeled age requirements and limit quantities beyond the time period where there is quality evidence to show it may help acute pain. This process is called prior authorization.

Research Questions:

1. What is the comparative efficacy or effectiveness suzetrigine in people acute pain?
2. What is the comparative safety of suzetrigine in people with acute pain?
3. Is there evidence to show that suzetrigine is more effective or safer in certain populations of people (based on diagnoses, disease characteristics, race, comorbidities [renal or hepatic impairment, history of opioid abuse], concomitant drug therapies, or socioeconomic status)?

Conclusions:

- Suzetrigine a sodium channel blocker the Food and Drug Administration (FDA) approved for moderate to severe acute pain in adults. It is not expected to have risk of addiction and is not classified as a controlled substance by the Drug Enforcement Agency.

Author: Sara Fletcher, PharmD, MPH, BCPS

- Suzetrigine was approved based on the findings of two fair-quality, phase 3, double-blind, randomized, multicenter, active- and placebo-controlled studies for moderate to severe acute postsurgical pain after abdominoplasty or bunionectomy.[1] Publication of results is available as a preprint, and full publication is pending.
    - There is moderate quality evidence that suzetrigine is superior to placebo by decreasing time-weighted sum of the pain intensity between hours 0 to 48 (SPID48) on the numeric pain rating scale (NPRS) in patients after bunionectomy (NAVIGATE 1: least squares mean [LSM] difference 29.3, 95% confidence interval [CI] 14.0 to 44.6, p=0.0002) and abdominoplasty (NAVIGATE 2: LSM difference 48.4, 95% CI 33.6 to 63.1, p<0.0001).[1]
    - There is moderate quality evidence that suzetrigine is not superior to low dose hydrocodone 5 mg/acetaminophen 325 mg given every 6 hours using the SPID48 after bunionectomy (NAVIGATE 1: LSM difference -20.2, 95% CI -32.7 to -7.7, p=0.0016 [favors hydrocodone/acetaminophen]) or abdominoplasty (NAVIGATE 2: LSM difference 6.6, 95% CI -5.4 to 18.7, p=0.281).[1]
- There is moderate quality evidence that suzetrigine is safe for use for 48 hours. Most side effects were mild and severe adverse events were generally not attributed to suzetrigine. Nausea and vomiting was less likely to occur with suzetrigine than hydrocodone/acetaminophen (number needed to harm [NNH] 7-13).[1]
- There is insufficient evidence based on one open-label, single arm study that suzetrigine is safe for use up to 14 days (mean 9.8 days).[2]
- Most patients included in clinical trials were White women after outpatient surgery. Abdominoplasty is often performed for cosmetic reasons and may not be representative of Medicaid post-operative patients.

Recommendations:

- Implement prior authorization for use beyond 48 hours and limit use to no more than 14 days.

Background:

Pain management is an important aspect for a variety of acute and chronic conditions. Acute pain is generally defined as pain lasting up to 30 days, usually in response to some form of tissue injury, such as surgery or trauma.[3] Both non-pharmacologic treatments (such as rehabilitative therapy, chiropractic or osteopathic manipulation, and acupuncture) and pharmaceutical analgesics play an important role in management of pain. Evidence supporting specific interventions varies depending on the condition, but current guidelines routinely recommend non-opioid pharmaceuticals and non-pharmacologic treatments for the initial treatment of acute or chronic pain. Most guidelines, medical societies, and public health agencies have recently recommended against routinely prescribing opioids due to increasing evidence of harms reported in observational and epidemiologic studies. These harms include increased mortality, development of opioid use disorder, overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.[4] Opioids have also been implicated in impaired cognitive function and development of new onset depression.[4]

Non-opioid pharmaceutical options currently available for pain management include acetaminophen, NSAIDs, certain antidepressants, topical agents, muscle relaxants, and some anticonvulsants (e.g., gabapentin, pregabalin). Acetaminophen and some NSAIDs are available over-the-counter without the need for a prescription. There has been interest in development of new pain medications which utilize non-addictive modalities and provide adequate pain relief.[3] The FDA issued non-binding industry guidance in February 2022 for the development of non-opioid analgesics for acute pain and recommended against the use of non-inferiority study designs because pain intensity can be influenced by study design factors (e.g., placebo effect, rescue medications) and the result of “no difference” could occur in a situation where neither product worked.[3]

Improvement in pain severity or intensity is one of the most commonly reported efficacy outcomes for pain studies. However, outcomes evaluating the impact of treatment on disability, function, and quality of life are equally important. Pain intensity measurements used in clinical trials include the visual analog scale (VAS; range 0-100 or 0-10) and numeric pain rating scale (NPRS; range 0-10).[5] The NPRS and VAS are highly correlated and can be interpreted equally. For acute pain, the minimum clinically important difference (MCID) in the 11-point VAS is 1.4 (95% CI, 1.2 to 1.6).[6] Similar MCID values have been shown with 100-point scales (correlating to about a 14 point change on a 100 point scale).[7] The Sum of Pain Intensity Difference (SPID) over a specified time period (often 24-48 hours) has been used in acute pain studies including tramadol and NSAIDs. A specific minimum clinically important difference (MCID) has not been established.[1,3,8,9]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 2**.

Clinical Efficacy:

Suzetrigine, a sodium channel blocker, works by selective inhibition of $Na_v1.8$, which is not expressed in the human brain or spinal cord. This presumably limits addictive potential.[10] It is approved for the treatment of moderate to severe acute pain in adults.[10] Use for acute pain has not been studied beyond 14 days.[10] It is dosed as 100 mg followed by 50 mg every 12 hours and is available in a 30-count bottle (~ 14 day supply) and a 100-count bottle.[10]

Suzetrigine has been studied in two, phase 3, double-blind, randomized, multicenter, active- and placebo-controlled studies for moderate to severe acute postsurgical pain after abdominoplasty (NAVIGATE 2; NCT05558410) or bunionectomy (NAVIGATE 1; NCT05553366).[1] Studies are currently published as a pre-print. Included adults were aged 18 to 80 years, had a moderate or severe verbal categorical rating scale (VRS; 4 levels ranging from “no pain” to “severe pain”), and pain of 4 or greater on the numeric pain rating scale (NPRS, a numerical version of the visual-analogue scale; range 0 to 10, higher score indicate more pain).[1] Patients in NAVIGATE 2 were assessed for pain within 4 hours of surgical completion after standard abdominoplasty under general anesthesia.[1] Surgical duration was less than 3 hours and those with liposuction were excluded.[1] In NAVIGATE 1, patients underwent primary unilateral bunionectomy with local blockade and regional anesthesia and were assessed for pain within 9 hours after removal of popliteal sciatic block on day 1.[1] All patients were required to stop chronic use of opioids or NSAIDS at least 5 half-lives or 2 days (whichever was longer) before admission.[1] Full inclusion and exclusion details are included in **Table 2**. Patients were randomized 2:1:2 to receive suzetrigine 100 mg followed by 50 mg every 12 hours plus dummy placebo every 12 hours (to mimic every 6 hour dosing), placebo every 6 hours, or hydrocodone 5 mg/acetaminophen 325 mg every 6 hours.[1]

Pain intensity was assessed using the NPRS at 19 timepoints (0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8 hours, then every 4 hours up to 48 hours) after the first dose of study drug.[1] Ibuprofen 400 mg orally every 6 hours was allowed as rescue medication after first dose of study drug, though all patients were encouraged to wait 90 minutes after the first study drug administration before requesting rescue medication to allow time for effect and reduce confounding from rescue medication. The primary endpoint in both studies was time-weighted sum of the pain intensity difference for suzetrigine versus placebo on NPRS from hours 0 to 48 hours (SPID48). Positive SPID48 scores indicate reduction in pain from baseline while larger numbers indicate greater pain reduction.[1] The expected MCID for SPID48 was not stated. Suzetrigine was superior to placebo using SPID48 (NAVIGATE 1: LSM difference 29.3, 95% CI 14.0 to 44.6, p=0.0002; NAVIGATE 2: LSM difference 48.4, 95% CI 33.6 to 63.1, p<0.0001).[1] The first key secondary endpoint was SPID48 of suzetrigine compared to hydrocodone/acetaminophen, and suzetrigine did not have superior pain improvement in either trial (NAVIGATE 1: LSM difference -20.2, 95% CI -32.7 to -7.7, p=0.0016 [favoring hydrocodone/acetaminophen]; NAVIGATE 2: LSM difference 6.6, 95% CI -5.4 to 18.7, p=0.281).[1] Due to hierarchical testing plan and failure to meet first key secondary endpoint, additional secondary endpoints are considered exploratory.[8] Additional endpoints are included in **Table 2**.

Rescue use of ibuprofen was similar between groups in NAVIGATE 1 (suzetrigine n=364, 85.4%, 800 mg total; placebo n=185, 85.6%, 800 mg total; hydrocodone/acetaminophen n=345, 80.0%, 400 mg total), and NAVIGATE 2 (suzetrigine n=362, 81.0%, 800 mg total; placebo n=196, 87.9%, 1200 mg total; hydrocodone/acetaminophen n=360; 82.6%, 800 mg total).[1] Efficacy of suzetrigine beyond 48 hours for acute pain is not known, and there is currently insufficient evidence for use in chronic pain. Combination use with an opioid has not been studied, and it is unclear if suzetrigine would reduce opioid exposure with concomitant use. Most participants were generally healthy females and based on surgical type and may not be representative of the Medicaid population. Suzetrigine was not superior to a low dose of hydrocodone/acetaminophen and the difference was more defined in the bunionectomy study. There was a large amount of attrition (>10%) due to perceived lack of efficacy in all groups for a short term (48 hour) study intervention.

Clinical Safety:
Suzetrigine is contraindicated with strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin) which increase exposure to suzetrigine and the M6-SUZ active metabolite.[10] The medication is an inducer of CYP3A and should be used with caution in those taking other CYP3A substrates, including certain hormonal birth contraceptives.[10] FDA labeling includes a warning/precaution for use in moderate to severe hepatic impairment. Use of suzetrigine should be avoided in Child-Pugh Class C and used only with dose modification for in people with Child-Pugh Class B.[10]

In NAVIGATE 1 and 2 the most common side effects were nausea, constipation, headache, dizziness, hypotension, and vomiting. These were mostly mild and usually occurred at lower rates than the placebo or hydrocodone/acetaminophen group. However, administration of the medication lasted only 48 hours. Those that occurred at greater rate than placebo are in **Table 1**.

Table 1. Adverse events of suzetrigine occurring in at least 1% of patients and greater than placebo[10]

Adverse event	**Placebo** (N=438) n (%)	**Suzetrigine** (N=874) n (%)	**Hydrocodone/acetaminophen** (N=879) n (%)
Pruritus	7 (1.6)	18 (2.1)	30 (3.4)
Muscle spasms	2 (0.5)	11 (1.3)	6 (0.7)
Increased blood creatine phosphokinase	2 (0.5)	10 (1.1)	7 (0.8)
Rash	2 (0.5)	10 (1.1)	6 (0.7)

In addition to the randomized controlled trials, suzetrigine has been studied in a published, phase 3, single-arm trial (NCT05661734) for moderate to severe surgical or non-surgical acute pain (n=256) in 15 United States centers.[11] The trial had high risk of bias due to lack of blinding, randomization, and a control group, and only the primary endpoint of safety will be detailed in this document. Suzetrigine 100 mg then 50 mg every 12 hours was given for up to 14 days or until pain resolution occurred in adult participants (age 18 to 80 years) with BMI between 18 and 40 kg/m^2 who were post-surgical or presenting to a medical facility with acute pain of new origin within 48 hours of onset.[11] Patients were anticipated to require less than a 24-hour admission.[11] Those with alcohol or illicit drug use within the past 3 years were excluded.[11] Pain was rated as moderate to severe on the VRS and 4 or higher on the NPRS.[11] Rescue with 650 mg acetaminophen or 400 mg ibuprofen every 6 hours was allowed and required by most patients who underwent surgery (n=187; 82.4%). In the total cohort 73% used both acetaminophen and ibuprofen.[11] Concomitant ibuprofen and acetaminophen was more common in surgical (177/222; 79.7%) than non-surgical (10/34; 29.4%) patients.[11] No other pain medications were permitted, and the specific amount of rescue medication was not reported.[11]

Patients were primarily female (n=173; 67.6%) and White (n=214; 83.6%) with a mean age of 43.9 years for females and 44.0 years for male participants.[11] The mean baseline NPRS was 6.7 and most patients were post-surgical (n=222; 86.7%).[11] In the post-surgical patients, orthopedic (n=93; 41.9%) and plastic surgery (n=83; 37.4%) were the most common types of surgery, and otorhinolaryngologic surgeries and hernia repairs each accounted for about 10% surgeries.[11] Non-surgical patients (n=34) most commonly presented with an upper extremity (n=25; 44.1%) or lower extremity (n=12; 35.3%) pain after an acute injury.[11] Three patients presented with pain in multiple regions.[11]

Treatment was completed prior to day 14 in 105 patients (41.0%) due to pain resolution, and the entire 14-day regimen was completed by 137 patients (53.5%). Differences in duration based on patient type (surgical or non-surgical) was not reported. The mean overall exposure of suzetrigine was 9.8 days.[11] A total of 14 patients discontinued suzetrigine, 5 (2.0%) due to adverse event (accidental overdose, arrhythmia, nausea, rash, somnolence), 4 (1.6%) due to lack of efficacy, 1 (0.4%) by sponsor decision, and the remaining 4 (1.6%) due to "other" reason.[11] The arrhythmia (n=1) resulting in discontinuation of suzetrigine did not resolve by the end of the study period and the affected patient had a history of sinus arrhythmia and cardiac murmur.[11]

Headache was the most common adverse event (n=18; 7.0%).[11] Constipation, nausea, fall, and rash were the other adverse events occurring in more than 2% of patients.[11] Those with falls had lower extremity surgeries prior to the event and did not report syncope or dizziness.[11] There were 94 patients who experienced any AE. Mild events (n=71; 27.7%) were more common than moderate (n=21; 8.2%) or severe events (n=2, cellulitis and suicidal ideation; 0.8%).[11]

There are no phase 3 data beyond 14 days of use. A 12-week, phase 2 study versus pregabalin or placebo for diabetic peripheral neuropathy has been conducted, and a phase 3 study is currently in progress (NCT06628908) in patients with pain associated with diabetic peripheral neuropathy.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improvement in pain severity or intensity
2) Avoidance of opioid use disorder
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Time-weighted sum of the pain intensity difference for suzetrigine versus placebo on NPRS from hours 0 to 48 (SPID48)

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. NAVIGATE 2[1] NCT05558410 MC, DB, PC/AC	1. Suzetrigine 100 mg orally once, then 50 mg every 12h with alternating placebo every 6h 2. Placebo orally every 6h	Demographics: -Mean Age 42 y -Ethnicity White 70% Black 27% -34% Hispanic/Latino -Female 98% -Mean baseline NPRS score 7.4	ITT: 1. 447 2. 223 3. 448 Attrition: 1. 51 (11.4%) 2. 55 (24.7%) 3. 66 (14.7%)	Primary Endpoint: SPID48 (LSM) 1. 118.4 2. 70.1 3. 111.8 LSM Difference 1 vs. 2 = 48.4 (95% CI 33.6 to 63.1) P<0.0001	NA	Discontinued due to AE: 1. 6 (1.3%) 2. 1 (0.4%) 3. 5 (1.1%) Discontinued due to lack of efficacy: 1. 42 (9.4%) 2. 48 (21.5%) 3. 59 (13.2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Stratified by clinical site and baseline NPRS score (<8 or ≥8) using block size of 5. Random allocation sequence by independent randomization vendor and enrollment with IWRS. Baseline characteristics well balanced. Performance Bias: (Unclear) Placebo dummy used to make all interventions dosed every 6 hours. Method of blinding not described.

	3. HB/APAP orally 5mg/325mg every 6h Duration: 48 hours 2:1:2 randomization	<u>Key Inclusion Criteria</u>: -Age 18-80 y -Moderate to severe acute pain after full abdominoplasty -Abdominoplasty lasted ≤ 3 hours -Lucid and able to follow commands -Able to swallow oral medications <u>Key Exclusion Criteria</u>: -Hx of previous abdominoplasty -Hx of recent surgery -Hx of intra-abdominal or pelvic surgery with complications -BMI <18 or >40 kg/m^2 -Hx of cardiac dysrhythmias within past 2 y -Non-standard abdominoplasty, collateral procedures (e.g., liposuction) or any surgical complication -Medical complication during surgery	Overall 84.6% completed treatment	<u>First Key Secondary Endpoint</u>: SPID48 (LSM) Difference: 1 vs. 3 = 6.6 (95% CI -5.4 to 18.7) P=0.2781 <u>Second Key Secondary Endpoint* (exploratory)</u>: Median time to meaningful pain relief (≥ 2 point reduction in NPRS) 1. 119 minutes 2. 480 minutes 3. NR 1 vs. 2 P<0.0001 Rescue Medication Use 1. 362 (81.0%) 2. 196 (87.9%) 3. 370 (82.6%)[8] Total Ibuprofen Use time 0-48 hours (median in mg) 1. 800 2. 1200 3. 800[8]		<u>SAE:</u> 1. 2.5% 2. 2.3% 3. 1.6% <u>Death:</u> 1. 0 2. 1 (pulmonary embolism following cardiogenic shock and DIC) 3. 0 <u>Vomiting or Nausea:</u> 1. 91 (20.3%) 2. NR 3. 150 (33.5%) P<0.0001	13.2%/ 7	<u>Detection Bias</u>: (Unclear) Method of blinding not described. Patients completed a pain assessment training video prior to surgical procedure. <u>Attrition Bias</u>: (Unclear) Greater than 10% attrition on short term study. Missing data and score imputation for primary and key secondary endpoints were as follows: 1) scores during the rescue period (within 6 hours after rescue medication) were replaced by the pre-rescue score; 2) missing scores following treatment discontinuation were imputed using the baseline score when discontinuation was due to an AE and with the last score prior to discontinuation when discontinuation was due to other reasons; 3) missing scores for subjects who completed the treatment but with missing data from a certain time point to 48 hours were imputed with the last score; and 4) intermittently missing scores were imputed using linear interpolation. <u>Reporting Bias</u>: (Unclear) Full protocol not published (similarly designed phase 2 protocol is available), extensive use and reporting of post-hoc analyses, and secondary endpoints generally only reported vs. placebo (HB/APAP data included in FDA review). <u>Other Bias</u>: (Unclear) Trials supported by manufacturer, multiple authors are manufacturer employees and own stock and/or options in the company. **Applicability**: <u>Patient</u>: Most patients were female and study included patients having outpatient surgical interventions. Abdominoplasty is typically a cosmetic procedure and not representative of the Medicaid population. <u>Intervention</u>: Frequent pain assessment during 48-hour post-operative period mirrors inpatient but not outpatient real-world use. No evidence for longer term acute or chronic therapy. Frequent use of rescue medication and high attrition for lack of efficacy may be indication inadequate early pain relief.

								Comparator: Placebo and opioids are appropriate comparators, though HB/APAP dosing was on low end of dosing range. Future studies using NSAID comparison would help define place in therapy. Outcomes: SPID48 is an acceptable outcome measurement for acute pain per FDA guidance. Setting: 12 US locations
2.NAVIGATE 1[1] NCT05553366 MC, DB, PC/AC	1. Suzetrigine 100mg orally once, then 50mg every 12h with alternating placebo every 6h 2. Placebo orally every 6h 3. HB/APAP orally 5mg/325mg every 6h Duration: 48 hours 2:1:2 randomization	Demographics: -Mean Age 48 y -Ethnicity White 71% Black 24% -35% Hispanic/Latino -Female 85% -Mean NPRS score 6.8 Key Inclusion Criteria: -Age 18-80 y -Moderate to severe acute pain on VRS after bunionectomy and NPRS score ≥4 after procedure -Primary unilateral bunionectomy with distal first metatarsal osteotomy and internal fixation under regional anesthesia -Lucid and able to follow commands Key Exclusion Criteria: -Hx of bunionectomy -BMI <18 or >40 kg/m^2 -Hx of cardiac dysrhythmias within past 2 y -Hx of recent surgery	ITT: 1. 426 2. 216 3. 431 Attrition: 1. 54 (12.7%) 2. 39 (18.1%) 3. 42 (9.7%) Overall 87.4% completed treatment	Primary Endpoint: SPID48 (LSM) 1. 99.9 2. 70.6 3. 120.1 LSM Difference 1 vs. 2 = 29.3 (95% CI 14.0 to 44.6) P=0.0002 First Key Secondary Endpoint: SPID48 (LSM) Difference: 1 vs. 3 = -20.2 (95% CI -32.7 to -7.7) P=0.0016 (in favor of HB/APAP) Second Secondary Endpoint* (exploratory): Median time to meaningful pain relief (≥ 2-point reduction in NPRS) 1. 240 minutes 2. 480 minutes 3. NR 1 vs. 2 P=0.0016 Secondary Endpoints: Rescue Medication Use 1. 364 (85.4%) 2. 185 (85.6%) 3. 345 (80.0%)[8]	NA	Discontinued due to AE: 1. 0 2. 0 3. 1 (0.2%) (pretreatment hypotension) Discontinued due to lack of efficacy: 1. 51 (12.0%) 2. 35 (16.2%) 3. 34 (7.9%) SAE: None Vomiting or Nausea: 1. 39 (9.2%) 2. NR 3. 71 (16.5%) P=0.0014	NA 7.3%/ 13	**Risk of Bias (low/high/unclear)**: Selection Bias: See NAVIGATE 2 Performance Bias: See NAVIGATE 2 Detection Bias: See NAVIGATE 2 Attrition Bias: See NAVIGATE Reporting Bias: See NAVIGATE 2 Other Bias: See NAVIGATE 2 **Applicability**: Patient: Most patients were female and study included patients having outpatient surgical interventions. Intervention: See NAVIGATE 2 Comparator: See NAVIGATE 2 Outcomes: See NAVIGATE 2 Setting: 21 US locations

		-Type 3 deformity requiring a base wedge osteotomy or concomitant hammertoe repair -Medical complication during surgery		Total Ibuprofen Use time 0-48 hours (median in mg) 1. 800 2. 800 3. 400[8]				

Abbreviations: AC = active-controlled; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; DIC = disseminated intravascular coagulation; FDA = Food and Drug Administration; h = hours; HB/APAP = hydrocodone bitartrate/acetaminophen; hx = history; ITT = intention to treat; IWRS = interactive web response system; LSM = least squares mean; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NPRS = 11-point numeric pain rating scale [range 0-10]; NR = not reported; NS = not significant; PC = placebo-controlled; PP = per protocol; SPID48 = time-weighted sum of the pain intensity difference from 0-48 hours; US = United States; VRS = verbal rating scale; y = years.

*based on hierarchical nature of secondary endpoints, after failure to meet the first key secondary endpoint, all subsequent endpoints were considered exploratory by the FDA.

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Appendix 1: Prescribing Information Highlights

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

JOURNAVX (suzetrigine) tablets, for oral use
Initial U.S. Approval: 2025

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

JOURNAVX is a sodium channel blocker indicated for the treatment of moderate to severe acute pain in adults. (1)

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

- Swallow JOURNAVX tablets whole and do not chew or crush. (2.1)
- Recommended starting JOURNAVX oral dose is 100 mg. Take the starting dose on an empty stomach at least 1 hour before or 2 hours after food. Clear liquids may be consumed during this time (e.g., water, apple juice, vegetable broth, tea, black coffee). (2.1)
- Starting 12 hours after the starting dose, take 50 mg of JOURNAVX orally every 12 hours. Take these doses with or without food. (2.1)
- Use JOURNAVX for the shortest duration, consistent with individual patient treatment goals. Use of JOURNAVX for the treatment of acute pain has not been studied beyond 14 days. (2.1)
- See the full prescribing information for the recommended dosage in patients with hepatic impairment (2.2), for JOURNAVX dosage modifications with concomitant use of CYP3A inhibitors (2.3), and recommendations regarding missed dose(s). (2.4)
- Avoid food or drink containing grapefruit during treatment with JOURNAVX. (2.3)

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

Tablets: 50 mg (3)

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

- Concomitant use with strong CYP3A inhibitors is contraindicated. (4)

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

Moderate and Severe Hepatic Impairment: Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Use in patients with moderate hepatic impairment may increase the risk of adverse reactions. The recommended dosage is lower in patients with moderate hepatic impairment (Child-Pugh Class B) than those with normal hepatic function. (5.4)

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

The most common adverse reactions (greater incidence in JOURNAVX-treated patients compared to placebo-treated patients) were pruritis, muscle spasms, increased creatine phosphokinase, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- *Strong and Moderate CYP3A inhibitors*: Concomitant use with strong CYP3A inhibitors is contraindicated. Reduce the JOURNAVX dose when used concomitantly with moderate CYP3A inhibitors. Avoid food or drink containing grapefruit. (2.3, 7.1, 12.3)
- *Strong and Moderate CYP3A inducers*: Avoid JOURNAVX use with strong or moderate CYP3A inducers. (7.1, 12.3)
- *CYP3A substrates*: If JOURNAVX is used concomitantly with sensitive CYP3A substrates or CYP3A substrates where minimal concentration changes may lead to loss of efficacy, refer to the Prescribing Information for the CYP3A substrates for dosing instructions. Dosage modification of the concomitant CYP3A substrates may be required when initiating or discontinuing JOURNAVX. (7.2, 12.3)
- *Hormonal contraceptives*: JOURNAVX-treated patients using hormonal contraceptives containing progestins other than levonorgestrel and norethindrone should use an additional nonhormonal contraceptive method or an alternative hormonal contraceptive during concomitant use and for 28 days after JOURNAVX discontinuation. (7.2)

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

Revised: 1/2025

Appendix 2: Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Selective blocker of the NaV1.8 voltage-gated sodium channel. NaV1.8 is expressed in peripheral sensory neurons including dorsal root ganglion neurons, where its role is to transmit pain signals (action potentials). By selectively inhibiting NaV1.8 channels, suzetrigine inhibits transmission of pain signals to the spinal cord and brain. M6-SUZ, a major active metabolite, is a less potent inhibitor of NaV1.8 than suzetrigine by 3.7-fold.
Oral Bioavailability	Max absorption: 3 hours (active drug), 10 hours (M6-SUZ active metabolite)
Distribution and Protein Binding	Volume of distribution: 495 L (active drug) Protein binding: 99% (active drug), 96% (M6-SUZ active metabolite)
Metabolism	CYP3A (active drug and M6-SUZ active metabolite)
Half-Life	23.6 hours (active drug), 33.0 hours (M6-SUZ active metabolite)
Elimination	Feces: 49.9% (9.1% as active drug) Urine: 44.0% (primarily as metabolites)

Appendix 3: Proposed Prior Authorization Criteria

Suzetrigine (Journavx™)

Goal(s):

- Allow use in accordance with available medical evidence for safety and efficacy.

Length of Authorization:

- Up to 14 days per acute injury/surgery

Requires PA:

- Suzetrigine quantities greater than 5 tablets total (50 mg tablets, a 48-hour supply) within 30 days

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 an adult 18 years or older?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for treatment of acute pain? Note: Acute pain is generally considered to last less than 30 days.	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the pain documented to be moderate to severe?	**Yes**: Go to #5 Record pain rating_____ using visual analogue scale (VAS), numeric pain rating scale (NPRS) or other validated measure.	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient already received 14 days of suzetrigine for this indication?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is there documentation that the patient is failing to receive adequate pain relief from, or have contraindications to, both acetaminophen and a non-steroidal anti-inflammatory agent?	**Yes:** Approved requested doses up to maximum 30 tablets (total includes any doses received before prior authorization requirement).	**No:** Pass to RPh. Deny; medical necessity.

P&T/DUR Review: 6/25 (SF)
Implementation: TBD

Drug Use Research & Management Program
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Drug Class Review: Topicals for Molluscum Contagiosum

Date of Review: June 2025 **End Date of Literature Search:** 01/06/2025

Purpose for Class Review:
To evaluate evidence for treatment of molluscum contagiosum, which is not currently funded on the 2025 Health Evidence Review Commission (HERC) List of Prioritized Health Services, and to develop specific prior authorization (PA) criteria for medical necessity and appropriateness of drugs that are Food and Drug Administration (FDA)-approved to treat molluscum contagiosum.

Plain Language Summary:
- The molluscum contagiosum virus generally causes a mild skin infection in children and adults. The virus can spread by skin-to-skin contact or by contact with an object that has the virus on it, such as a used towel, washcloth, or shared clothing. MC appears as small, skin-colored bumps on the skin that will usually heal on their own after a few months.
- Most providers wait to see if molluscum contagiosum treatment will heal on its own because many of the treatments may cause pain or skin discoloration. Sometimes patients with molluscum contagiosum are treated to stop the spread of infection to other body areas or to other people. Patients with weak immune systems may need treatment to prevent infections that could worsen their health.
- Effective treatment for molluscum contagiosum may include cutting away the skin infection or use of topical medicines applied to the affected area of the skin. However, these procedures do not cure molluscum contagiosum and there are no current care guidelines for providers to follow.
- Cantharidin and berdazimer, are 2 topical medicines approved by the Food and Drug Administration to treat molluscum contagiosum.
- Two studies with cantharidin showed that when about 3 people were treated with cantharidin for 12 weeks, one person would have complete clearance of molluscum contagiosum skin infection.
- In 3 studies with berdazimer, results were mixed. One study showed that when about 8 people were treated with berdazimer for 12 weeks, one person had complete clearance of molluscum contagiosum skin infection. Two studies did not show a clear benefit with use of berdazimer compared to no medicine.
- Providers must explain to the Oregon Health Authority why their patient needs a medicine to treat molluscum contagiosum before Oregon Health Plan will pay for it. This process is called prior authorization.

Research Questions:
1. What is the comparative efficacy and effectiveness of FDA-approved treatments (cantharidin topical solution 0.7%; berdazimer gel 10.3%) for severe infections caused by the molluscum contagiosum (MC) virus?
2. What is the evidence for harms of agents used to treat MC?
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)?

Author: David Engen, PharmD June 2025

Conclusions:

- There was one systematic review that evaluated comparative efficacy and safety of select treatments for MC.[1] There was moderate-quality evidence that imiquimod 5% topical cream was no more effective than its vehicle in clinical cure or short-term improvements, however, imiquimod 5% topical cream may result in more harms such as application site reactions.[1] There was insufficient evidence to assess differences between treatments or for other drugs used off-label to treat MC lesions.[1]
- The FDA recently approved two new agents for the treatment of MC: cantharidin topical solution 0.7% (YCANTH) and berdazimer gel 10.3% (ZELSUVMI).[2-5]
- Data from 2 identical, phase 3, randomized, double blind, placebo-controlled, multicenter trials conducted over 12 weeks demonstrated that in patients treated with cantharidin 0.7% topical solution there was a 30-40% difference in the proportion of patients who achieved complete clearance of MC lesions compared to patients treated with placebo vehicle (CAMP-1: 46.3% vs. 17.9%, respectively; CAMP-2: 54.0% vs. 13.4%, respectively; P < .001 for both trials; low-quality evidence).[2,3,6] Refer to **Table 3** for specific results.
- Berdazimer was evaluated in three phase 3, 12-week, randomized, double-blind, placebo-controlled trials in patients with MC. In the B-SIMPLE4 trial, complete clearance of all MC lesions at 12 weeks was observed in a greater proportion of patients treated with berdazimer 10.3% topical gel compared to people treated with placebo (32.4% vs. 19.7%, respectively; treatment difference 12.7%; p < 0.001; low-quality evidence).[4,5,7] In 2 other trials, berdazimer failed to reach statistical significance in the primary outcome measure of MC lesion clearance compared to placebo.[5,7]
- Adverse reactions that were reported in clinical trials (≥1%) for both cantharidin and berdazimer included, but were not limited to, pain, vesicle formation, pruritus, erythema, and skin discoloration (**Table 8** summarizes specific adverse events).[2-7]

Recommendations:

- Create a new Preferred Drug List (PDL) class for agents to treat molluscum contagiosum.
- Add cantharidin topical solution 0.7% (YCANTH) and berdazimer gel 10.3% (ZELSUVMI) to the Molluscum Contagiosum Drugs PDL class.
- Implement PA criteria for cantharidin and berdazimer to establish specific medical necessity and appropriateness criteria for members with the Early Periodic Screening Diagnostic and Treatment (EPSDT) Benefit.

Background:

Molluscum contagiosum is a common, highly contagious, benign skin infection caused by a DNA poxvirus.[8,9] MC is commonly observed in younger children but may also occur in older children and adults.[8,9] Prevalence of MC for children in the United States is estimated to be less than 5% (roughly 8% worldwide) with the largest incidence in children aged 0 to 14 years.[8,9] There do not appear to be gender differences in the frequency of MC infection.[9] Transmission of the virus can occur via autoinoculation, through close physical contact with an infected individual, or by passive vector.[10] The risk for MC infection may be higher in immunocompromised patients or in warm, moist areas where the virus tends to thrive such as community swimming pools or day care centers, and during close physical contact.[8,11] Some research has identified that atopic dermatitis may be a risk factor for MC, but the relationship is uncertain.[12] Once infected, the incubation period ranges from 2 to 6 weeks.[11] Most cases of MC are self-limiting and will resolve without treatment in 6 to 18 months but some cases may persist for years.[8,9,11]

Molluscum contagiosum is characterized by individual or multiple small flesh-colored raised papules with central umbilication or dimpled center.[8,11] The papules typically present on the trunk, axillae, and extremities except for the soles of the feet and palms of hands.[8,11] The virus may appear as a single lesion or up to 30 lesions that can range from 1 millimeter up to 1 centimeter in size.[8,11] In children, MC is more commonly found on the trunk and limbs.[8] In adults, MC may arise in the genital area and be transmitted by sexual contact.[11] Although mostly asymptomatic, patients may experience pruritus or tenderness in the affected

area(s).[8,11] Immunocompromised patients may experience more widespread, larger (≥15 mm diameter) MC lesions that extend to atypical regions such as the neck, face, and eyelids.[8,11]

MC virus (MCV) replication takes place in the cytoplasm of infected epidermal cells.[10,11,13] There are 4 different known genotypes: MCV-1, MCV-2, MCV-3, and MCV-4.[10,13] The most common genotype is MCV-1 which occurs in 76% to 97% of diagnosed individuals.[13] As infected cells mature, they increase in size and migrate to the surface.[10,11,13] Cells eventually become overrun by the virus and develop the characteristic molluscum bodies that exist in 3 or 4 layers above the basal cells themselves.[11] Molluscum contagiosum virus maturation takes place in about 5 days.[11] There is typically little to no inflammation present in undisturbed lesions which indicates that, in immunocompetent hosts, the virus is undetectable for most of the infection period.[11] However, once detected MCV elicits a powerful immune response by the host.[11,13] The presence of severe, persistent MC lesions may be indicative of advanced disease in HIV positive patients due to the depletion of CD-4 T-helper lymphocytes.[11,13]

There is no known cure for MC and there are no established care guidelines for the management of molluscum contagiosum. For non-mucosal and non-genital MC, medical procedures and pharmaceutical options are limited and have demonstrated varied levels of success.[8,11] Although evidence to support symptomatic treatment is limited, patients may seek treatment for cosmetic concerns, to reduce discomfort, lessen chance of autoinoculation, avoid viral transmission to family and friends, or to prevent secondary infections.[14] Common treatment options may include topical agents (see **Table 1**), cryotherapy, or surgical mechanical procedures to eradicate MC lesions.[8,11] Cryotherapy is liquid nitrogen applied directly to the lesion to freeze the virus.[8,11,15] Treatment via cryotherapy may require multiple applications every 2 to 3 weeks until complete resolution is attained.[8,11,15] Curettage employs the use of a small device to cut away and remove MC lesions.[8,11,15] This method may be a reasonable option in older children and adult populations in non-sensitive areas where the lesion count is minimal.[8,11,15] There is a potential for pain, bleeding, blistering, scarring and/or and dyspigmentation associated with cryotherapy and curettage. [8,11,15] Another mechanical method known as pulsed dye laser therapy may be used as a second-line option for difficult-to-treat MC, but the potential for skin discoloration and relatively high cost greatly limits its widespread use.[11,15] There have been few randomized controlled trials (RCTs) of topical agents to treat MC lesions. Imiquimod 5% cream has been studied for off-label treatment of MC lesions in adult patients who were refractory to previous therapy, but the data to support efficacy were mixed and inconclusive.[1,16] Selected off-label drug therapies and non-pharmacologic treatments are summarized in **Table 1.** [1,8,11]

Table 1. Non-pharmacologic and Off-Label Drug Interventions for Molluscum Contagiosum[1,8,11]

Intervention	Protocol	Common Adverse Effects
Cryotherapy	Liquid nitrogen applied to each lesion for 10-20 seconds for 1 or 2 cycles; may repeat after 1 week	Pain, burning, dyspigmentation, erythema, vesicles/bullae, scarring
Curettage	Scraping away of lesions via curette	Pain, anxiety, bleeding, scarring
Pulsed dye laser	Each lesion receives single pulse; may repeat after 2-3 weeks	Pain, pruritus, dyspigmentation
Benzoyl peroxide 10% cream	Applied to each lesion twice daily for 4 weeks	Mild dermatitis
Cimetidine	Oral dose 40 mg/kg daily in 2 or 3 divided doses for 2 months	Drug interaction potential
Imiquimod 5% cream	Applied to skin for 8 hours duration then washed off; repeat 3 to 5 times weekly until resolution for up to 16 weeks	Pain, burning, erythema, pruritus, ulceration, dyspigmentation
Phenol 10%	Lesions pierced with sharp instrument laced with phenol	Scarring
Podophyllotoxin 0.3-0.5% cream	Applied twice daily for 3 days, wait 4 days, then repeat. Continue for up to 4 weeks.	Erythema, pruritus

Potassium hydroxide aqueous solution 5-10%	Apply to lesions with cotton swab twice daily until superficial ulceration/inflammation	Dyspigmentation, mild stinging
Retinoic acid 0.5% cream	Applied to each lesion twice daily for 4 weeks	Mild dermatitis
Salicylic acid gel 12%	Applied to each lesion once or twice weekly for 4 weeks	Mild pain, stinging

There are 2 FDA-approved topical medications that can be used to treat MC lesions: cantharidin solution and berdazimer gel.[2,4] **Table 2** is a summary of the FDA-approved indications and dosing for berdazimer gel and cantharidin topical solution.[2,4]

Table 2. Indications and Dosing of Cantharidin and Berdazimer.[2,4]

Drug Name (Trade name)/ Manufacturer	Indication(s)	Strength/Route	Dose and Frequency
Cantharidin (YCANTH)/ Verrica Pharmaceuticals	Topical treatment of molluscum contagiosum in adult and pediatric patients 2 years of age and older.	0.7% Topical solution	Apply a single application 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.
Berdazimer (ZELSUVMI) EPIH SPV	Topical treatment of molluscum contagiosum in adults and pediatric patients 1 year of age and older	10.3% Topical gel	Mix together per dosing guide and immediately apply a thin layer once daily to each molluscum contagiosum lesion for up to 12 weeks.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings, and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), Scottish Intercollegiate Guidelines Network (SIGN), and Oregon Mental Health Clinical Advisory Group (MHCAG) 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 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 - Interventions for Cutaneous Molluscum Contagiosum[1]
The use of topical and systemic interventions used to treat molluscum contagiosum lesions in children and adults was evaluated in a 2017 Cochrane review.[1] There were 22 studies identified (N=1650) that compared interventions (topical, surgical, systemic, or combination treatments) versus placebo (or waiting for natural

resolution) in immunocompetent patients with cutaneous, non-genital molluscum contagiosum.[1] Cantharidin and berdazimer were not included in the review. The primary outcome was short-term clinical cure (defined as complete clearance) of MC lesions up to 3 months after start of treatment.[1] Medium and long-term clinical cure rates, recurrence, adverse effects, and disease-related quality of life were assessed as secondary outcomes.[1]
Most studies had insufficient information to assess risk of bias and had unclear risk of bias related to allocation concealment and selective reporting.[1] Only 5 of the studies had low risk of bias, and the majority of included studies involved imiquimod 5% topical cream.[1] Imiquimod 5% topical cream was similar to placebo for the outcome of short-term clinical cure based on moderate quality evidence.[1] Low quality evidence demonstrated that 5% imiquimod was less effective than cryotherapy for short-term clinical cure.[1] Imiquimod 5% topical treatment had higher rates of application site reactions (e.g. pain, erythema, burning, etc.), but treatment did not lead to serious adverse effects (moderate-quality evidence).[1] There was insufficient evidence to assess differences between various treatments or for other drugs used off-label to treat MC lesions.[1]

After review, 2 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).[17,18]

Guidelines:
High Quality Guidelines:
None identified.

Randomized Controlled Trials:
A total of 63 citations were manually reviewed from the initial literature search. After further review, 61 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in **Table 2** and **Table 3**. Full abstracts are included in **Appendix 2**.

Cantharidin 0.7% solution (YCANTH™) for topical treatment is a drug-device combination product approved to treat MC in patients 2 years of age and older.[2] Cantharidin is a naturally occurring terpenoid compound extracted from the blister beetle which has been used medicinally to treat MC for over 70 years, but until recently was never formally approved by FDA for that indication.[19] Cantharidin acts as a vesicant but its mechanism in the treatment of MC lesions is unknown.[3,6] FDA approval was obtained with data from two identical, phase 3, randomized, double blind, placebo vehicle-controlled, multicenter trials conducted over 12 weeks (CAMP-1 and CAMP-2).[2,3,6] Patients were treated once every 3 weeks until complete lesion clearance was achieved or a maximum of 4 applications was administered.[3,6] The primary efficacy endpoint was the proportion of cantharidin-treated participants achieving complete clearance of all treatable baseline and new molluscum lesions after 12 weeks.[3,6] Enrolled patients were mostly 11 years of age or younger (~90%) with a mean age of 7.5 years, White (~90%), and had a mean of 22 and 19 MC lesions at baseline for the two trials.[3,6] There were equal proportions of male and female participants.[3,6] About 16% of participants had a history of atopic dermatitis, and over 50% of the patients required at least 4 treatments.[3,6] Over the 2 trials, cantharidin 0.7% topical solution demonstrated a 30-40% difference in the proportion of patients who achieved complete clearance of MC lesions compared to patients treated with placebo vehicle (low-quality evidence).[2,3,6] Additional details regarding CAMP1 and CAMP-2 trials may be found in **Table 3** below.

Table 3. Cantharidin Clinical Trials Summary [3,6]

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
CAMP-1 (N=266)		Male and female patients at least	Difference in proportion of patients who achieved	Cantharidin: 46% Vehicle: 18%	Trials used total body lesion count, so the number of treatments needed

CAMP-2 (N=262)	Cantharidin topical solution 0.7% vs. placebo vehicle	2 years of age diagnosed with MC.	complete clearance of all treatable baseline and new molluscum lesions at week 12 (day 84).	MD: 29% (95% CI 19% to 38%); P<0.001 Cantharidin: 54% Vehicle: 13% MD: 40% (95% CI 30% to 51%); P<0.001	for clearance per lesion is unknown (individual molluscum lesions were not tracked). Long-term efficacy and safety of cantharidin use beyond 12 weeks in the treatment of MC is unknown.

Berdazimer 10.3% topical gel (ZELSUVMI) is approved for the treatment of MC in patients at least 1 year of age.[4] Berdazimer sodium gel when mixed with a proton-donating hydrogel is a nitric oxide-releasing agent.[4,5] The mechanism of action for berdazimer gel in the treatment of MC is unknown.[4,5,7] FDA approval was obtained with data from three phase 3, randomized, double-blind, vehicle-controlled trials in patients with MC over 12 weeks (Trials B-SIMPLE1/B-SIMPLE2/B-SIMPLE4).[5,7] The primary endpoint was the difference in the percentage of patients treated with berdazimer achieved complete clearance of all treatable MC lesions (lesion count = 0) at week 12 compared to placebo vehicle.[4,5,7] The mean age of participants was 6.5 years, most were White (85.5%), with roughly equal representation of males and females.[5,7] In B-SIMPLE4, the baseline MC lesion count was slightly higher in the berdazimer gel group compared to vehicle (23.1 and 20.5, respectively).[5,7] In the B-SIMPLE4 trial, complete clearance of all MC lesions at 12 weeks was observed in a greater proportion of patients treated with berdazimer 10.3% topical gel than vehicle recipients (32.4% vs. 19.7%, respectively; treatment difference 12.7%; p < 0.001; low-quality evidence).[4,5,7] Trials B-SIMPLE1 and B-SIMPLE2 failed to reach statistical significance in the primary outcome measure.[5,7] Details regarding B-SIMPLE trials 1, 2, and 4 may be found in **Table 4.** Although the observed treatment effect in the B-SIMPLE1 and B-SIMPLE2 trial was smaller than in the B-SIMPLE4 trial, the FDA recommended approval based on results of a post-hoc sensitivity analysis and a treatment effect trending in favor of the berdazimer gel.[5]

Table 4. Berdazimer Clinical Trials Summary [5,7]

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
B-SIMPLE1 (N=352)	Berdazimer gel 10.3% vs. placebo vehicle	Male and female patients 6 months and older with 3 to 70 MC lesions	Difference in proportion of patients who achieved complete clearance of all treatable MC lesions (lesion count = 0) at week 12	Berdazimer: 25.8% Vehicle: 21.6% MD: 4.3% (95% CI -5% to 18.6%); P=0.3637 *Not Statistically Significant*	Two of the 3 trials did not demonstrate efficacy on the primary endpoint. Efficacy in patients with sexually transmitted MC is unknown. Concomitant use with other topical therapies for MC was not evaluated. Long-term efficacy and safety of berdazimer use beyond 12 weeks in the treatment of MC is unknown.
B-SIMPLE2 (N=355)				Berdazimer: 30% Vehicle: 20.3% MD: 9.2% (95% CI -0.04% to 18.4%); P=0.0510 *Not Statistically Significant*	
B-SIMPLE4 (N=891)				Berdazimer: 32.4% Vehicle: 19.7% MD: 12.7% (95% CI 7.1% to 18.6%); P<0.0001	

Abbreviations: MD = mean difference; MC = molluscum contagiosum

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Appendix 1: Specific Drug Information

Table 5. Clinical Pharmacology and Pharmacokinetics of Cantharidin and Berdazimer.[2-5]

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
Cantharidin (YCANTH)	Cantharidin is a vesicant; the mechanism of action in the treatment of molluscum contagiosum is unknown.	Children 2 to 15 years of age: Systemic absorption negligible.	N/A	• Half-life: N/A • Cmax: N/A • AUC: N/A • Vd: N/A
Berdazimer (ZELSUVMI)	Berdazimer is a nitric oxide–releasing agent. The mechanism of action for the treatment of molluscum contagiosum is unknown.	Minimal to no systemic absorption.	N/A	• Half-life: N/A • Cmax: N/A • AUC: N/A • Vd: N/A

Table 6. Use in Specific Populations for Cantharidin and Berdazimer.[2,4]

Drug Name	Pregnancy	Lactation	Pediatric Use	Geriatric Use
Cantharidin (YCANTH)	There are no available data to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. No animal reproduction studies were conducted. Systemic exposure to drug following topical administration was low; therefore, maternal use is not expected to result in fetal exposure to cantharidin.	Avoid application to areas with increased risk for potential ingestion by or ocular exposure to the breastfeeding child. There are no data on the presence of cantharidin in either human or animal milk, or the effects on the breastfed infant or on milk production. Breastfeeding not expected to result in exposure of the child to the drug due to the low systemic absorption.	For use in patients 2 years of age and older.	Drug has not been studied in geriatric patients.
Berdazimer (ZELSUVMI)	There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of berdazimer to pregnant rats and rabbits increased malformations in the presence of severe maternal toxicity.	There are no data on the presence of the drug or its metabolite in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for the drug and any potential adverse effects on the breastfed infant or from the underlying maternal condition.	For use in pediatric patients 1 year of age and older.	Clinical studies did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

Drug Safety:

Table 7. Warnings and Precautions for Cantharidin and Berdazimer.[2,4]

Drug Name	Warning/Precaution
Cantharidin (YCANTH)	-**For topical use only**. Not for oral, mucosal, or ophthalmic use. Life threatening or fatal toxicities can occur if administered orally. -**Local skin reactions**. Avoid application near the eyes and mucosal tissues, and to adjacent healthy skin. Avoid other topical products (e.g. creams, lotions, or sunscreen) on treated areas until 24 hours after treatment or until washing. If severe blistering, severe pain or other severe adverse reactions occur, remove prior to the recommended 24 hours after administration by washing with soap and water. -**Flammable liquid** (even after drying). Avoid fire, open flames, or smoking near lesion(s) during treatment and after application until removed.
Berdazimer (ZELSUVMI)	-**Application Site Reactions**. Application site reactions, including allergic contact dermatitis, have occurred in patients treated with this agent. Suspect allergic contact dermatitis in the event of pain, pruritus, swelling or erythema at the application site lasting longer than 24 hours. If allergic contact dermatitis occurs, discontinue drug and initiate appropriate therapy.

Table 8. Adverse Reactions Reported in Clinical Trials (Incidence ≥1%) for Cantharidin and Berdazimer.[2,4]

Description		**Cantharidin**	**Berdazimer**
Occurred at Application Site	Pain	x	x
	Vesicles	x	x
	Pruritus	x	x
	Scab	x	
	Erythema	x	x
	Discoloration	x	x
	Dryness	x	
	Edema/Swelling	x	
	Erosion	x	
	Exfoliation		x
	Dermatitis		x
	Irritation		x
	Infection		x
Pyrexia			x
Contact dermatitis		x	
Vomiting			x
Upper Respiratory Tract Infection			x
Pain		x	
Pruritus		x	
Scab		x	
Erythema		x	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 6, 2025
1) berdazimer.mp./24
2) exp Cantharidin/901
3) exp Molluscum Contagiosum/1564
4) 1 or 2/923
5) 4 and 5/62

Appendix 3: Key Inclusion Criteria

Population	Adults and children with molluscum contagiosum
Intervention	Topical therapies: Cantharidin, Berdazimer
Comparator	Placebo or active treatment
Outcomes	Molluscum lesion reduction, adverse reactions
Timing	Not applicable
Setting	Outpatient therapy

Molluscum Contagiosum

Goal(s):

- Ensure that medications for molluscum contagiosum (MC) are used appropriately for OHP-funded conditions.
- Define medically appropriate and necessary therapy supported by the medical literature for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 weeks

Requires PA:

- Cantharidin (pharmacy and provider administered claims) and berdazimer for pharmacy claims.

Table 1. FDA-Approved Dosing

Product Name (BRAND NAME)	Indication	Dosing and Duration	Maximum Duration
Cantharidin (YCANTH)	Topical treatment of molluscum contagiosum in adults and pediatric patients 2 years of age and older.	Apply a single application directly to each lesion every 3 weeks as needed; do not use more than 2 applicators during a single treatment session.	4 treatments
Berdazimer (ZELSUVMI)	Topical treatment of molluscum contagiosum (MC) in adults and pediatric patients 1 year of age and older.	Apply a thin even layer once daily to each lesion	12 weeks

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 for the age and diagnosis submitted?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review, Pass to RPh. Deny; not funded by the OHP. If eligible for EPSDT Review, Go to #4
4. Have the patient's lesions been present and unresolved for 6 months or longer?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Have the patient's lesions been previously treated with the requested agent?	**Yes:** Go to #6	**No:** Go to #7
6. Has the patient already received the maximum duration of therapy recommended in **Table 1**? • 4 or more treatment doses of cantharidin OR • 12 or more weeks of berdazimer	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is the requested agent being prescribed by or in consultation with a dermatologist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the provider performed an objective baseline assessment and determined one of the following: • The molluscum contagiosum lesions are extremely troublesome (e.g. pain, itching, etc.) OR • Patient is immunocompromised.	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the requested agent being used to treat lesions in or near the mouth, eyes, or mucosal tissues?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the agent requested being used in combination with another treatment modality for MC (e.g. cryotherapy, curettage, or another agent listed in **Table 1**)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 weeks Cumulative treatment not to exceed 12 weeks of therapy.

P&T/DUR Review: 6/25 (DE)
Implementation: TBD

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Prior Authorization Criteria Update: Nutritional Supplements

Plain Language Summary:

- Herbal and nutritional supplements are regulated and tested differently than medicines approved by the Food and Drug Administration. Nutritional supplements available as tablets or capsules are not covered by the Oregon Health Plan as medicines.
- Inborn errors of metabolism are conditions where a person cannot properly break down food. These conditions cause harm to a person because they are unable to clear certain food components from the body.
- For patients with some inborn errors of metabolism it is necessary for health to take specific nutritional supplements.
- We recommend that the Oregon Health Plan pay for specific nutritional supplements when members have an inborn error of metabolism.

Purpose of Update:

Oral pharmaceutical dosage forms (e.g., tablets, capsules, drops) of nutritional supplements are not regulated the same as Food and Drug Administration approved medications.[1] Vitamins, minerals, herbs and botanicals, amino acids, other supplements intended increase dietary intake of a substance, and concentrates, metabolites, and extracts can fall into this category.[1] Occasionally a product will go through the FDA approval pathway to be considered a drug (usually prescription) while other forms of the product are marketed as supplements. Levocarnitine is an example of this situation.[2] The Oregon Health Plan covers enteral and oral nutritional formula for members with conditions described in OAR 410-148-0260 (**Table 1**). However, this policy excludes oral pharmaceutical dosage forms.

Urea cycle disorders and other inborn errors of metabolism inhibit the body's ability to properly metabolize food by defects or absence of specific enzymes.[3,4] This results in buildup of toxic byproducts and significant morbidity. There is evidence to support chronic use of some nutritional supplements to bypass these metabolic defects, but some of these supplements are not covered by the Oregon Health Plan. Several drug-diagnoses combinations have been identified for initial inclusion in this policy. Drugs for urea cycle disorders are expected to be used with dietary protein restriction and, in some cases, supplementation with arginine and citrulline.[5-8] Carnitine deficiency can result from primary disorders of carnitine metabolism or secondarily from other conditions such as fatty acid oxidation disorders.[2] Several rare disorders of amino acid metabolism may be treated with creatine and specific amino acids such as glycine or ornithine.[9]

This policy outlines proposed coverage requirements for nutritional supplements that are available as oral dosage forms if FDA approved versions do not exist or are unavailable in an appropriate dosage for the required dose, but which are evidence based and necessary as standard of care. Products in this category may currently be allowed as part of the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) program.[10] Coverage expansion beyond the EPSDT benefit may require expansion of Oregon Health Authority state plan coverage.

Author: Sara Fletcher, PharmD, MPH, BCPS June 2025

Table 1. Approved conditions for nutritional deficiencies (OAR 410-148-0260)

Diagnosed acute or chronic malnutrition
Documentation of weight, either currently or historically, supported by oral nutritional supplements
Increased metabolic need resulting from severe trauma
Malabsorption difficulties (e.g., short-gut syndrome, fistula, cystic fibrosis, renal dialysis)
Inborn errors of metabolism (e.g., fructose intolerance, galactosemia, maple syrup urine disease [MSUD], or phenylketonuria [PKU])
Ongoing cancer treatment, advanced Acquired Immune Deficiency Syndrome (AIDS) or pulmonary insufficiency
Oral aversion or other psychological condition making it difficult for a client to consume their recommended caloric/protein or micronutrient needs through regular, liquified, blenderized, or pureed foods in any modified texture or form

Recommendation:

- Recommend OHA consider adding coverage for oral solid dosage forms, powders, and concentrated liquids of nutritional supplements for people with inborn errors of metabolism. Liquids used as enteral nutrition formulas are covered under other policies.
- Implement prior authorization to limit coverage to specific nutritional supplements based on current standards of care for those eligible with the EPSDT benefit.

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Appendix 1. Proposed Prior Authorization

Nutritional Supplements as Prescribed Drugs for Special Conditions

Goal(s):

- Provide a pathway to coverage for non-rebatable nutritional supplement oral dosage forms for special conditions in OAR 410-148-0260
- Limit use to diagnoses where there is sufficient evidence of benefit.

Length of Authorization:

- 12 months with life-long auto approval for continued treatment.

Requires PA:

- Oral solid dosage forms (e.g., tablets, capsules), powders, and low volume liquids* of nutritional supplements in HIC3 = C5C, C5F, C5G, C5U, C5B, C5X that are not covered by other policies.

Covered Alternatives:

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

Table 1. Included Nutritional supplements with oral dosage form

Supplement	Conditions
Arginine or L-arginine	• Creatine transporter (CRTR) deficiency (ICD10 E72.8) • Urea cycle disorders (various; ICD10 E72.2x)
Carnitine or L-carnitine	• Fatty acid oxidation disorders with secondary carnitine deficiency (various; ICD10 E71.3x) • Disorders of carnitine metabolism (various; ICD10 E71.4x)
Creatine	• Arginine:glycine amidinotransferase (AGAT) deficiency (ICD10 E72.8) • Guanidinoacetate methyltransferase (GAMT) deficiency (ICD10 E72.8) • Creatine transporter (CRTR) deficiency (ICD10 E72.8)
Citrulline or L-citrulline	• Urea cycle disorders (various; ICD10 E72.2x)
Glycine	• Creatine transporter (CRTR) deficiency (ICD10 E72.8)
Ornithine	• Guanidinoacetate methyltransferase (GAMT) deficiency (ICD10 E72.8)

Author: Fletcher June 2025

Table 2. Approved conditions for nutritional deficiencies (OAR 410-148-0260)

Diagnosed acute or chronic malnutrition
Documentation of weight, either currently or historically, supported by oral nutritional supplements
Increased metabolic need resulting from severe trauma
Malabsorption difficulties (e.g., short-gut syndrome, fistula, cystic fibrosis, renal dialysis)
Inborn errors of metabolism (e.g., fructose intolerance, galactosemia, maple syrup urine disease [MSUD], or phenylketonuria [PKU])
Ongoing cancer treatment, advanced Acquired Immune Deficiency Syndrome (AIDS) or pulmonary insufficiency
Oral aversion or other psychological condition making it difficult for a client to consume their recommended caloric/protein or micronutrient needs through regular, liquified, blenderized, or pureed foods in any modified texture or form

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a member with the EPSDT benefit?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; product not covered by OHP.
3. Is the product requested for a relevant diagnosis in Table 1?	**Yes**: Approve for 12 months	**No:** Go to #4
4. Does the patient have an inborn error of metabolism? Examples include, but are not limited to: fructose intolerance, galactosemia, maple syrup urine disease, phenylketonuria, urea cycle disorders (e.g., arginase deficiency, argininosuccinate lyase deficiency, etc.)	**Yes:** Go to #5	**No:** Go to #6
5. Is the request by, or in consultation with, a prescriber specializing in inborn errors of metabolism (e.g., medical geneticist)?	**Yes:** Approve for 12 months Please forward to Oregon DMAP for potential modification of Table 1.	**No:** Go to #7

Approval Criteria		
6. Is there documentation of a condition specified in Table 2?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical necessity.
7. All other drug-diagnoses combinations must be evaluated for evidence for clinical benefit and documentation that currently covered nutritional supplements are inappropriate. If the provider supplies evidence to support medically necessary and appropriate treatment, the pharmacist may use clinical judgement to APPROVE for 1 month starting today to allow time for appeal. Message "Although the request has been denied for long term use because oral solid, powder, and low volume liquid* nutritional supplements are not covered by the Oregon Health Plan, it has also been APPROVED for one month to allow time for appeal." 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).		

** Intended to refer to drops, suspensions, and other liquid dosage forms for a product that includes one or few individual specific nutritional components, not liquid enteral nutrition which is meant to provide the majority of dietary intake. Enteral nutrition is covered under the general "Nutritional Supplements" prior authorization.*

P&T/DUR Review: 6/25 (SF)
Implementation: TBD

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New Drug Evaluation: Dextromethorphan/Quinidine (NUEDEXTA), capsules

Date of Review: June 2025
Generic Name: dextromethorphan Hbr/quinidine

End Date of Literature Search: 02/14/2025
Brand Name (Manufacturer): NUEDEXTA (Avanir Pharmaceuticals, Inc)

Dossier Received: no

Plain Language Summary:

- This review looks at the evidence for the use of NUEDEXTA (dextromethorphan/quinidine) for management of pseudobulbar affect.
- People with pseudobulbar affect have uncontrollable emotional outbursts such as laughing or crying that do not match the person's mood or situation. This condition often happens after damage to the brain from a stroke, multiple sclerosis, amyotrophic lateral sclerosis, dementia, or traumatic brain injury.
- Only one medicine, the combination of dextromethorphan 20 mg and quinidine 10 mg, is Food and Drug Administration approved to treat pseudobulbar affect. A study in people with multiple sclerosis and amyotrophic lateral sclerosis showed that those taking the medication had less laughing and crying episodes than those taking the placebo.
- Side effects reported with dextromethorphan/quinidine include diarrhea, vomiting, flu-like symptoms, dizziness, cough, and gas.
- Providers must explain to the Oregon Health Authority why someone needs the combination product dextromethorphan/quinidine. This process is called prior authorization.

Research Questions:

1. What is the evidence for efficacy of the combination product dextromethorphan/quinidine for the treatment of pseudobulbar affect (PBA)?
2. What is the evidence for the safety of dextromethorphan/quinidine in the treatment of PBA?
3. Are there subpopulations of adults (i.e., age, gender, ethnicity, disease duration or severity) for whom dextromethorphan/quinidine is more effective or associated with more harms?

Conclusions:

- A 12-week, double-blind randomized controlled trial (RCT) conducted at 60 centers in the United States and South America evaluated the efficacy and safety of dextromethorphan 20 mg/quinidine 10 mg compared with placebo in people with PBA and multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS).[1] The primary efficacy outcome was a patient's change from baseline in the number of PBA episodes (laughing and/or crying) per day, as recorded in the patient's daily diary.[1] The 12-week mean change in daily episode rate was −3.9 for dextromethorphan/quinidine versus −3.0 for placebo (difference = 0.9 points; 95% confidence interval not reported; p=0.0048; low-quality evidence).[1] A minimal clinically effective difference has not been established for this outcome. Additional study details are presented in **Table 2**.

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- The most frequently reported adverse events reported in this 12-week RCT included diarrhea, dizziness, cough, vomiting, asthenia, and peripheral edema (moderate-quality evidence). See **Table 1** for adverse event rates compared to placebo.[2] There were no proarrhythmic events reported and changes from baseline in QT interval were mild (no greater than 60 msec) in patients who received dextromethorphan/quinidine.[1] Of note, patients with any clinically significant abnormality on the electrocardiogram or with a family history of a congenital prolonged QT interval syndrome were excluded from the study.
- The study was only conducted in adults aged 18 to 80 years of age with PBA attributed to ALS or MS. There is insufficient evidence to assess the efficacy of dextromethorphan/quinidine in people with PBA due to other neurologic conditions.

Recommendations:
- Implement prior authorization (PA) criteria for dextromethorphan/quinidine to define medical necessity under Early Periodic Screening Diagnostic and Treatment (EPSDT) Benefit.
- Maintain designation of dextromethorphan 20 mg/quinidine 10 mg as nonpreferred on the Prioritized Drug List (PDL).

Background:
Pseudobulbar affect is a neurologic condition characterized by involuntary outbursts of laughing or crying that is incongruous or disproportionate for the patient's emotional state.[3] This condition is associated with underlying neurodegenerative diseases, including stroke, traumatic brain injury, Parkinson's disease, Alzheimer's disease, ALS, and MS.[1] Pseudobulbar affect is thought to occur as a result of injury or disease that disrupts pathways regulating emotional expression, or affect, including the corticobulbar tracts and basal ganglia.[4] Prevalence studies have reported that PBA affects 11% of patients 1 year after a stroke,[5] 11% of patients during the first year after traumatic brain injury,[6] 18% of patients with Alzheimer disease,[7] 10% of patients with MS,[8] and 49% of patients with ALS.[9] In addition to the effects of the underlying disorder, PBA can have a severe impact on well-being and social functioning and can be highly disabling, in part due to the stigma attached to loss of emotional control.[1] Differentiating PBA from other common mood disorders, such as depression, anxiety, and bipolar disorder, can be challenging for clinicians, contributing to its high rate of misdiagnosis and leading to ineffective and insufficient treatment.[10] Researchers found that 41% of individuals with PBA symptoms who discussed their inability to control emotional responses during clinical visits were diagnosed and only 52% of those received treatment.[11] Pseudobulbar affect (ICD-10 code F48.2) is not currently funded on the 2025 Health Evidence Review Commission (HERC) Prioritized List.[12] In 2024, approximately 65 people enrolled in the Oregon Health Plan (OHP) Fee-for-Service (FFS) program had a diagnosis of PBA.

A 2022 systematic review evaluated the benefits and harms of pharmaceutical treatment in people with unpredictable crying or laughing after a stroke.[13] Five RCTs involving 213 people met inclusion criteria.[13] Low-quality evidence showed off-label use of antidepressants may reduce the frequency and severity of crying or laughing episodes when compared to placebo.[13] Despite lack of substantial clinical evidence supporting their use for PBA, the serotonergic actions of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) seem to reduce the frequency of PBA episodes by increasing serotonin activity.[10]

In the randomized controlled trial (RCT) evaluating the efficacy of dextromethorphan 20 mg/quinidine 10 mg, 3 patient-reported assessments were used as secondary endpoints.[1] The Center for Neurologic Study-Lability Scale (CNS-LS) is a patient-reported measure of affective lability that was first used in people with ALS.[14] The reliability of this tool was evaluated in a total of 99 patients with ALS[14] and 90 patients with MS.[15] The 7-item questionnaire is composed of two subscales measuring labile laughter (4 items) and labile tearfulness (3 items).[14] Each item is rated on a scale from 1 (applies never) to 5 (applies most of the time).[16] The total score is calculated as the sum of the item values that resulted in a score ranging from 7 (no symptoms) to 35 (maximum symptom severity and frequency).[16] The American Academy of Neurology (AAN) considers this assessment as possibly effective and may be considered for screening in people with MS (weak recommendation; moderate-quality evidence).[16] The Beck Depression Inventory-II (BDI-II) is a 21-item self-assessment of symptoms of depression.[16] A

total score of 14–19 is considered mild, 20–28 is moderate, and 29–63 is severe.[1] The Neuropsychiatric Inventory (NPI) is a caregiver questionnaire covering 12 neuropsychiatric symptom domains; it provides a brief, informant-based assessment of neuropsychiatric symptoms and caregiver distress.[17] This tool was validated in 60 patients with Alzheimer's Disease.[17] The NPI severity score is based on a 4-point scale (0=absent, 1=mild to 3 = severe).[1] Minimal clinically important differences have not been determined for any of the 3 assessments used in this trial.

A 2009 guideline issued by the AAN stated that dextromethorphan 20 mg/quinidine 10 mg is probably effective for treatment of PBA in people with ALS, although side effects may limit its usefulness (moderate recommendation; high-quality evidence).[18] No other pharmacologic agents were addressed in the guideline. Guidance issued by the AAN in 2014 provided recommendations for management of psychiatric disorders in people with MS.[16] This guidance suggests that dextromethorphan/quinidine is possibly effective and safe and may be considered for treating individuals with MS and PBA (weak recommendation; moderate-quality evidence)[16]

Several studies have evaluated the efficacy of dextromethorphan 30 mg in combination with quinidine 10 mg (this combination is not commercially available) in patients with agitation due to Alzheimer's disease.[19] A 10-week, phase 2 RCT showed a decrease in agitation as measured by a neuropsychiatric inventory-agitation and aggression scale, compared to placebo (127 subjects).[20] Based on these results, two phase 3 trials (NCT02442765 and NCT02442778) were conducted using a modified formulation of dextromethorphan with contradictory findings.[19] The full dataset from both studies is not published in any peer-reviewed journals.[19] The FDA[2] has not approved an expanded indication for use of dextromethorphan/quinidine in agitation associated with Alzheimer's disease and this indication is not listed as compendial, off-label use for dextromethorphan/qunidine in Micromedex.[21]

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:
NUEDEXTA, a combination drug containing dextromethorphan and quinidine, received FDA-approval for the treatment of PBA in 2010.[2] Quinidine is FDA-approved as an antiarrhythmic administered at doses ranging from 200 to 400 mg every 6 hours.[21] Dextromethorphan is available over the counter for use as a cough suppressant at a dose of 10 to 20 mg every 4 hours.[21] Dextromethorphan is an N-methyl-D-aspartate (NDMA) receptor antagonist and high affinity sigma-1 receptor agonist, but the mechanism of action of dextromethorphan in treating PBA is not known.[2] The addition of quinidine, an antiarrhythmic agent at therapeutic doses, is provided at subtherapeutic dosing to inhibit the rapid hepatic CYP2D6 metabolism of dextromethorphan, thereby increasing the bioavailability of dextromethorphan.[10] The starting dose of dextromethorphan 20 mg/quinidine 10 mg is one capsule once daily for 7 days.[2] After 7 days, the dose is increased to one capsule every 12 hours.[2] The clinical trial which contributes to the efficacy data for this indication is described and evaluated below in **Table 2**. Specific drug information for dextromethorphan combined with quinidine is presented in **Appendix 2** including pharmacokinetics and pharmacodynamics.

A 12-week, randomized, double-blind, placebo-controlled, 3-arm, parallel-group study conducted at 60 centers in the United States and South America evaluated the efficacy and safety of dextromethorphan/quinidine in PBA.[1] For entry, men or women 18 to 80 years old were required to have clinically significant PBA, with a score ≥13 on the CNS-LS, and a diagnosis either of ALS or MS.[1] Patients with a history of major psychiatric disorder were excluded from the trial. The authors did not report on the use of concomitant drugs that may interact with dextromethorphan or quinidine. Patients were randomized (1:1:1) to

receive placebo, dextromethorphan 30 mg/quinidine 10 mg or dextromethorphan 20 mg/quinidine 10 mg.[1] For the first treatment week, patients took a single capsule of study drug in the morning. During weeks 2 through 12, they took study drug once in the morning and once in the evening. Follow-up visits occurred at 2, 4, 8, and 12 weeks. In addition, for 1 week prior to baseline and throughout the trial, patients were required to maintain a diary recording the daily number of laughing and/or crying episodes experienced, the medications they took, and any adverse experiences.[1] The primary efficacy endpoint was the change from baseline in the number of PBA episodes (laughing and/or crying) per day, as recorded in the patient's daily diary.[1] The mean baseline was 5 PBA episodes per day. The 12-week mean change in daily episode rate was −4.1 for dextromethorphan 30 mg/quinidine 10 mg and −3.9 for dextromethorphan 20 mg/quinidine 10 mg, versus −3.0 for placebo (95% confidence interval [CI] not reported; p=0.0099 and p=0.0048, respectively).[1]

Secondary endpoints included change from baseline on CNS-LS, which was administered at baseline and at each follow-up visit, the BDI-II and the NPI, which were administered at baseline and at 12 weeks.[1] Among secondary endpoints, the 12-week mean reduction from baseline CNS-LS score was statistically significantly greater at both dextromethorphan/quinidine dosage levels than for placebo.[1] On BDI-II, mean improvement was statistically significantly greater for dextromethorphan 30 mg/quinidine 10 mg than for placebo, but not for the 20 mg/10 mg dose. On the caregiver NPI assessment, total scores showed no significant change for either dosage versus placebo (see **Table 2** for results).[1]

Trial Limitations:
This study required a baseline CNS-LS of 13 or greater in people PBA due to underlying ALS or MS.[1] Because its subjects were carefully screened, the findings should be cautiously generalized to a broader spectrum of patients with PBA due to other neurologic conditions or those with a CNS-LS score less than 12.[1] There was a substantial placebo effect on reduction of PBA episodes per day. Although the results were statistically significant, the clinical relevance of a decrease of 1 PBA episode per day is not clear. Compared with the dextromethorphan 30 mg/quinidine 10 mg group, there were higher attrition rates in the dextromethorphan 20 mg/quinidine 10mg group and placebo group due to AEs due to withdrawal of consent. The intention to treat analysis was used for outcome assessment; it is not clear how missing data were handled.

Clinical Safety:
The most frequently reported adverse events reported over 12 weeks in the RCT included diarrhea, dizziness, cough, vomiting, asthenia, and peripheral edema.[2] There were no proarrhythmic events reported and changes from baseline in QT interval were mild (no greater than 60 msec) in patients who received dextromethorphan/quinidine.[1] Of note, patients with any clinically significant abnormality on the electrocardiogram or with a family history of a congenital prolonged QT interval syndrome were excluded from the study. Seven deaths were reported, all in ALS patients.[1] All deaths were classified by an independent mortality adjudication committee as having a respiratory cause likely to be the result of progression of the underlying neurologic disease.[1] Discontinuation rates attributable to adverse events were 9.3% (10 patients) with dextromethorphan 20 mg/quinidine 10 mg, and 1.8% (2 patients) with placebo.[1] **Table 1** provides a summary of all the reported adverse events with dextromethorphan 20 mg/quinidine 10 mg in comparison with placebo.

Table 1. Adverse Drug Reactions that Occurred with Dextromethorphan/Quinidine-Treated Patients versus Placebo-Treated Patients[2]

Adverse Drug Reaction	Dextromethorphan 20 mg /Quinidine 10 mg (n=107)	Placebo (n=109)
Diarrhea	13%	6%
Dizziness	10%	5%
Cough	5%	2%

Vomiting	5%	1%
Asthenia	5%	2%
Peripheral Edema	5%	1%
Urinary Tract Infection	4%	1%
Influenza	4%	1%
Increased gamma-glutamyltransferease	3%	0%
Flatulence	3%	1%

Contraindications

Avoid concomitant use of dextromethorphan/quinidine with quinidine, quinine, or mefloquine.[2] Avoid use in patients with atrioventricular (AV) block, prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure.[2] Dextromethorphan/quinidine should not be used with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping an MAOI due to the risk of serotonin syndrome.[2] Drugs that both prolong the QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide) should not be administered concomitantly with dextromethorphan/quinidine.[2]

Drug Interactions

Use of SSRIs or TCAs with dextromethorphan/quinidine increases the risk of serotonin syndrome.[2] Dextromethorphan/quinidine inhibits CYP2D6 and may decrease the safety or efficacy of concomitant CYP2D6 metabolized drugs.[2]

Look-alike / Sound-alike Error Risk Potential: Neulasta

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Number of laughing and crying episodes
2) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in PBA episodes (laughing/crying episodes) from baseline

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. Piro et al. 2010.[1] DB, PC, MC RCT	1. Dextromethorphan 30 mg + Quinidine 10 mg one capsule PO daily x 7 days, then BID weeks 2-12. 2. Dextromethorphan 20 mg + Quinidine 10 mg one capsule PO daily x 7 days, then BID weeks 2-12. 3. Matched placebo at same dosing as active comparator Duration: 12 weeks	Demographics: -Mean age: 51 y -Female: 54% -Race/Ethnicity: White: 75% Hispanic: 19% Black: 3% Other: 2% -ALS: 61% -MS: 39% -PBA episodes per day: ~5 -Mean baseline CNS-LS score: 20 Key Inclusion Criteria: -Age 18 to 80 y with PBA -CNS-LS score ≥ 13 -Diagnosis of ALS or MS Key Exclusion Criteria: -Abnormality on ECG -FH of congenital QT syndrome -History of major psychiatric disturbance -Diagnosis of myasthenia gravis	ITT: 1. 110 2. 107 3. 109 PP: 1. 101 2. 88 3. 94 Attrition: 1. 9 (8%) 2. 19 (18%) 3. 15 (14%)	Primary Endpoint: Change from baseline in number of PBA episodes per day (ITT analysis) 1. -4.1 2. -3.9 3. -3.0 1 vs. 3: difference = 1.1; 95% CI NR; p=0.0099 2 vs. 3: difference = 0.9; 95% CI NR; p=0.0048 Secondary Endpoints: Change from baseline in CNS-LS score (range 1-35) (ITT analysis) 1. -8.2 2. -8.2 3. -5.7 1 vs. 3: difference = -2.5; 95% CI NR: p=0.0002 2 vs. 3: difference = -2.5; 95% CI NR; p=0.0113 -Change from baseline in BDI-II score (ITT analysis) 1. -1.6 2. -1.0 3. 0.02 1 vs. 3: difference = -1.58; 95% CI NR; p=0.0368 2 vs. 3: difference = -0.98; NS -Change from baseline in 4-point NPI score (ITT analysis) 1. -1.6 2. -2.6 3. -1.3 1 vs. 3: difference: 0.3; NS	NA NA NA NS NS NS	Any AE: 1.90 (82.7%) 2.84 (79.4%) 3.90 (82.6%) Serious AE: 1.8 (7.3%) 2.9 (8.4%) 3.10 (9.2%) Discontinuation due AE: 1. 6 (5.5%) 2. 10 (9.3%) 3. 2 (1.8%) 95% CI and p-values NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via computer generated process. Baseline demographics were well matched between groups. Performance Bias: Unclear. Patients and investigators blinded to treatment assignment. Method of blinding not described. Study drug and placebo supplied in blister packs of identical-looking capsules. Detection Bias: Unclear. Patients maintained a diary recording daily PBA episodes. Subjective outcome reporting increases the risk of bias. Attrition Bias: High. Higher attrition rates in 20 mg/10mg group and placebo group due to AEs and due to withdrawal of consent. ITT analysis used for outcome assessment; not clear how missing data were handled. Reporting Bias: High. Protocol available online. All outcomes reported as stated in the protocol. Statistical analysis does not include confidence interval reporting. Other Bias: High. Manufacturer funded study. Several authors reported conflicts of interest due to financial support from the manufacturer. **Applicability**: Patient: Enrolled patients had PBA and either MS or ALS, which limits PBA due to other causes (stroke, traumatic brain injury). Intervention: 20/10 mg dosing approved by FDA and available in US. Comparator: Since no medications are approved for treatment of PBA, placebo is an appropriate comparator to establish efficacy. Outcomes: Change in frequency of PBA episodes is an appropriate metric. Quality of life would be a better outcome assessment. Secondary endpoints do not have defined MCIDs and were validated in small populations of patients with MS or ALS. Setting: 60 sites in the United States and South America

				2 vs. 3: difference: 1.3; NS				

Abbreviations: AE = adverse events; ALS = amyotrophic lateral sclerosis; ARR = absolute risk reduction; BDI-II = Beck Depression Inventory; CI = confidence interval; CNS-LS = Center for Neurologic Study-Lability Scale; DB = double blind; ECG = electrocardiogram; FH = family history; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; MMSE = Mini-Mental State Examination; MS = multiple sclerosis; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NPI = Neuropsychiatric Inventory; NR = not reported; NS = not statistically significant; OL = open label; PBA = pseudobulbar affect; PC = placebo controlled; PO = oral; PP = per protocol; TBI = traumatic brain injury; y = years.

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Appendix 1: Prescribing Information Highlights

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

NUEDEXTA (dextromethorphan hydrobromide and quinidine sulfate) capsules, for oral use
Initial U.S. Approval: 2010

----------INDICATIONS AND USAGE----------
NUEDEXTA is a combination product containing dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 agonist) and quinidine sulfate (a CYP450 2D6 inhibitor) indicated for the treatment of pseudobulbar affect (PBA). (1)

----------DOSAGE AND ADMINISTRATION----------
- Starting dose: one capsule daily by mouth for 7 days. (2.1)
- Maintenance dose: After 7 days, 1 capsule every 12 hours. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: Dextromethorphan hydrobromide 20 mg/quinidine sulfate 10 mg. (3)

----------CONTRAINDICATIONS----------
- Concomitant use with quinidine, quinine, or mefloquine. (4.1)
- Patients with a history of quinidine, quinine or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions. (4.2)
- Patients with known hypersensitivity to dextromethorphan. (4.2)
- Use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping NUEDEXTA before starting an MAOI. (4.3)
- Prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure. (4.4)
- Complete atrioventricular (AV) block without implanted pacemaker, or patients at high risk of complete AV block. (4.4)
- Concomitant use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide). (4.4)

----------WARNINGS AND PRECAUTIONS----------
- Thrombocytopenia or other hypersensitivity reactions: Discontinue if occurs. (5.1)
- Hepatitis: Discontinue if occurs. (5.2)
- QT Prolongation: Monitor ECG if concomitant use of drugs that prolong QT interval cannot be avoided or if concomitant CYP3A4 inhibitors used. (5.3)
- Left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD): Monitor ECG in patients with LVH or LVD. (5.3)
- CYP2D6 substrate: Nuedexta inhibits CYP2D6. Accumulation of parent drug and/or failure of metabolite formation may decrease safety and/or efficacy of concomitant CYP2D6 metabolized drugs. Adjust dose of CYP2D6 substrate or use alternative treatment when clinically indicated. (5.4, 12.4)
- Dizziness: Take precautions to reduce falls. (5.5)
- Serotonin syndrome: Use of NUEDEXTA with selective serotonin reuptake inhibitor (SSRIs) or tricyclic antidepressants increases the risk. Discontinue if occurs. (5.6, 7.4)
- Anticholinergic effects of quinidine: Monitor for worsening in myasthenia gravis and other sensitive conditions. (5.7)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence of ≥ 3% and two-fold greater than placebo) in patients taking NUEDEXTA are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Avanir Pharmaceuticals, Inc. at 1-855-4NUEDEX (468-3339) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Desipramine: Exposure increases 8-fold. Reduce desipramine dose and adjust based on clinical response. (7.5, 12.4)
- Paroxetine: Exposure increases 2-fold. Reduce paroxetine dose and adjust based on clinical response. (7.5, 12.4)
- Digoxin: Increased digoxin substrate plasma concentration may occur. (7.6)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 6/2019

Appendix 2: Specific Drug Information

Table 3. Pharmacology and Pharmacokinetic Properties of Combination Dextromethorphan/Quinidine.[21,22]

Parameter	
Mechanism of Action	• Dextromethorphan: NMDA receptor antagonist and Sigma-1 receptor agonist: mechanism of action in PBA is unknown • Quinidine: Competitively inhibits CYP2D6 metabolism of dextromethorphan, which increases and prolongs plasma levels of dextromethorphan
Oral Bioavailability	• Bioavailability of dextromethorphan is increased ~20 fold when administered with quinidine
Distribution and Protein Binding	• Dextromethorphan: 60% to 70% protein bound • Quinidine: 80% to 89% protein bound • Volume of distribution not reported
Elimination	• Quinidine: 5 to 20% renally excreted - pH affects extent of clearance, more acidic urine increases extent of excretion
Half-Life	• Dextromethorphan: 13 hours in extensive metabolizers • Quinidine: 7 hours in extensive metabolizers
Metabolism	• Dextromethorphan: Extensive hepatic metabolism via CYP2D6 • Quinidine: Extensive hepatic metabolism via CYP3A4

Abbreviations: NMDA = N-methyl-D-aspartate; PBA = pseudobulbar affect

Dextromethorphan/Quinidine (NUEDEXTA)

Goal(s):
- To ensure appropriate drug use and restrict to indications supported by medical literature.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- NUEDEXTA (Combination of dextromethorphan 20 mg and quinidine 10 mg capsule)

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 a patient with pseudobulbar affect (involuntary outbursts of laughing or crying that are inappropriate to the patient's emotional state) associated with a chronic neurological condition (e.g., amyotrophic lateral sclerosis, multiple sclerosis, stroke, dementia, Parkinson's disease, traumatic brain injury)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient eligible for EPSDT review?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP

Approval Criteria		
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 medication prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there documentation of the number of baseline laughing or crying episodes?	**Yes:** Approve for 6 months. Document results here: Number of crying or laughing episodes per day_____ Date:_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of improvement in frequency of laughing or crying episodes from baseline as assessed by the prescribing provider?	**Yes**: Approve for 60 months.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/25 (DM)
Implementation: TBD