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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, December 4th, 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	T. Douglass (OHA)
	E. Mental Health Clinical Advisory Group Update	A. Gibler (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. The Mental Health Clinical Advisory Group	
	2. Pharmacotherapeutic Options for Treating Adolescents with Opioid Use Disorder	
	3. Medication Safety Update	
	IV. NEW BUSINESS	
1:40 PM	A. Antifungals Class Update	K. Sentena (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

2:55 PM	B. Epidermolysis Bullosa New Drug Evaluations 1. Vyjuvek® (beremagene geperpavec) New Drug Evaluation 2. Zevaskyn™ (prademagene zamikeracel) New Drug Evaluation 3. Filsuvez® (birch triterpenes) New Drug Evaluation 4. Prior Authorization Criteria 5. Public Comment 6. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
2:15 PM	C. Carbaglu® (carglumic acid) New Drug Evaluation 1. New Drug Evaluation 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:30 PM	D. Niemann-Pick Type C New Drug Evaluations 1. Miplyffa™ (arimoclomol) New Drug Evaluation 2. Aqneursa™ (levacetylleucine) New Drug Evaluation 3. Prior Authorization Criteria 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
2:50 PM	BREAK	
3:05 PM	E. Papzimeos™ (zopapogene imadenovec-drba) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
3:20 PM	F. Sohonos® (palovarotene) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
3:35 PM	G. Topicals for Inflammatory Skin Disease Class Update with New Drug Evaluations 1. Class Update/Prior Authorization Criteria 2. Anzupgo® (delgocitinib) New Drug Evaluation 3. Hyftor™ (sirolimus) New Drug Evaluation 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
4:00 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

Drug Use Research & Management Program
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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
500 Summer Street NE, E35; Salem, OR 97301-1079
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, October 2nd, 2025
1:05 PM - 4:45 PM
Via Zoom webinar

MEETING MINUTES

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

Members Present: Stacy Ramirez, PharmD; Samara Stevens, ND; Bridget Bradley, PharmD; Douglas Carr, MD; Pat DeMartino, MD; Russ Huffman, PMHNP; Tim Langford, PharmD; Cat Livingston, MD; Eriko Onishi, MD; Eddie Saito, PharmD; Jeanne Savage, MD;

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Dan Hartung, PharmD; Megan Herink, PharmD Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Trevor Douglass, DC; Lan Starkweather, PharmD; Brandon Wells; Kyle Hamilton; Michael Yu, DC; Rose Hong, PharmD Candidate

Audience: Jessica Jay*, Vertex; Carla McSpadden*, Galaderma; Kathryn Disney*, Amgen; Valerie Ng*; LEO Pharma; Adam Furman*, Sanofi; Rochelle Yang, Teva; Shannon DiBartolo*, Amgen; Rick Melby*, UCB; Erin Nowak*, Abbvie; Gary Parenteau*, Dexcom; Jenna Doerr, Artia Solutions; Connie Brooks, Galaderma; Michael Foster, Ultragenyx; Shawn Akey; Dale Fisher; Cari Hall, Merck; Lee Stout, Chiesi; Bill McDougall, Biogen; Brent Fushimi; Lewis Backus, OHA; Shauna Wick; Melissa Snider, Gilead; Gloria Zepeda, AllCare; Divine Marcelo, Amgen; Aaron Feyos, BMS; Lisa Pulver; Jennifer Lankford, Lily; Reya Nematian; Shannon Sturtevant; Lynda Finch, Biogen; Chris Ferrin, IHN; Rosalie Elliott, Umpqua Health; Oyinda; Ann Nelson; Kim-Giau Tran, Trillium; Christine Dube; Brett Freund; Matt Prokop; Courtney Cooper, OHSU; Mark Kantor, AllCare Health; Jen Tamburo; Herbeert Starr; Amy Hale, J&J; Aliethia McLeod, trillium; Drew Larson, OHSU; Jill Carroll, BMS;

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

D. Department Update provided by Andrew Gibler, PharmD

II. CONSENT AGENDA TOPICS

A. P&T Annual Report

B. CMS Annual Report

C. Iron Replacement, Oral Literature Scan
Recommendations:
- No changes to the PDL are recommended based on review of the evidence
- Maintain ferric maltol as nonpreferred on the PDL
- Evaluate costs in executive session

D. Multiple Sclerosis Literature Scan
Recommendations:
- Maintain Ocrevus Zunovo™, and Tyruko® (natalizumab biosimilar) as non-preferred and add to the **Multiple Sclerosis, Injectable Drugs** PA criteria
- No other changes to the PDL are recommended based on review of the evidence
- Based upon FDA safety alerts, revise the **Multiple Sclerosis, Oral Drugs** PA criteria to include a skin exam prior to initiation of S1P receptor modulators
- Evaluate costs in executive session

E. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Modeyso™ (dordaviprone) and Hernexeos® (zongertinib) to Table 1 in the **Oncology Agents** PA criteria
ACTION: Motion to approve, 2nd, all in favor

III. NEW BUSINESS

A. Oral Cystic Fibrosis Modulators Class Update: Megan Herink, PharmD
Recommendations:
- Maintain Alyftrek as non-preferred on the PDL
- Add to the **Cystic Fibrosis Modulators, Oral** PA criteria and update with new indications and dosing and to address appropriate step-therapy based on current guidelines
- Evaluate comparative costs in executive session

Public Comment: Jessica Jay, Vertex
ACTION: Motion to approve, 2nd, all in favor

B. Targeted Immune Modulators (TIMs) for Asthma and Atopic Dermatitis (AD) Class Update and New Drug Evaluations: Deanna Moretz, PharmD and Dan Hartung, PharmD
Recommendations:
- Update the **Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis** PA criteria to:
    - Include Ebglyss, Nemluvio, and expanded indications for dupilumab and mepolizumab

- Define coverage of Chronic spontaneous urticaria (CSU) under EPSDT
- Remove requirement for co-prescribed EpiPen for all TIMs except omalizumab
- Remove required trial of an oral immunosuppressant before initiating dupilumab for management of AD in adolescent and pediatric patients

- Maintain nemolizumab and lebrikizumab as non-preferred on the PDL
- Evaluate comparative costs in executive session

Public Comment: Carla McSpadden, Galderma; Kathryn Disney, Amgen; Valerie Ng, LEO Pharma; Adam Furman, Sanofi

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

C. Targeted Immune Modulators Class Update: Deanna Moretz, PharmD

Recommendations:

- Modify **Targeted Immune Modulators for Autoimmune Conditions** PA criteria as proposed to include expanded indications for recent FDA approvals and reflect recent recommendations from published guidelines
- Consider whether another higher efficacy treatment for UC to should be preferred along with adalimumab based upon American Gastroenterological Association 2024 guidance
- Evaluate comparative costs in executive session

Public Comment: Rochelle Yang, Teva; Shannon DiBartolo, Amgen; Rick Melby, UCB; Erin Nowak, Abbvie

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

D. Non-drug Item Evaluation of Omnipod® (tubeless insulin pump): Kathy Sentena, PharmD

Recommendations:

- Designate the OP5 as non-preferred and implement proposed **Omnipod Insulin Pump** PA criteria

ACTION: Modify renewal criteria to assess compliance instead of A1C goals; and remove quantity limit for PODs

Motion to approve, 2nd, all in favor

E. Non-drug Item Evaluation of Continuous Glucose Monitoring Devices: Sara Fletcher, PharmD

Recommendations:

- Update the **Continuous Glucose Monitoring (CGM)** PA criteria as proposed
- No changes to the PDL are recommended based on review of the evidence
- Evaluate comparative costs in executive session

Public Comment: Gary Parenteau, Dexcom

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

F. Sleep-wake Medications for Hypersomnia and Shift Work Disorder Class Update: Dave Engen, PharmD

Recommendations:

- Add all sodium oxybate formulations to the **Sleep-Wake Medication** PDL class
- Update **Sleep-Wake Medications** PA criteria as proposed and apply criteria to all sodium oxybate formulations
- Evaluate comparative costs in executive session

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

G. Antifungals Class Update
Topic Deferred

IV. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Samara Stevens, ND; Douglas Carr, MD; Pat DeMartino, MD; Russ Huffman, PMHNP; Tim Langford, PharmD; Cat Livingston, MD; Eriko Onishi, MD; Eddie Saito, PharmD

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

V. RECONVENE for PUBLIC RECOMMENDATIONS

A. Oral Iron Replacement
Recommendation: Make all single ingredient iron products costing less than $0.25 preferred. This includes formulations of:
- ferrous gluconate tablets
- iron polysaccharide complex capsules, liquid, chewable tablets, and tablets
- ferrous fumarate tablets and chew tablets
- ferrous sulfate ER tablet, solution, drops, elixir

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

B. Multiple Sclerosis
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

C. Oral Cystic Fibrosis Modulators
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

D. Targeted Immune Modulators for Asthma and Atopic Dermatitis
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

E. Targeted Immune Modulators
Recommendation: Make generic infliximab preferred (Tier 1), make one ustekinumab biosimilar (Pyzchiva®, vial and syringe) preferred, Tier 2, and make guselkumab (Tremfya®) preferred, Tier 2.
ACTION: Motion to approve, 2nd, all in favor

F. Continuous Glucose Monitors
Recommendations: Make Freestyle Libre and Dexcom preferred; make all other products non-preferred
ACTION: Motion to approve, 2nd, all in favor

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

VI. ADJOURN – Meeting concluded at approximately 4:20 p.m.

Drug Use Research & Management Program
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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: April 2024 - March 2025

Eligibility	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
Total Members (FFS & Encounter)	1,249,346	1,239,354	1,231,095	1,226,816	1,235,264	1,241,007	1,247,678	1,254,503	1,257,986	1,241,274	1,243,854	1,234,473	1,241,888
FFS Members	105,128	103,204	102,443	98,771	97,509	96,865	99,056	99,856	98,868	99,039	93,047	91,577	98,780
OHP Basic with Medicare	8,737	8,820	8,839	8,606	8,437	8,250	8,222	7,915	7,437	7,659	7,451	7,022	8,116
OHP Basic without Medicare	9,533	9,402	9,417	9,308	9,241	9,221	9,278	9,034	8,899	8,472	8,170	8,072	9,004
ACA	86,858	84,982	84,187	80,857	79,831	79,394	81,556	82,907	82,532	82,908	77,426	76,483	81,660
Encounter Members	1,144,218	1,136,150	1,128,652	1,128,045	1,137,755	1,144,142	1,148,622	1,154,647	1,159,118	1,142,235	1,150,807	1,142,896	1,143,107
OHP Basic with Medicare	106,369	106,771	106,835	107,175	107,413	106,294	103,103	98,130	90,342	82,625	80,472	75,440	97,581
OHP Basic without Medicare	67,120	66,762	66,760	66,835	66,785	66,566	66,469	66,271	65,605	64,002	63,793	62,866	65,820
ACA	970,729	962,617	955,057	954,035	963,557	971,282	979,050	990,246	1,003,171	995,608	1,006,542	1,004,590	979,707

Gross Cost Figures for Drugs	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	YTD Sum
Total Amount Paid (FFS & Encounter)	$128,355,586	$134,133,750	$121,145,505	$132,186,127	$130,472,161	$128,325,991	$141,630,007	$127,014,133	$139,379,192	$145,661,559	$132,626,468	$147,971,349	$1,608,901,829
Mental Health Carve-Out Drugs	$10,728,919	$10,949,691	$10,274,356	$11,168,297	$10,946,436	$10,689,620	$12,019,306	$10,894,746	$12,706,697	$13,016,153	$12,002,014	$13,203,563	$138,599,799
OHP Basic with Medicare	$6,918	$10,172	$13,561	$3,424	$76	$6,734	$10,098	$9,432	$1,298	$6,525	$5,748	$2,268	$76,256
OHP Basic without Medicare	$3,840,988	$3,850,749	$3,671,250	$3,895,813	$3,906,849	$3,671,626	$4,141,140	$3,642,223	$4,213,793	$4,137,994	$3,852,162	$4,170,539	$46,995,124
ACA	$6,405,522	$6,605,119	$6,178,704	$6,799,195	$6,627,150	$6,582,492	$7,361,665	$6,783,482	$7,935,666	$8,032,807	$7,336,694	$8,129,294	$84,777,789
FFS Physical Health Drugs	$2,585,546	$2,393,813	$2,307,163	$2,648,655	$2,373,131	$2,406,174	$2,326,823	$1,883,061	$2,229,083	$2,443,354	$2,310,441	$2,279,623	$28,186,868
OHP Basic with Medicare	$31,589	$35,640	$31,427	$32,220	$29,409	$27,900	$30,154	$27,450	$28,994	$29,956	$29,079	$27,655	$361,474
OHP Basic without Medicare	$839,973	$822,877	$774,930	$901,940	$759,731	$735,884	$773,194	$584,578	$661,176	$678,914	$711,053	$675,514	$8,919,764
ACA	$1,417,647	$1,297,929	$1,292,910	$1,512,234	$1,415,072	$1,406,288	$1,328,584	$1,065,968	$1,283,210	$1,372,298	$1,217,963	$1,281,406	$15,891,508
FFS Physician Administered Drugs	$1,416,784	$1,113,163	$1,290,005	$1,302,297	$1,521,940	$922,119	$1,360,147	$1,642,274	$1,247,627	$1,798,416	$1,648,753	$1,379,831	$16,643,356
OHP Basic with Medicare	$150,964	$106,581	$130,277	$127,195	$164,201	$131,847	$132,532	$86,055	$123,575	$157,370	$84,528	$102,677	$1,497,803
OHP Basic without Medicare	$267,038	$215,197	$491,581	$192,566	$295,895	$53,454	$313,663	$432,161	$191,592	$236,124	$104,334	$245,065	$3,038,670
ACA	$385,580	$356,640	$328,101	$422,186	$478,164	$461,233	$501,349	$648,395	$529,933	$747,382	$569,752	$401,758	$5,830,473
Encounter Physical Health Drugs	$86,131,260	$88,001,569	$79,046,103	$88,361,706	$87,199,579	$87,207,837	$94,552,821	$85,593,749	$92,615,294	$94,476,599	$87,550,220	$96,911,540	$1,067,648,277
OHP Basic with Medicare	$387,862	$375,696	$370,305	$391,030	$390,475	$397,938	$429,468	$352,744	$334,683	$367,973	$335,988	$353,815	$4,487,976
OHP Basic without Medicare	$18,648,154	$18,990,095	$17,207,207	$19,373,919	$19,026,731	$18,242,071	$19,945,473	$17,880,411	$19,432,695	$19,740,215	$17,820,354	$19,505,026	$225,812,350
ACA	$56,246,740	$57,519,774	$51,566,432	$57,146,435	$56,666,111	$57,569,875	$61,603,044	$56,157,377	$60,990,235	$61,146,758	$56,775,544	$62,917,788	$696,306,113
Encounter Physician Administered Drugs	$27,493,078	$31,675,515	$28,227,879	$28,705,171	$28,431,074	$27,100,241	$31,370,909	$27,000,302	$30,580,491	$33,927,036	$29,115,040	$34,196,791	$357,823,528
OHP Basic with Medicare	$1,185,675	$1,154,208	$1,045,134	$1,091,252	$1,007,178	$973,020	$1,130,483	$802,285	$802,289	$1,162,234	$857,199	$759,302	$11,970,258
OHP Basic without Medicare	$5,899,297	$5,709,433	$5,410,488	$6,248,826	$6,150,655	$5,450,494	$6,358,293	$5,339,922	$5,809,326	$5,618,587	$5,937,166	$9,419,903	$73,352,391
ACA	$16,975,843	$21,279,302	$18,790,394	$18,034,325	$17,818,817	$16,972,489	$19,837,369	$17,667,801	$19,657,199	$22,583,073	$17,537,098	$19,094,717	$226,248,428

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

Last Updated: October 24, 2025

Drug Use Research & Management Program
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Pharmacy Utilization Summary Report: April 2024 - March 2025

YTD Percent Paid Amounts

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

Last Updated: October 24, 2025

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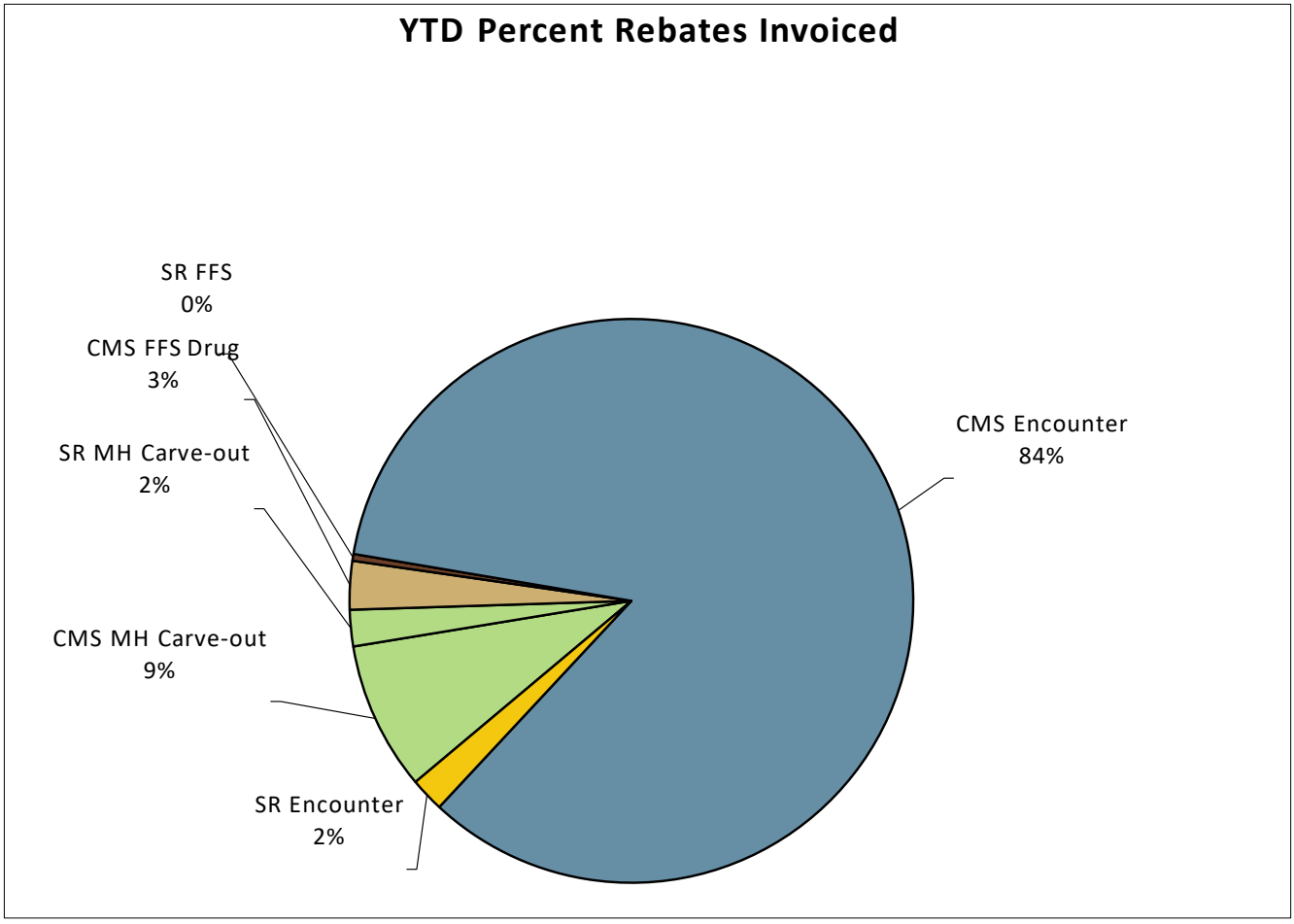
Pharmacy Utilization Summary Report: April 2024 - March 2025

Quarterly Rebates Invoiced	2024-Q2	2024-Q3	2024-Q4	2025-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$127,664,360	$121,920,376	$123,970,805	$210,250,101	$583,805,642
CMS MH Carve-out	$11,691,500	$11,618,564	$12,294,815	$14,131,432	$49,736,310
SR MH Carve-out	$2,860,832	$2,916,938	$3,355,530	$3,057,769	$12,191,070
CMS FFS Drug	$4,212,195	$4,299,266	$3,377,505	$4,330,319	$16,219,286
SR FFS	$634,385	$508,561	$481,787	$651,850	$2,276,583
CMS Encounter	$104,982,416	$99,398,231	$101,282,815	$186,330,722	$491,994,183
SR Encounter	$3,283,032	$3,178,816	$3,178,353	$1,748,009	$11,388,210

Quaterly Net Drug Costs	2024-Q2	2024-Q3	2024-Q4	2025-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$255,970,482	$269,063,903	$284,052,527	$216,009,275	$1,025,096,187
Mental Health Carve-Out Drugs	$17,400,634	$18,268,852	$19,970,405	$21,032,528	$76,672,418
FFS Phys Health + PAD	$6,259,893	$6,366,490	$6,829,723	$6,878,249	$26,334,356
Encounter Phys Health + PAD	$232,309,954	$244,428,562	$257,252,399	$188,098,497	$922,089,413



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

Last Updated: October 24, 2025

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: April 2024 - March 2025

Gross PMPM Drug Costs (Rebates not Subtracted)	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$102.74	$108.23	$98.40	$107.75	$105.62	$103.40	$113.51	$101.25	$110.80	$117.35	$106.63	$119.87	$107.96
Mental Health Carve-Out Drugs	$8.59	$8.83	$8.35	$9.10	$8.86	$8.61	$9.63	$8.68	$10.10	$10.49	$9.65	$10.70	$9.30
FFS Physical Health Drugs	$24.59	$23.19	$22.52	$26.82	$24.34	$24.84	$23.49	$18.86	$22.55	$24.67	$24.83	$24.89	$23.80
FFS Physician Administered Drugs	$13.48	$10.79	$12.59	$13.19	$15.61	$9.52	$13.73	$16.45	$12.62	$18.16	$17.72	$15.07	$14.08
Encounter Physical Health Drugs	$75.28	$77.46	$70.04	$78.33	$76.64	$76.22	$82.32	$74.13	$79.90	$82.71	$76.08	$84.79	$77.82
Encounter Physician Administered Drugs	$24.03	$27.88	$25.01	$25.45	$24.99	$23.69	$27.31	$23.38	$26.38	$29.70	$25.30	$29.92	$26.09

Claim Counts	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
Total Claim Count (FFS & Encounter)	1,311,853	1,326,145	1,213,179	1,279,636	1,250,833	1,238,322	1,339,412	1,233,469	1,318,474	1,370,286	1,243,093	1,354,761	1,289,955
Mental Health Carve-Out Drugs	213,459	214,281	196,674	213,676	208,369	205,161	222,279	204,603	221,402	229,445	209,783	228,658	213,983
FFS Physical Health Drugs	32,213	31,783	27,840	28,233	25,571	25,278	26,894	24,325	26,450	29,523	26,323	27,676	27,676
FFS Physician Administered Drugs	9,217	9,560	8,599	8,717	8,219	8,015	8,332	7,251	7,726	9,799	8,617	8,719	8,564
Encounter Physical Health Drugs	920,181	931,426	851,740	895,499	876,533	872,272	941,315	865,906	926,341	954,998	862,992	946,638	903,820
Encounter Physician Administered Drugs	136,783	139,095	128,326	133,511	132,141	127,596	140,592	131,384	136,555	146,521	135,378	143,070	135,913

Gross Amount Paid per Claim (Rebates not Subtracted)	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$97.84	$101.15	$99.86	$103.30	$104.31	$103.63	$105.74	$102.97	$105.71	$106.30	$106.69	$109.22	$103.89
Mental Health Carve-Out Drugs	$50.26	$51.10	$52.24	$52.27	$52.53	$52.10	$54.07	$53.25	$57.39	$56.73	$57.21	$57.74	$53.91
FFS Physical Health Drugs	$80.26	$75.32	$82.87	$93.81	$92.81	$95.19	$86.52	$77.41	$84.28	$82.76	$87.77	$82.37	$85.11
FFS Physician Administered Drugs	$153.71	$116.44	$150.02	$149.40	$185.17	$115.05	$163.24	$226.49	$161.48	$183.53	$191.34	$158.26	$162.84
Encounter Physical Health Drugs	$93.60	$94.48	$92.81	$98.67	$99.48	$99.98	$100.45	$98.85	$99.98	$98.93	$101.45	$102.37	$98.42
Encounter Physician Administered Drugs	$201.00	$227.73	$219.97	$215.00	$215.16	$212.39	$223.13	$205.51	$223.94	$231.55	$215.06	$239.02	$219.12

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.13	$22.20	$21.91	$22.70	$22.85	$22.86	$22.57	$22.12	$22.30	$22.20	$22.27	$22.64	$22.39
Mental Health Carve-Out Drugs	$14.20	$14.26	$14.13	$14.10	$14.05	$13.96	$13.94	$13.90	$15.29	$15.32	$15.29	$15.25	$14.47
FFS Physical Health Drugs	$24.04	$23.63	$23.40	$21.65	$23.80	$24.72	$21.59	$21.62	$20.83	$22.42	$22.68	$23.22	$22.80
Encounter Physical Health Drugs	$24.04	$24.11	$23.79	$24.94	$25.09	$25.11	$24.83	$24.25	$24.15	$23.97	$24.08	$24.54	$24.41

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$785.90	$794.60	$775.84	$812.99	$802.30	$713.19	$727.00	$753.07	$816.97	$828.59	$867.42	$867.93	$795.48
Mental Health Carve-Out Drugs	$1,437.96	$1,446.06	$1,466.19	$1,440.39	$1,446.18	$1,432.76	$1,473.50	$1,462.05	$1,511.11	$1,501.46	$1,504.78	$1,494.77	$1,468.10
FFS Physical Health Drugs	$468.25	$430.28	$466.32	$536.03	$500.21	$456.53	$480.48	$432.36	$498.82	$490.11	$522.66	$490.00	$481.00
Encounter Physical Health Drugs	$760.26	$770.47	$746.26	$784.35	$773.76	$683.84	$692.98	$721.94	$782.34	$796.10	$836.02	$837.15	$765.46

Generic Drug Use Percentage	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
Generic Drug Use Percentage	91.7%	91.7%	91.6%	91.5%	91.3%	90.1%	90.2%	90.7%	91.3%	91.5%	91.7%	91.6%	91.3%
Mental Health Carve-Out Drugs	97.5%	97.4%	97.4%	97.3%	97.3%	97.3%	97.3%	97.3%	97.2%	97.2%	97.2%	97.1%	97.3%
FFS Physical Health Drugs	87.3%	87.3%	86.6%	86.0%	85.5%	83.7%	85.9%	86.4%	86.7%	87.1%	87.0%	87.3%	86.4%
Encounter Physical Health Drugs	90.6%	90.6%	90.4%	90.3%	90.1%	88.6%	88.7%	89.3%	90.0%	90.3%	90.5%	90.4%	90.0%

Preferred Drug Use Percentage	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Avg Monthly
Preferred Drug Use Percentage	89.95%	89.91%	89.84%	88.88%	88.58%	88.52%	88.47%	88.41%	88.34%	88.44%	88.42%	88.46%	88.9%
Mental Health Carve-Out Drugs	92.53%	92.48%	92.38%	86.71%	86.67%	86.51%	86.49%	86.52%	86.36%	86.28%	86.35%	86.27%	88.0%
FFS Physical Health Drugs	94.48%	94.61%	94.60%	94.53%	94.59%	94.31%	94.46%	94.65%	94.56%	94.41%	93.68%	94.20%	94.4%
Encounter Physical Health Drugs	89.24%	89.20%	89.13%	89.26%	88.88%	88.87%	88.81%	88.72%	88.67%	88.81%	88.80%	88.86%	88.9%

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

Last Updated: October 24, 2025

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2025

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	VRAYLAR*	Antipsychotics, 2nd Gen	$6,549,027	12.6%	4,825	$1,357	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$5,898,447	11.4%	2,156	$2,736	Y
3	REXULTI*	Antipsychotics, 2nd Gen	$3,387,952	6.5%	2,445	$1,386	V
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,889,954	5.6%	1,172	$2,466	Y
5	SPRAVATO*	Antidepressants	$2,157,624	4.2%	1,637	$1,318	V
6	CAPLYTA*	Antipsychotics, 2nd Gen	$1,962,914	3.8%	1,337	$1,468	V
7	INVEGA TRINZA	Antipsychotics, Parenteral	$1,603,155	3.1%	196	$8,179	Y
8	TRINTELLIX	Antidepressants	$1,147,907	2.2%	2,447	$469	V
9	ARISTADA	Antipsychotics, Parenteral	$1,092,186	2.1%	435	$2,511	Y
10	AUVELITY	Antidepressants	$1,061,400	2.0%	1,066	$996	V
11	LYBALVI*	Antipsychotics, 2nd Gen	$842,163	1.6%	563	$1,496	V
12	BUPROPION XL	Antidepressants	$831,073	1.6%	61,028	$14	Y
13	ABILIFY ASIMTUFII	Antipsychotics, Parenteral	$745,224	1.4%	141	$5,285	Y
14	SERTRALINE HCL	Antidepressants	$731,913	1.4%	64,257	$11	Y
15	TRAZODONE HCL	Antidepressants	$664,608	1.3%	54,704	$12	V
16	ESCITALOPRAM OXALATE	Antidepressants	$633,227	1.2%	50,006	$13	Y
17	FLUOXETINE HCL	Antidepressants	$633,023	1.2%	50,219	$13	Y
18	DULOXETINE HCL	Antidepressants	$632,155	1.2%	41,157	$15	Y
19	QELBREE*	ADHD Drugs	$610,805	1.2%	1,305	$468	Y
20	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$436,591	0.8%	32,604	$13	
21	LAMOTRIGINE	Antiepileptics, Outpatient	$420,298	0.8%	33,672	$12	Y
22	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$355,285	0.7%	23,879	$15	Y
23	INVEGA HAFYERA	Antipsychotics, Parenteral	$345,832	0.7%	18	$19,213	Y
24	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$340,406	0.7%	2	$170,203	
25	BIKTARVY	HIV	$327,996	0.6%	102	$3,216	Y
26	UZEDY	Antipsychotics, Parenteral	$299,116	0.6%	94	$3,182	Y
27	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$288,229	0.6%	22,261	$13	Y
28	ATOMOXETINE HCL*	ADHD Drugs	$269,944	0.5%	10,855	$25	Y
29	VENLAFAXINE HCL ER	Antidepressants	$257,009	0.5%	18,906	$14	Y
30	Inj Pembrolizumab	Physican Administered Drug	$246,959	0.5%	45	$5,488	
31	SERTRALINE HCL	Antidepressants	$234,702	0.5%	1,472	$159	V
32	COBENFY*	Antipsychotics, 2nd Gen	$219,913	0.4%	137	$1,605	V
33	MIRTAZAPINE	Antidepressants	$213,695	0.4%	14,513	$15	Y
34	OLANZAPINE*	Antipsychotics, 2nd Gen	$208,886	0.4%	14,489	$14	Y
35	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$207,543	0.4%	20	$10,377	Y
36	EVEROLIMUS*	Antineoplastics, Newer	$200,499	0.4%	16	$12,531	
37	GUANFACINE HCL ER	ADHD Drugs	$199,850	0.4%	14,111	$14	Y
38	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	$196,686	0.4%	321	$613	N
39	DAYBUE*	STC 99 - Miscellaneous	$191,715	0.4%	6	$31,952	N
40	LAMOTRIGINE ER	Antiepileptics, Outpatient	$189,803	0.4%	4,998	$38	V
		Top 40 Aggregate:	**$39,725,718**		**533,617**	**$7,223**	
		All FFS Drugs Totals:	**$51,929,167**		**785,124**	**$722**	

*** 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: October 24, 2025

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$340,406	3.8%	2	$170,203	
2	BIKTARVY	HIV	$327,996	3.7%	102	$3,216	Y
3	Inj Pembrolizumab	Physican Administered Drug	$246,959	2.8%	45	$5,488	
4	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$207,543	2.3%	20	$10,377	Y
5	EVEROLIMUS*	Antineoplastics, Newer	$200,499	2.2%	16	$12,531	
6	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	$196,686	2.2%	321	$613	N
7	DAYBUE*	STC 99 - Miscellaneous	$191,715	2.1%	6	$31,952	N
8	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$186,925	2.1%	97	$1,927	Y
9	Inj Givosiran 0.5 Mg	Physican Administered Drug	$177,165	2.0%	2	$88,582	
10	Inj Fam-Trastu Deru-Nxki 1mg	Physican Administered Drug	$172,674	1.9%	14	$12,334	
11	JARDIANCE	Diabetes, SGLT-2 Inhibitors	$138,820	1.5%	382	$363	Y
12	ELIQUIS	Anticoagulants, Oral and SQ	$131,605	1.5%	323	$407	Y
13	Canakinumab Injection	Physican Administered Drug	$131,027	1.5%	4	$32,757	
14	HUMIRA(CF) PEN*	Targeted Immune Modulators	$127,151	1.4%	23	$5,528	Y
15	MOUNJARO*	Diabetes, GLP-1 Receptor Agonists and GIP The	$109,627	1.2%	155	$707	N
16	TRULICITY*	Diabetes, GLP-1 Receptor Agonists and GIP The	$103,876	1.2%	152	$683	Y
17	TRIKAFTA*	Cystic Fibrosis	$103,091	1.2%	23	$4,482	N
18	FINTEPLA*	Antiepileptics, Outpatient	$103,073	1.2%	8	$12,884	N
19	IMCIVREE*	Weight Management Drugs	$98,328	1.1%	3	$32,776	
20	EPIDIOLEX*	Antiepileptics, Outpatient	$94,702	1.1%	61	$1,552	N
21	Supprelin La Implant	Physican Administered Drug	$81,936	0.9%	1	$81,936	
22	BRIXADI	Substance Use Disorders, Opioid & Alcohol	$77,520	0.9%	46	$1,685	Y
23	STELARA*	Targeted Immune Modulators	$75,083	0.8%	6	$12,514	N
24	XIFAXAN*	Rifamycins	$71,650	0.8%	31	$2,311	N
25	LISDEXAMFETAMINE DIMESYLATE*	ADHD Drugs	$68,017	0.8%	861	$79	Y
26	Aflibercept Injection	Physican Administered Drug	$64,252	0.7%	169	$380	
27	RINVOQ*	Targeted Immune Modulators	$62,820	0.7%	18	$3,490	N
28	DEXCOM G7 SENSOR*	Diabetic Supplies, CGM	$61,096	0.7%	269	$227	Y
29	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$60,671	0.7%	3	$20,224	
30	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$60,069	0.7%	972	$62	Y
31	CREON	Pancreatic Enzymes	$58,860	0.7%	49	$1,201	Y
32	Daratumumab, Hyaluronidase	Physican Administered Drug	$57,963	0.6%	19	$3,051	
33	Injection, Burosumab-Twza 1m	Physican Administered Drug	$57,788	0.6%	2	$28,894	
34	KISQALI*	Antineoplastics, Newer	$53,563	0.6%	5	$10,713	
35	ADVATE	Antihemophilia Factors	$51,858	0.6%	2	$25,929	
36	WEGOVY*	Weight Management Drugs	$49,986	0.6%	52	$961	
37	SLYND	Contraceptives	$49,701	0.6%	176	$282	
38	IBRANCE*	Antineoplastics, Newer	$49,416	0.6%	3	$16,472	
39	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$48,557	0.5%	1,847	$26	Y
40	Mifepristone, Oral, 200 Mg	Physican Administered Drug	$45,499	0.5%	573	$79	
		Top 40 Aggregate:	**$4,596,172**		**6,863**	**$15,997**	
		All FFS Drugs Totals:	**$8,956,272**		**89,354**	**$722**	

*** Drug requires Prior Authorization**

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

Last updated: October 24, 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
Imlunestrant	INLURIYO
pembrolizumab;berahyaluronidase alfa-pmph	KEYTRUDA QLEX

Recommendation:

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

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Populations:

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

Covered Alternatives:

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

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

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

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

		RPh. Deny; not funded by the OHP **If eligible for EPSDT review:** Go to #5.
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity.
6. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Go to #8	**No:** Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Go to #8	**No:** Go to #9
8. Are there equally or higher recommended alternative agents based on NCCN categories of evidence (Table 1) for the requested indication and place in therapy?	**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	**No:** Go to #10

	experimental or investigational therapies.	
10. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. All other diagnoses must be evaluated for evidence of clinical benefit. The prescriber must provide the following documentation: • medical literature or guidelines supporting use for the condition, • clinical chart notes documenting medical necessity, and • documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Table 1. Oncology agents which apply to this policy (Updated 11/3/2025)
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
avutometinib and defactinib	AVMAPKI FAKZYNJA CO-PACK
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capivasertib	TRUQAP
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA

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

Generic Name	Brand Name
Imlunestrant tosylate	INLURIYO
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lazertinib	LAZCLUZE
lenvatinib mesylate	LENVIMA
lifileucel	AMTAGVI
linvoseltamab-gcpt	LYNOZYFIC
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
melphalan hcl/hepatic delivery kit (HDS)	HEPZATO KIT
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
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

Generic Name	Brand Name
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
omidubicel-onlv	OMISIRGE
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pembrolizumab;berahyaluronidase alfa-pmph	KEYTRUDA QLEX
pemigatinib	PEMAZYRE
penpulimab-kcqx	none
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
quizartinib	VANFLYTA
ramucirumab	CYRAMZA
regorafenib	STIVARGA
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

Generic Name	Brand Name
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
sunvozertinib	ZEGFROVY
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
taletrectinib	IBTROZI
talimogene laherparepvec	IMLYGIC
talquetamab-tgvs	TALVEY
tarlatamab-dlle	IMDELLTRA
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
telisotuzumab vedotin-tllv	EMRELIS
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tislelizumab-jsgr	TEVIMBRA
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
toripalimab-tpzi	LOQTORZI
tovorafenib	OJEMDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
trastuzumab-strf	HERCESSI
tremlimumab	IMJUDO
treosulfan	GRAFAPEX
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vimseltinib	ROMVIMZA
vismodegib	ERIVEDGE
vorasidenib	VORANIGO
zanidatamab-hrii	ZIIHERA
zanubrutinib	BRUKINSA
zenocutuzumab-Zbco	BIZENGRI
ziv-aflibercept	ZALTRAP
zongertinib	HERNEXEOS

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

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. Updated orphan drugs

Generic (BRAND) Name
Asfotase alfa (STRENSIQ)
Elosulfase alfa (VIMIZIM)
Galsulfase (NAGLAZYME)
Idursulfase (ELAPRASE)
Vestronidase alfa-vjbk (MEPSEVII)

Recommendation:

- Modify PA criteria to include new orphan drugs.
- Remove drugs for which specific PA criteria is proposed.
- Update PA criteria to clarify the high-cost drugs that will be covered by fee-for-service (FFS).

Orphan Drugs

Goal(s):

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

Length of Authorization:

- Up to 6 months

Requires PA:

- See Table 1 (pharmacy and provider administered claims)

Covered Alternatives:

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

Table 1. Included orphan drugs

Drug	Covered Population
ADAMTS13, recombinant-krhn (ADZYNMA)	FFS
Allogeneic processed thymus tissue-agdc (RETHYMIC)	FFS and CCO populations beginning 1/1/26
Alpelisib (VIJOICE)	FFS
Asfotase alfa (STRENSIQ)	FFS and CCO populations beginning 1/1/26
~~arimoclomol citrate (MIPLYFFA)~~	~~FFS and CCO~~
Atidarsagene autotemcel (LENMELDY)	FFS and CCO populations beginning 1/1/26
Avacopan (TAVNEOS)	FFS
Axatilimab-csfr (NIKTIMVO)	FFS
Belumosudil (REZUROCK)	FFS
~~Beremagene geperpavec-svdt (VYJUVEK)~~	~~FFS and CCO~~
~~Birch triterpenes (FILSUVEZ)\~~	~~FFS and CCO~~
Burosumab-twza (CRYSVITA)	FFS
Cerliponase alfa (BRINEURA)	FFS
Chenodiol (CTEXLI)	FFS and CCO populations beginning 1/1/26
Crinecefont (CRENESSITY)	FFS
Crovalimab-akkz (PIASKY)	FFS
Danicopan (VOYDEYA)	FFS
Eculizumab (SOLIRIS)	FFS
Eculizumab-aagh (EPYSQLI)	FFS

Eculizumab-aeeb (BKEMV)	FFS
Eladocagene exuparvovec-tneq (KEBILDI)	FFS and CCO populations beginning 1/1/26
Elafibranor (IQIRVO)	FFS
Elapegademase-lvlr (REVCOVI)	FFS and CCO populations beginning 1/1/26
Elivaldogene autotemcel (SKYSONA)	FFS and CCO populations beginning 1/1/26
Elosulfase alfa (VIMIZIM)	FFS and CCO populations beginning 1/1/26
Fosdenopterin (NULIBRY)	FFS
Galsulfase (NAGLAZYME)	FFS and CCO populations beginning 1/1/26
Givosiran (GIVLAARI)	FFS
Idursulfase (ELAPRASE)	FFS and CCO populations beginning 1/1/26
Inebilizumab-cdon (UPLIZNA)	FFS
Iptacopan (FABHALTA)	FFS
Leniolisib (JOENJA)	FFS
~~Levacetylleucine (AQNEURSA)~~	~~FFS and CCO~~
Levoketoconazole (RECORLEV)	FFS
Lonafarnib (ZOKINVY)	FFS and CCO populations beginning 1/1/26
Lumasiran (OXLUMO)	FFS and CCO populations beginning 1/1/26
Luspatercept (REBLOZYL)	FFS
Maralixibat (LIVMARLI)	FFS and CCO populations beginning 1/1/26
Mavacamten (CAMZYOS)	FFS
Mavorixafor (XOLREMDI)	FFS
Mirdametinib (GOMEKLI)	FFS
Mitapivat (PYRUKYND)	FFS
Nedosiran (RIVFLOZA)	FFS
Nipocalimab-aahu (IMAAVY)	FFS
Odevixibat (BYLVAY)	FFS and CCO populations beginning 1/1/26
Olipudase alfa-rpcp (XENPOZYME)	FFS and CCO populations beginning 1/1/26
~~Palovarotene (SOHONOS)~~	~~FFS and CCO~~
Palopegteriparatide (YORVIPATH)	FFS
Pegcetacoplan (EMPAVELI)	FFS
Plasminogen, human-tvmh (RYPLAZIM)	FFS
Pozelimab-bbfg (VEOPOZ)	FFS and CCO populations beginning 1/1/26
Ravulizumab-cwvz (ULTOMIRIS)	FFS
Remestemcel-L-rknd (RYONCIL)	FFS
Rezafungin (REZZAYO)	FFS
Rozanolixizumab-noli (RYSTIGGO)	FFS
Satralizumab-mwge (ENSPRYNG)	FFS
Seladelpar (LIVDELZI)	FFS

Sodium thiosulfate (PEDMARK)	FFS
Sutimlimab-jome (ENJAYMO)	FFS
Tofersen (QALSODY)	FFS
Trientine tetrahydrochloride (CUVRIOR)	FFS
Velmanase alfa-tycv (LAMZEDE)	FFS and CCO populations beginning 1/1/26
Vestronidase alfa-vjbk (MEPSEVII)	FFS and CCO populations beginning 1/1/26
Zilucoplan (ZILBRYSQ)	FFS

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in the FDA label (see links in **Table 1)**? Note: This includes all information required in the FDA-approved indication, including but not limited to, the following as applicable: diagnosis, disease severity, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
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: 8/25; 6/25; 4/25; 2/25; 12/24; 10/24; 8/24; 4/24; 12/23; 10/23; 6/23; 2/23; 12/22; 6/22; 4/22; 12/21; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: 9/15/25; 5/12/25; 3/10/25; 1/1/25; 9/1/24; 5/1/24; 1/1/24; 11/1/23; 7/1/23; 4/1/23; 1/1/23; 7/1/22; 5/1/22; 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20

ProDUR Report for July through September 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	6	3	0	3	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,258	616	0	1,642	1.2%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	10,206	3,522	1	6,675	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**	**115,320**	**28,098**	**125**	**87,093**	**62.5%**	**24.4%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	42,443	12,485	5	30,225	23.0%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	933	227	0	705	0.5%	N/A
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	5	4	0	1	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	793	292	0	501	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	330	124	0	205	0.1%	N/A
PA (Drug/Age Precaution)	Products containing Codeine being billed and patient is less than 18 years of age	Set alert/Pay claim	9	2	0	7	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**172**	**76**	**0**	**96**	**0.1%**	**44.2%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	11,847	3,694	0	8,144	6.4%	N/A
		Totals	**184,322**					

ProDUR Report for July through September 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)	8,879	1,998	6,881	95,293	9.4%	22.5%
ER	Prozac (Fluoxetine)	6,607	1,458	5,148	72,243	9.3%	22.1%
ER	Lexapro (Escitalopram)	6,543	1,452	5,091	70,399	9.4%	22.2%
ER	Celexa (Citalopram)	1,945	437	1,508	22,513	8.6%	22.5%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	10,061	2,077	7,984	106,955	9.5%	20.6%
ER	Trazodone	8,313	2,041	6,272	74,614	11.3%	24.6%
ER	Cymbalta (Duloxetine)	6,258	1,571	4,687	56,619	10.7%	25.1%
ER	Effexor (Venlafaxine)	3,161	732	2,429	32,509	9.7%	23.2%
ER	Remeron (Mirtazapine)	2,428	571	1,857	20,821	11.7%	23.5%
ER	Elavil (Amitriptyline)	1,876	514	1,362	19,599	9.7%	27.4%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	5,864	1,677	4,187	39,145	15.2%	28.6%
ER	Abilify (Aripiprazole)	4,841	1,046	3,795	36,549	13.3%	21.6%
ER	Zyprexa (Olanzapine)	3,278	895	2,383	23,820	14.2%	27.3%
ER	Risperdal (Risperidone)	2,253	572	1,680	15,369	15.0%	25.4%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	4,847	1,125	3,721	46,160	10.6%	23.2%
ER	Lorazepam	332	127	205	13,094	2.5%	38.3%
ER	Alprazolam	193	56	137	7,264	2.6%	29.0%
ER	Diazepam	141	56	85	4,452	3.1%	39.7%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	7,999	1,922	6,076	59,417	13.5%	24.0%
ER	Intuniv (Guanfacine ER)	2,438	442	1,996	20,359	12.2%	18.1%
ER	Depakote (Divalproex)	1,989	600	1,389	13,858	14.6%	30.2%
ER	Suboxone (Buprenorphine/Naloxone)	70	33	37	1,455	5.0%	47.1%

ProDUR Report for July through September 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	July	6,215	196	267	681	2	4,851	12	1	205
ER	August	6,829	165	266	762	6	5,402	22	0	206
ER	September	6,525	181	267	722	4	5,127	17	1	206
	Total	**19,569**	**542**	**800**	**2,165**	**12**	**15,380**	**51**	**2**	**617**
	Percentage of Total Overrides		**2.8%**	**4.1%**	**11.1%**	**0.1%**	**78.6%**	**0.3%**	**0.0%**	**3.2%**

ProDUR Report for July through September 2025			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
July	DC	1	$80.59
	DD	14	$1,615.54
	ER	66	$33,871.10
	HD	1	$44.94
	ID	6	$482.23
	LR	1	$1,194.63
	MX	1	$104.06
	PG	1	$17.69
	TD	2	$178.10
	July Total	**93**	**$37,588.88**
August	DC	8	$967.34
	DD	42	$8,788.52
	ER	439	$136,481.01
	HD	1	$199.99
	ID	48	$7,573.61
	LR	4	$170.57
	MX	2	$301.46
	TD	16	$15,029.59
	August Total	**560**	**$169,512.09**
September	DC	1	$82.99
	DD	39	$3,416.16
	ER	33	$12,513.46
	ID	10	$1,755.61
	TD	5	$2,339.55
	September Total	**88**	**$20,107.77**
	Total 3Q2025 Savings		**$227,208.74**

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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	73	67
		Total Claims Identified	59	53	74	70
		Claims reviewed	3	4	5	20
		Estimated Savings	$0	$0	$0	$0
	OCC 4 with OCC 2 for different NDC	Total Patients Identified	16	20	14	16
		Total Claims Identified	17	20	16	16
		Claims reviewed			5	2
		Estimated Savings			$8,645	$0
	OCC 4 with OCC 2 for the same NDC	Total Patients Identified	6	20	4	2
		Total Claims Identified	6	22	5	2
	OCC 4 with Primary Payer Rejection Code	Total Patients Identified	4	5	8	9
		Total Claims Identified	4	5	8	9
		Claims reviewed		2	2	4
		Estimated Savings		$0	$0	$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
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	11	11	12	15
		Unique Patients Identified	11	11	12	15
		Total Faxes Successfully Sent	8	8	10	9
		Prescriptions Changed to Recommended Within 6 Months of Intervention	2	4	6	1
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$565	$2,145	$5,162	$2,038
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	96	72	112	127
		Unique Patients Identified	96	72	115	133
		Total Faxes Successfully Sent	79	43	81	98
		Prescriptions Changed to Recommended Within 6 Months of Intervention	43	31	60	72
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$70,564	$41,203	$66,862	$50,310

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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	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0	$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	909	927
		High risk patients identified	9	7	15	7
		Prescribers successfully notified	8	7	15	6
		Patients with change in antipsychotic drug in following 90 days	1	1		
		Patients with continued antipsychotic therapy in the following 90 days	8	6	13	7
		Patients with discontinuation of antipsychotic therapy in the following 90 days			3	

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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	44	70
		Total prescribers identified	60	53	44	70
		Prescribers successfully notified	60	53	43	70
		Patients with claims for the same antipsychotic within the next 90 days	33	23	21	34
		Patients with claims for a different antipsychotic within the next 90 days	2	2	3	2

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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
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	63	55	65	68
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	18	25	26	19
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	156	188	155	153
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	35	20	37	27
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	22	23	29	22
		Letters Sent To Providers	15	16	15	11
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	28	23	29	21
		Letters Sent To Providers	31	25	31	15
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	23	24	19	14
		Letters Sent To Providers	16	13	9	10
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	23	23	19	15
		Letters Sent To Providers	5	9	16	11
	Lock-In	RetroDUR Profiles Reviewed	8	8	4	3
		Locked In	0	0	0	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
Safety Net	Antipsychotics for ages <=5 years	Patients identified with an ending PA	15	17	31	18
		Total prescribers identified	14	16	31	17
		Prescribers successfully notified	13	13	25	14
		Patients with paid claims within next 60 days	10	13	23	15
		Patients with denied claim within next 60 days	14	13	25	14

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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	53	84
		Total prescribers identified	71	47	53	84
		Prescribers successfully notified	67	45	51	84
		Patients with discontinuation of therapy within next 90 days	19	12	20	38
		Patients with new prescription for naloxone within next 90 days		3	1	3
		Average number of sedative drugs dispensed within next 90 days	23	23	20	14
		Average number of sedative prescribers writing prescriptions in next 90 days	23	23	20	14
	Oncology Denials	Total patients identified	3	2	2	
		Total prescribers identified	3	2	2	
		Prescribers successfully notified	2	2	2	
		Patients with claims for the same drug within the next 90 days	2	1	2	
		Patients with claims for any oncology agent within the next 90 days	2	1	2	
	TCAs in Children	TCA Denials in Children	35	36	30	24
		Total patients identified	11	12	11	6
		Total prescribers identified	11	11	10	6
		Prescribers successfully notified	6	5	8	3
		Patients with claims for a TCA within the next 90 days	2	3	3	1
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days		1	1	

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March 2025 Volume 15 Issue 3

The Mental Health Clinical Advisory Group

Andrew Gibler Pharm.D., Oregon State University Drug Use Research and Management Group

Introduction

The Mental Health Clinical Advisory Group (MHCAG) was established in the Oregon Health Authority (OHA) by the Oregon Legislature in 2017. According to Oregon statute ORS 414.359, MHCAG must develop evidence-based treatment algorithms and guidance for Oregon providers, including treatment with mental health drugs.

According to statute, the MHCAG treatment recommendations must be based on:

- The efficacy and safety of treatment
- Patient-specific considerations; and
- Cost of treatment.

The MHCAG may also provide recommendations to OHA and the Oregon Pharmacy & Therapeutics Committee on:

- Implementation of evidence-based treatment guidance for OHA's Medicaid program;
- The preferred drug list (PDL) of mental health drugs used by the OHA's fee-for-service Medicaid program;
- Coordinating with the Oregon Psychiatric Access Line (OPAL) at Oregon Health & Science University, which is available to Oregon providers who prescribe mental health drugs.

Composition

The MHCAG consists of 18 members appointed by OHA as defined by ORS 414.359. Members of MHCAG represent several groups that care and advocate for individuals with mental disorders (see **Table 1**). All published recommendations are approved by consensus vote of members.

Table 1. MHCAG Member Representation (number)

Psychiatrists (2)
Child/Adolescent Psychiatrist (2)
Clinical Psychologists (2)
Psychiatric Nurse Practitioner (1)
Primary Care Physicians (2)
Pharmacists (2)
Mental health advocacy organizations (2)
Coordinated care organizations (2)
Consumer of mental health services (1)
Federally Recognized Oregon Indian Tribe (1 (open)
Department of Corrections (1)

Research Methods

The MHCAG adopted research methods in 2021 that emphasize high quality evidence and follows the standard hierarchy of evidence, prioritizing systematic reviews and randomized clinical trials before observational studies and non-controlled studies. The MHCAG research methods are available on the MHCAG website and include the tools used to grade the quality of systematic reviews and clinical practice guidelines, as well as assess biases and applicability of clinical trials.

Clinical Practice Recommendations

The MHCAG continues to develop treatment algorithms and other clinical practice recommendations and resources for clinicians and patients. All documents are available on the website under MHCAG Recommendations and Resources. Below are brief summaries that highlight a small sample of the recommendations previously published. Interested readers are encouraged to read each document for more detail and to explore all the published documents on the website. The recommended non-pharmacological and pharmacological treatments are covered under Oregon's Medicaid program, most without requirement of prior authorization.

Table 2. Schizophrenia

Link: Treatment with Antipsychotic Medications
All antipsychotics are effective for schizophrenia
Clozapine is the most effective antipsychotic medication
Choice of an antipsychotic should depend on: • Side effect profile • Availability of a long-acting formulation
Long-acting formulations: • Include aripiprazole, risperidone and paliperidone • Reduce risk of hospitalization and relapse • Offer convenience • Help providers assess adherence • Use a trauma-informed approach to care in patients with history of trauma or coercive injection of antipsychotics.
Offer clozapine to patients who do not respond to adequate trials of two different antipsychotics

Table 3. Bipolar Disorder

Link: Treating Acute Bipolar Depression
Offer each patient a psychosocial treatment and first-line medication: • Lamotrigine • Lithium • Quetiapine
Second-line options: cariprazine, divalproex or lurasidone
Combination therapy (commonly with lamotrigine)
Avoid antidepressant monotherapy
Link: Treating Acute Bipolar Mania
Offer each patient a psychosocial treatment and first-line combination medication therapy: • Quetiapine and lithium • Quetiapine and divalproex
Second-line monotherapy options: aripiprazole, asenapine, cariprazine, risperidone, ziprasidone
Consider clozapine for severe symptoms (as always, providers can utilize OPAL for treatment help)
Avoid lamotrigine for treatment of acute mania only

Table 4. Tapering Benzodiazepines

Link: How to Approach a Benzodiazepine Taper
The provider must establish realistic expectations with themselves and the patient
Create a plan to manage anxiety symptoms
Taper the benzodiazepine using the following approach: • Individualized (no 'one-size-fits-all' approach) • Slow (with possible pauses in taper)
Rate of taper depends on: • Severity of withdrawal symptoms • Original dose, type, potency, duration of action, and length of use of benzodiazepine • Reason the benzodiazepine was originally prescribed • Personality and vulnerability of the patient, their lifestyle, personal stresses and social support
Most patients will benefit by switching to diazepam before tapering
Benzodiazepines like diazepam or lorazepam can provide short-term relief of severe somatic symptoms

Table 5. Generalized Anxiety Disorder

Link: Treating Adults with Generalized Anxiety Disorder
Offer psychosocial treatment and a first-line medication: • Escitalopram • Sertraline • Duloxetine • Venlafaxine (extended release)
Adjunctive therapy: • First-line adjunct: pregabalin • Second-line adjunct: buspirone

Table 6. Insomnia Disorder

Link: Treating Insomnia Disorder
Due diligence is recommended to figure out why a patient has disordered sleep; address modifiable causes
Goal is to achieve restorative sleep, not simply to reduce latency to sleep onset
Sleep disturbances are commonly reported in menopausal transition
Offering sleep hygiene recommendations alone is not effective

Use a harm reduction approach for treating insomnia disorder:
• Cognitive behavioral therapy for insomnia (CBT-I)
• Online CBT-I programs and mobile apps
• Limit medication to 4 weeks only after CBT-I has been tried:
  ○ Doxepin
  ○ Trazodone
  ○ Lemborexant
  ○ Suvorexant
  ○ Eszopiclone
  ○ Zolpidem

Table 7. Post-Traumatic Stress Disorder (PTSD)

Link: Treating PTSD
Use a trauma informed approach to care (Trauma Informed Oregon)
Perform safety, lethal means, and environmental assessment
Complex PTSD may be a distinct disorder from PTSD and borderline personality disorder
Do not delay PTSD treatment in patients with co-occurring mental health or substance use disorders
Psychotherapy: • Trauma-focused cognitive behavioral therapy • Cognitive processing therapy • Eye movement desensitization reprocessing • Prolonged exposure therapy
Pharmacotherapy (adults): • Paroxetine • Sertraline • Venlafaxine (extended release) • Prazosin (for nightmares)
Avoid starting benzodiazepines. Benzodiazepines: • Are i**neffective at preventing or treating PTSD,** • **Reduce the effectiveness of trauma-specific psychotherapy, and** • **Have high potential for abuse and patient harm**

Peer Reviewed By: Nick Kashey, MD, MPH, Clinical Vice President, Population Health, Legacy Health and Kaja Wagner, PharmD, BCPP, Clinical Pharmacy Manager at Oregon State Hospital

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AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
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Treating Adolescents with Opioid Use Disorder

Deanna Moretz, PharmD. BCPS, Clinical Pharmacy Specialist, Drug Use Research and Management Team

Over the last 2 decades, opioid-related morbidity and mortality have risen in many settings globally.[1] Unfortunately, the surge in illicit fentanyl substances has recently contributed to the increased number of overdose deaths.[2,3] In a 12-month period ending in October 2022, there were more than 101,750 fatal opioid overdoses reported in the United States (U.S).[4] In 2022, illicitly manufactured fentanyl contributed to 65.5% of all overdose deaths in Oregon, making it the most prevalent illicit drug involved in overdose fatalities.[5] Deaths from opioids occur most often in adults 18 to 65 years of age and in adolescents 15 to 19 years of age.[6] Medication for opioid use disorder (MOUD) is associated with reduced mortality, fewer relapses to opioid use, and enhanced recovery and retention in addiction care.[7] However, a study published in the *Journal of the American Medical Association* (JAMA) highlighted that despite an increasing rate of opioid-associated overdose deaths among young people, only one in four adolescent residential treatment centers provide MOUD to this population.[8] This newsletter reviews OUD management guidelines in adolescents and summarizes studies evaluating use of MOUD in adolescents. Finally, Oregon Health Plan (OHP) policies for OUD treatments are presented to enhance provider awareness.

Medications for Opioid Use Disorder in Adolescents

In the U.S, there are currently three medications for the treatment of OUD: methadone, buprenorphine (including sublingual buprenorphine–naloxone, buprenorphine transdermal patch, implant, or injection), and naltrexone (oral or extended release [XR]).[9] In the U.S., methadone can only be administered for treatment of OUD in opioid treatment programs (OTPs), but buprenorphine and naltrexone can be prescribed and/or administered in non-OTP, office-based settings.[10] In adults, treatment with buprenorphine or methadone, which are opioid agonists, or with naltrexone, an opioid antagonist, is associated with fewer opioid cravings, less withdrawal, fewer relapses, and enhanced recovery and retention in addiction care.[1] Retention in buprenorphine or methadone treatment is associated with reduced mortality.[7] Methadone and naltrexone are Food and Drug Administration (FDA)-approved for use in adults aged 18 years and older.

Currently, there are no large-scale clinical trials testing the efficacy of naltrexone in adolescents.[9] A major drawback of oral naltrexone is the lack of its established efficacy in preventing relapse.[9] A challenge with long-acting naltrexone is that, compared with opioid agonists, it may be more difficult to initiate because of the need for detoxification before induction.[9] An additional concern with XR-naltrexone is that overdose risk is elevated in cases of premature discontinuation or with missed dosages of XR-naltrexone.[9] In addition, individuals receiving oral naltrexone could be at increased risk of overdose if they are not adherent to it because of a loss of tolerance to opioids, which makes them more sensitive to respiratory depression with lower doses of opioids.[9]

Buprenorphine products are FDA-approved for adolescents aged 16 years or older and adults with OUD.[1] Buprenorphine is typically used in the early stage of OUD treatment, while the combination of buprenorphine and naloxone is used for long-term maintenance therapy after detoxification. Naltrexone, taken as a daily tablet or once monthly injection (Vivitrol®), can be prescribed off-label for adolescents, but they must fully abstain from opioids for 7 to 10 days before starting therapy to avoid precipitating withdrawal. A retrospective study comparing trends in buprenorphine and naltrexone use in adolescents with OUD found buprenorphine was prescribed more frequently than naltrexone (89% versus 11%) in the first 6 months after diagnosis.[11]

Three randomized controlled trials (RCTs) examined the efficacy of buprenorphine combined with behavioral therapy in adolescents.[12-14] In the first RCT conducted in 2005, 36 adolescents 13 to 18 years of age with OUD were enrolled in the trial.[12] Most of the adolescents were withdrawing from snorted or injected heroin. The participants were assigned to once daily buprenorphine 6 to 8 mg sublingually (depending on body weight and self-reported heroin intake) or clonidine 0.1 to 0.3 mg via transdermal patch (depending on severity of withdrawal symptoms) for 28 days.[12] The buprenorphine doses are in the lower range of doses that have been used with youth and opioid-dependent adults.[12] A greater percentage of adolescents who received buprenorphine were retained in treatment (72%) relative to those who received clonidine (39%; p=0.04).[12] For those in the buprenorphine group, a higher percentage of scheduled urine test results were opiate negative compared with the clonidine group (64% vs. 32%; p=0.01).[12]

The second RCT conducted in 2008, included 152 adolescents and young adults aged 15 to 21 years with OUD entering treatment for opioid withdrawal.[13] Patients were randomized to 2 weeks (detoxification) or 12 weeks of buprenorphine-naloxone.[13] Patients in the 2-week detoxification group received up to 14 mg buprenorphine-naloxone per day and ended their buprenorphine-naloxone

taper by day 14.[13] Patients in the 12-week buprenorphine-naloxone group received up to a maximum amount of 24 mg per day and began a taper at week 9 that ended by week 12.[13] Adolescents who received 12 weeks of buprenorphine-naloxone had lower rates of illicit opioid use; however, the differences quickly disappeared once the medication was discontinued.[13] The findings led the authors to conclude that there is no reason to stop buprenorphine in adolescent patients who are doing well on the medication.[13]

A third 2016 study randomized 16 to 24 year old patients with OUD (n=53) to a 56- versus 28-day buprenorphine taper.[14] The primary outcome was the proportion of opioid-negative urine samples over the 63-day trial period.[14] Youth randomized to the 56-day taper submitted a higher proportion of opioid-negative urine samples than those in the 28-day taper (35% vs.17%).[14] In addition to showing improvements in opioid use, these studies suggest improved treatment retention among youth randomized to the longer course of buprenorphine.[9]

Although methadone and buprenorphine have the potential risk of overdose when misused or used illegally, evidence suggests this risk is much lower for buprenorphine than methadone.[9] The combination of buprenorphine and naloxone was developed to deter the abuse of buprenorphine. Extensive experience with adults has established evidence supporting the safety of buprenorphine, and although not as well studied among youth so far, research and clinical experience to date have not identified any age-specific safety concerns with buprenorphine.[15]

Providing early, effective treatment for OUD is critical to preventing worsening addiction and the potential for lifelong harm.[1] However, one study showed that among youth and young adults, fewer than one-quarter with OUD receive treatment with buprenorphine or naltrexone.[8] Provision of MOUD is often hampered by the misconception that adolescents should first have a trial of behavioral therapy that does not include pharmacotherapy, and that medications should be used as a last resort, or not at all.[16] Guidance from the 2020 Society for Adolescent Health and Medicine (SAHM) states that medications for OUD, including buprenorphine, should be offered with behavioral therapy to all adolescents and young adults with OUD.[1] Although naltrexone and methadone are not approved by the FDA for use among adolescents under 18 years of age, clinical guidelines recommend MOUD for adolescents who meet criteria for OUD without age limitations.[1] The risks of harm from use of off-label buprenorphine, methadone, or naltrexone may offset the risks of continued opioid use in adolescents. Other barriers cited by SAHM include insufficient number of addiction treatment programs that offer MOUD to adolescents, lack of health insurance among adolescents, high copays for medications and clinical visits, and pervasive disparities in offered treatment and access to healthcare by race and ethnicity.[1] The guidance recommends that adolescents who do not pursue behavioral therapy should not be denied medications for OUD.[1]

Guidance from the American Academy of Pediatrics (AAP) and American Society for Addiction Medicine (ASAM), also recommend that providers consider offering MOUD to adolescents with OUD.[15,17] The 2016 AAP guidance advocates for increasing resources to improve access to MOUD for adolescents and young adults with OUD.[15] Pediatricians have access to an AAP-endorsed training course to treat OUD in adolescents at https://www.aap.org/mat.[15] The AAP recommends that pediatricians consider offering MOUD to their adolescent and young adult patients with severe OUD or discuss referrals to other providers for this service.[15] The 2020 ASAM guidance states that clinicians should consider treating adolescents who have OUD using the full range of treatment options, including pharmacotherapy.[17] This guidance recommends that a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacological treatment of OUD, with appropriate medication management.[17]

Trends in Buprenorphine Prescribing for Adolescents

A 2023 study identified treatment centers that serve adolescents in the U.S., primarily through a database maintained by the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA).[8] The investigators identified 354 national residential treatment centers, but less than half of them served adolescents.[8] Of 160 facilities that served adolescents, 39 (24.4%) offered buprenorphine, including through partnership with outside clinicians.[8] Only 12 facilities (7.5%) offered buprenorphine initiation but discontinued therapy before discharge, 17 (10.6%) initiated buprenorphine and offered ongoing treatment, and 3 (1.9%) offered buprenorphine for ongoing treatment only.[8]

Among the 121 facilities that did not offer buprenorphine or were unsure, 57 (47.1%) indicated that adolescents who were prescribed buprenorphine by their own clinician could continue receiving it, at least temporarily, although some facilities indicated they would discontinue buprenorphine before discharge, and 27 (22.3%) required adolescents to not be receiving buprenorphine at admission.[8] Sixty-three facilities (39.4%) indicated that adolescents could undergo on-site withdrawal.[8] Of those facilities, 18 (28.6%) offered buprenorphine for on-site withdrawal while some did not offer any medication adjuncts.[8]

Only 1 in 4 U.S. facilities offered buprenorphine and 1 in 8 offered buprenorphine for ongoing treatment.[8] By comparison, nearly two-thirds of adult residential facilities offer buprenorphine.[18] The average parent would need to call 9 facilities on the SAMHSA Treatment Locator list to find one that offered buprenorphine and 29 facilities to find one for an adolescent younger than 16 years.[8]

Another 2023 study reinforces these findings and demonstrates that buprenorphine dispensing is low among youth in the U.S.[19] Over the study period from 2015 to 2020, only 336,000 total prescriptions were dispensed to 22,000 youth who were 19 years of age or younger.[19] However, during that time, an estimated 87,000 adolescents 12 to 17 years of age were diagnosed with OUD.[19] These statistics likely underestimate the national prevalence of OUD in adolescents.[19] With an average of only 4,169 youth receiving buprenorphine annually, a relatively small proportion of youth with self-reported OUD were receiving buprenorphine from a retail pharmacy.[19] These findings suggest that many youth with OUD who could benefit from MOUD are not receiving it.[19]

A 2024 study published in JAMA evaluated trends in buprenorphine dispensing among adolescents and young adults in the U.S.[20] This cross-sectional study analyzed 2020-2023 data from the IQVIA Total Patient Tracker, an all-payer pharmaceutical claims database capturing 93% of prescriptions dispensed from retail pharmacies in the U.S.[20] Estimates of unique individuals who were dispensed buprenorphine are projected by IQVIA to be representative of all prescriptions dispensed from retail pharmacies in the U.S.[20] Between 2020 and 2023, the overall number of adolescents and young adults dispensed buprenorphine declined 6.5% annually (95% confidence interval [CI], −7.0% to −6.0%; p<0.001), from 47,759 individuals in 2020 to 38,907 in 2023.[20] Barriers to buprenorphine access among adolescents and young adults may include limited treatment facilities, lack of comfort prescribing MOUD to youth, and stigma related to OUD.[21]

Oregon Health Plan Policies

The standard for outpatient opioid treatment programs are addressed in Chapter 415 (Addiction Services) of the Oregon statutes. Health Systems Division: Addiction Services. The dispensing restrictions for methadone do not apply to buprenorphine products. OHP policies permit unrestricted access to patients requiring treatment with buprenorphine products according to prescribing guidelines. OHP policies are presented in **Figure 1**.

Figure 1. Oregon Health Plan Preferred Opioid Use Disorder Therapies without PA requirement

- Buprenorphine sublingual tablets and subcutaneous long-acting injection
- Buprenorphine/Naloxone sublingual film and sublingual tablets
- Methadone tablets administered in an OTP

Conclusion

Despite the availability and efficacy of MOUD for adolescents with OUD, studies show this population is severely undertreated.[8,19,20] Treatment for OUD with buprenorphine is associated with reduced mortality, fewer relapses to opioid use, and enhanced recovery and retention in addiction care.[6] Although not as well studied among youth so far, research and clinical experience to date have not identified any age-specific safety concerns with buprenorphine.[15] Clinicians serving adolescents and young adults can expand access to buprenorphine through clinician education, improving clinic resources for supportive services related to substance use care for youths, offering or referring patients for medications therapy and behavioral health services, and addressing stigma and other barriers to care.[21]

Peer Reviewed By:

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Medication Safety Update

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Clinical trials are a valuable pathway to identifying medication safety issues; however, selection of patients with specific characteristics and short trial durations are limitations in determining the risks in broader populations and long-term use. Post-marketing reports of adverse reactions are integral to safe prescribing practices. The Food and Drug Administration (FDA) releases important drug updates to alert providers of safety findings after drugs have been approved. These findings can include newly identified safety issues or removal of previously assigned warnings. Medication safety concerns also include the rise of online pharmacies selling prescription drugs. This newsletter will discuss new safety warnings, changes to drug labeling and risks to obtaining medications online.

Newly Identified Warnings

Glatiramer (COPAXONE®, GLATOPA®)

Glatiramer is a drug used for the treatment of relapsed multiple sclerosis (MS).[1] In January 2025, the FDA issued a safety alert for glatiramer on the risk of anaphylaxis, leading to hospitalization and death.[2] The risk is rare but can occur at any time during glatiramer therapy, from the first injection to months or years after starting therapy. The reported median time to onset of anaphylaxis was 5 months. Symptoms of allergic reaction usually occur within one hour of injection.[2] The FDA is adding this risk as part of a new *Boxed Warning* to glatiramer prescribing information.[1]

Glatiramer is injected once daily or 3 times weekly.[1] Allergic symptoms can present similarly to common adverse reactions associated with glatiramer post-injection.[1] The immediate post-injection reactions occurred in 16% of glatiramer 20 mg/mL treated patients compared to 4% of placebo treated patients in clinical studies.[1] Post-injection reactions can present within seconds to 1 hour after administration and include: flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat and urticaria.[1] Most symptoms are transient and don't require any intervention. Since these symptoms overlap with anaphylaxis symptoms it is important to not delay treatment if anaphylaxis is suspected.

Fezolinetant (VEOZAH®)

Fezolinetant is a neurokinin 3 (NK3) receptor antagonist used for moderate to severe vasomotor symptoms due to menopause.[3] In September 2024, the FDA issued a safety warning on the risk of serious liver injury.[4] The new warning is accompanied with the recommendation to increase liver function testing (LFTs) to monthly tests for the first 2 months following initiation and then at months 3, 6 and 9 of treatment.[4]

The new recommendation is in response to one case report of a women with elevated LFTs (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and total bilirubin) diagnosed with acute mixed hepatocellular cholestatic drug-induced liver injury. The event occurred within 40 days of initiation of fezolinetant. Hepatic enzymes returned to normal levels after medication discontinuation.[4]

Fezolinetant should be discontinued if there are symptoms of hepatic dysfunction to avoid worsening hepatic injury and increase the likelihood of reversal and restoration of normal hepatic function. Symptoms of liver injury included feeling fatigued, nausea, vomiting, unusual itching, light-colored stools, jaundice and swelling or pain in the abdomen.[4] Fezolinetant should not be started in patients with LFTs that exceed two times the upper limit of normal (ULN).[3] Additionally, fezolinetant should be stopped if LFTs exceed five times the ULN or if LFTs exceed three times the upper limit of normal and total bilirubin is more than two times the ULN.[3]

GLP-1 RAs

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are used most often for the treatment of type 2 diabetes (T2D) and in adults with overweight or obesity. The FDA is performing an ongoing evaluation of the risk of suicidal thoughts or actions in patients taking GLP-1 RAs.[5] An initial review has not demonstrated evidence of an increased risk. The FDA is continuing to monitor reports to the FDA Adverse Event Reporting System (FAERS), as the small number of reports of suicidal thoughts in patients treated with GLP-1 Ras, and in those in control groups, could have failed to identify a potential small risk to patients.[5] Providers should report any suicidal thoughts, worsening of depression or other changes in mood identified in patients taking GLP-1 RAs.[5]

Levetiracetam (KEPPRA®) and Clobazam (ONFI®)

Levetiracetam and clobazam are antiseizure medications. Levetiracetam can be used as monotherapy or in combination with other medications for partial seizures, myoclonic seizures or tonic-clonic seizures.[6] Clobazam is a benzodiazepine approved for seizures due to Lennox-Gastaut syndrome.[7] In November 2023, the FDA released a safety warning on the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with both levetiracetam and clobazam.[8] Prescribing information for levetiracetam has added the risk of DRESS to

the *Warnings and Precautions* section. Clobazam will have prescribing information updated to include a new warning specifically related to DRESS.[8]

Severe inflammation is the underlying pathology associated with DRESS. Symptoms of DRESS may start with a rash but can progress to organ injury in the liver, kidneys, lungs, heart, or pancreas, leading to hospitalization and death.[8] Patients should be counseled to seek emergency care if they have an unexplained rash, fever, or swollen lymph nodes. Rash may or may not be visible with the onset of DRESS.[8] The occurrence of DRESS can occur during any time while taking these medications, but it is most reported within 2 to 8 weeks of starting therapy. Patients should also be made aware of the risk of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) which have also been reported with both levetiracetam and clobazam.[8]

The new warnings of DRESS associated with levetiracetam and clobazam were a result of a medical literature search and reports to the FAERS database.[8] The incidence of DRESS was identified in 32 adults and children taking levetiracetam and 10 adults and children taking clobazam. Two patients taking levetiracetam died and all patients taking either levetiracetam or clobazam required hospitalization.[8] The most common symptoms were rash and fever. Other benzodiazepines do not have the same association with DRESS and other serious skin conditions.

Warning Removal

Clozapine (CLOZARIL®)

Clozapine is an effective antipsychotic with limited use due to risks of severe neutropenia. Until recently, prescribers, pharmacies and patients were required to participate in the Risk Evaluation and Mitigation Strategies (REMS) program for clozapine.[9] The REMs program required absolute neutrophil count (ANC) blood tests before dispensing clozapine. The REMs requirement was removed by the FDA in February 2025 to increase access to clozapine.[10]

Clozapine still carries a boxed warning for the risk of agranulocytosis, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis and cardiomyopathy, and increased mortality in elderly patients with dementia-related psychosis.[9] The FDA recommends that ANC still be monitored as described in the labeling. The ANC should be monitored weekly for 6 months upon clozapine initiation, every 2 weeks for 6-12 months and every 4 weeks for treatment durations of 12 months and beyond.[9] Additional monitoring recommendations are available in the prescribing information for patients with abnormal hematological values and when discontinuing clozapine therapy.[9] Information on the use of clozapine for schizophrenia is available from the Oregon Mental Health Clinical Advisory Group: *Treatment of Schizophrenia with Antipsychotic Medications*.

Online Medication Safety

Many patients are obtaining medications online due to supply issues, lower cost alternatives and discreetness of ordering. With the increase in this practice, safety issues have been identified. The Center for Disease Control (CDC) has announced a public health risk related to counterfeit medications from online pharmacies.[11] The United States Department of Justice (DOJ) has indicted individuals for advertising, selling, manufacturing, and shipping unregulated counterfeit prescription medications. Often these drugs contain fentanyl and methamphetamine.[11]

Online pharmacies offer prescription drugs at reduced prices and without a prescription. The National Association of Boards of Pharmacy (NABP) report that almost 95% of prescription-only online pharmacies are operating illegally and 96% of these pharmacies did not require a prescription to obtain a prescription medication.[12]

Characteristics of an Illegal Online Pharmacy[11]

- No prescription required
- Medication prices are much lower than other pharmacies
- Not a licensed pharmacy in the U.S. or state-licensed online pharmacy
    - Authorized online pharmacies can be found at: Locate a State-Licensed Online Pharmacy

Many patients are obtaining medications for weight loss from online pharmacies. Most commonly patients seek GLP-1 RAs, such as semaglutide, for this purpose; however, these pharmacies also offer oral medications. Online sites, such as *ForHers,* offer medication kits containing topiramate, bupropion XL, metformin, vitamin B12 and naltrexone with an online provider consult.[13] Providers should inquire if patients are obtaining medications through online sites and educate patients on appropriate use and screen for drug interactions and/or duplicate therapy.

Reporting Adverse Events

Reporting safety issues to the FDA MedWatch program is an important component of identifying medication safety concerns after a drug has been approved. Providers can report adverse events at MedWatch.

Conclusion

Medication safety updates are a component of staying current with prescribing recommendations and trends in consumer patterns. Recognizing early signs of serious adverse events is critical to seeking appropriate medical care and should be discussed with patients. Patients should be educated on the importance of getting medication from a licensed online pharmacy to avoid unnecessary risks.

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Drug Class Update: Antifungals

Date of Review: December 2025

Date of Last Review: December 2023
Dates of Literature Search: 10/01/2023 - 07/09/2025

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

Purpose for Class Update:
Evidence for the use of topical, oral and vaginal antifungals was reviewed by the Oregon Pharmacy & Therapeutics (P&T) Committee December 2023. Literature examining the comparative evidence published since the last review will be evaluated and presented.

Plain Language Summary:
- Providers prescribe antifungal medicines to treat infections that are caused by fungus. Antifungals can be applied on the skin, injected or infused into the bloodstream, or taken by mouth.
- People with weakened immune systems are more likely to get a fungal infection. The National Institutes of Health recently published antifungal treatment recommendations for people with human immunodeficiency virus (HIV), which weakens the immune system. Antifungal treatment recommendations were also updated for people with fungal infections.
- Cresemba (isavuconazonium) received approval from the U.S. Food and Drug Administration (FDA) for invasive aspergillosis or invasive mucormycosis.
- FDA issued new warnings and precautions for 4 antifungal treatments to assist providers in monitoring patients for specific side effects.
- Oregon Health Authority (OHA) will pay for antifungals to treat serious fungal infections. Antifungals can be covered for minor fungal infections if people have conditions that could lead to complications. The Drug Use Research and Management group does not recommend any changes to this policy to OHA.

Research Questions:
1. Is there new comparative evidence related to efficacy for the oral and topical antifungals for important outcomes (e.g., clinical cure or mycological cure)?
2. Is there new comparative evidence for harms for oral and topical antifungals?
3. Are there any populations based on certain demographic characteristics (i.e., age, sex, race, ethnicity, socioeconomic status, comorbidities) who may benefit more or suffer more harm from specific antifungal agents?

Conclusions:
- A search of the literature identified one new guideline, one new indication and 6 antifungal safety updates.

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- The National Institutes of Health (NIH) updated guidance related to the prevention and treatment of opportunistic infections in adults and adolescents with human immunodeficiency virus (HIV). Recommendations align with current policy for the coverage of antifungals for patients who are immunocompromised.[1]
- A new indication for the use of isavuconazonium injection was approved in December of 2023 for invasive aspergillosis (IA) and invasive mucormycosis (IM) treatment in pediatric patients 1 year and older and for the capsules to be used in those patients 6 years and older for the same indications who weigh 16 kg or greater.[2] Evidence used to obtain the approval in pediatric patients (n=31) was from a phase 2, open-label, noncomparative study in patients 1 to less than 18 years with probable or definitive IA or IM which demonstrated a reduction in mortality.
- There were 6 new safety updates since the last review that pertain to the following drugs: itraconazole, posaconazole, miconazole, and voriconazole (**Table 4**).[3–6]

Recommendations:
- No changes to the Oregon Health Plan (OHP) fee-for-service preferred drug list (PDL) for the antifungals drug class.
- Evaluate drug costs in the executive session.

Summary of Prior Reviews and Current Policy:
- The antifungals were reviewed in December of 2023. After the executive session, terconazole, butoconazole, miconazole kits, miconazole 3 vaginal suppositories were designated non-preferred. Clotrimazole (cream and tablet), clotrimazole 3-day cream, miconazole 3- and 7-day creams, miconazole suppositories, terconazole cream and tioconazole ointment are preferred vaginal antifungals.
- Oral antifungals that are preferred are clotrimazole, fluconazole, and nystatin. Preferred topical antifungals are miconazole, and nystatin.
- The OHP does not fund the treatment of candidiasis of the mouth, skin, nails or dermatophytosis of nail, groin, scalp, and other dematophytosis in immune competent patients. Coverage for these conditions in those under 21 years may be available through the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) program on a case-by-case basis.
- Ninety-eight percent of the oral antifungal utilization was for preferred therapies in the first quarter of 2025. For the topical antifungals, 71% of utilization was for preferred therapies and 96% for vaginal antifungals.

Background:
Oral and topical antifungal drugs are used to treat a wide spectrum of infections (**Table 1**). Fungal infections can occur on the skin and nails, mucosal surfaces, genitourinary tract, gastrointestinal tract and systemically.[7] Fungal infections of the skin, hair and nails are caused by dermatophyte infections and lead to conditions such as tinea pedis, tinea corporis, tinea cruris, tinea capitis and dermatophyte onychomycosis.[7] Mucosal fungal infections include oropharyngeal candidiasis, esophageal candidiasis and vulvovaginal candidiasis. Serious fungal infections are usually seen in individuals with compromised immune systems, such as prolonged neutropenia, allogenic hematopoietic stem cell transplant and acquired immunodeficiencies.

Table 1. Antifungals Categories[7,8]

Class	Drug Examples	Mechanism	Used For
Azoles	Fluconazole Isavuconazole Itraconazole	Inhibit ergosterol synthesis (cell membrane disruption)	Candidiasis, dermatophytosis, systemic mycoses (i.e., aspergillosis)

	Ketoconazole Oteseconazole Posaconazole Voriconazole		
Polyenes	Amphotericin B Nystatin	Bind ergosterol, form membrane pores	Systemic infections (Amphotericin B), superficial candidiasis (Nystatin)
Echinocandins	Caspofungin Micafungin Anidulafungin	Inhibit 1,3-β-D-glucan synthase (cell wall)	Invasive candidiasis, aspergillosis, empiric therapy in neutropenia
Allylamines	Terbinafine Naftifine	Inhibit squalene epoxidase (ergosterol synthesis)	Dermatophyte infections: onychomycosis, tinea pedis, tinea corporis, tinea cruris
Pyrimidine Analogues	Flucytosine	Converted to 5-FU, inhibits DNA/RNA synthesis	Cryptococcal meningitis (with Amphotericin B), Candida (with Amphotericin B)
Other	Griseofulvin	Disrupts mitotic spindle (inhibits mitosis)	Tinea capitis, tinea corporis (especially in children)
	Tolnaftate	Inhibits squalene epoxidase (topical)	Topical treatment for tinea infections
	Ciclopirox	Disrupts membrane transport, metal chelation	Topical use in dermatomycoses, onychomycosis, seborrheic dermatitis
	Selenium sulfide Zinc pyrithione	Cytostatic effect on epidermal cells, antifungal	Shampoos for seborrheic dermatitis, tinea versicolor

Choice of antifungal depends on indication, causative organism and resistance patterns. Fungal infections are commonly caused by yeasts, which are unicellular, or less commonly by molds, which are filamentous. Causative organism helps direct antifungal selection. Serious fungal infections typically require oral or intravenous antifungal therapy.[9,10] Antifungals can be categorized as azoles, echinocandins, polyenes, allylamines or nucleoside analogs (**Table 1**). Fluconazole is most commonly recommended first-line for a majority of fungal infections due to efficacy and tolerability.[7] Of the azole antifungals, posaconazole and isavuconazole have the broadest spectrum of action and are not associated with nephrotoxicity. There is wide variability between the different antifungals in their bioavailability and types of drug interactions (due to metabolism via the cytochrome P450 enzyme system). Gastrointestinal issues are the most common adverse reactions associated with antifungal therapy. Hepatic manifestations from mild elevations in liver enzymes to hepatic failure have occurred. For these reasons, transaminase monitoring is recommended for patients receiving extended treatment with antifungal therapy. Drug monitoring is a recommended for itraconazole, voriconazole, and posaconazole to ensure efficacy and avoid toxicity.[9]

Important outcomes to determine antifungal efficacy include symptom improvement, clinical cure (clinical symptoms), mycological cure (negative mycological test) and mortality.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo, if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence

(NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:
None identified.

After review, 12 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[11–23]

New Guidelines:
High Quality Guidelines:

NIH – Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV
In December 2024, recommendations for the treatment of opportunistic infection in those individuals with HIV were updated.[1] Opportunistic infections can be more frequent or more severe from immunosuppression from HIV. The main updates pertaining to the use of antifungals were for the treatment of coccidioidomycosis and histoplasmosis.[1]

For the treatment of coccidioidomycosis, isavuconazole sulfate was added as a treatment alternative for mild to moderate pulmonary infections (**Table 2**).[1] Coccidioidomycosis often presents with focal pneumonia, diffuse pneumonia, extrathoracic involvement, including meningitis. The recommended fluconazole dose for the treatment of coccidioidal meningitis was updated.[1] The use of azole antifungals during pregnancy was modified. Primary antifungal prophylaxis for coccidioidomycosis is not recommended (Grade A, Level III evidence).[1]

Table 2. Antifungals for the Treatment of Coccidioidomycosis in Adults and Adolescents[1]

Indication	Medication	Dose	Strength of Recommendation	Quality of Evidence
Mild to Moderate Pulmonary Infections				
Preferred Therapy	Fluconazole	400 mg PO once daily	A	II
	Itraconazole	200 mg PO three times daily for three days and the twice daily	A	II
Alternative Therapy	Voriconazole	Loading dose 400 mg PO twice daily on day 1, followed by 200 mg PO twice daily	B	II
	Posaconazole delayed-release tablet	300 mg PO twice daily on Day 1, followed by 300 mg once daily	B	III

	Isavuconazole sulfate	372 mg (isavuconazole 200 mg) PO every 8 hours for 6 doses followed by 372 mg PO once daily	B	III
Severe Pulmonary or Extrapulmonary Infections (Except Meningtitis)				
Preferred Therapy	Amphotericin B deoxycholate*	0.7 to 1.0 mg/kg IV daily	A	III
	Lipid formulation amphotericin B*	3-5 mg/kg IV daily	A	III
Alternative Therapy	Amphotericin B deoxycholate or lipid formulation amphotericin B. with a triazole as initial therapy	Doses as above	C	III
Meningeal Infection				
Preferred Therapy	Fluconazole	800-1,200 mg PO once daily	A	III
Alternative Therapy	Itraconazole	200 mg PO 2-3 times daily	B	II
	Voriconazole	200-400 mg PO twice daily	B	III
	Posaconazole delayed release tablet	300 mg PO twice daily on day 1, followed by 300 mg PO once daily	C	III
	Isavuconazole sulfate	372 mg (isavuconazole 200 mg) every 8 hours for 6 doses, followed by isavuconazole sulfate 372 mg PO once daily	C	III
	Intrathecal amphotericin B deoxycholate when triazole antifungals are not effective	No dosing provided.	A	III
Treatment in Pregnancy				
Preferred Therapy During First Trimester	Lipid formulation amphotericin B	3-5 mg/kg IV daily	A	III
	Amphotericin B deoxycholate	0.7-1 mg/kg IV daily	A	III
After the first trimester	Fluconazole or itraconazole		A	III
Key: * Use until clinical improvement and then switch to triazole (fluconazole 400 mg PO daily or itraconazole 200 mg PO twice daily) Abbreviations: IV = intravenous; kg = kilogram; mg = milligram; PO = by mouth				

Histoplasmosis develops due to inhalation of microconidia.[1] Infections in the lungs and disseminated infection is common. People with CD4 counts less than 150 cells/mm^3 and have a risk due to occupational exposure or in areas with a high incidence of histoplasmosis are candidates for preventative therapy (**Table 3**).[1] For the treatment of histoplasmosis, the importance of monitoring serum concentrations of itraconazole and voriconazole were updated. Random itraconazole serum concentrations should be monitored 2 weeks after initiation to verify absorption and assess changes in hepatic metabolism due to drug interactions.[1] Random levels of itraconazole should be measured in all patients after 2 weeks of treatment for histoplasmosis and should be 1.0-2.0 mcg/mL. Voriconazole trough levels for histoplasmosis should be measured 5 days after initiation, with goal levels of 1-5 mcg/mL.[1] Serum concentration of voriconazole can vary due to

varying metabolism and drug interactions. Serum concentrations of voriconazole greater than 5 mcg/mL are associated with neurotoxicity and hepatoxicity. Posaconazole serum concentrations for histoplasmosis should be higher than 1 mcg/mL and should be measured after 5 days of therapy.[1]

Table 3. Antifungal Treatments for Histoplasmosis[1]

Indication	Medication	Dose	Strength of Recommendation	Quality of Evidence
Preventative Therapy				
Preferred	Itraconazole	200 mg PO once daily	B	I
Severe Disseminated Disease				
Preferred Induction	Liposomal Amphotericin B	3 mg/kg IV daily	A	I
Alternate Induction	Amphotericin B lipid complex	5 mg/kg IV daily	A	III
Maintenance Therapy	Itraconazole	200 mg PO 3 times daily for 3 days, then 200 mg 2 times a day	A	II
Alternate Therapy	Posaconazole	300 mg extended-release tablet PO twice daily for 1 day, then 300 mg PO once daily	B	III
	Voriconazole	400 mg PO 2 times a day for 1 day, then 200 mg twice daily	B	III
	Fluconazole	800 mg once daily	C	II
Histoplasmosis Meningitis				
Preferred Induction	Liposomal amphotericin B	5 mg/kg IV daily	A	III
Alternative Induction	Amphotericin B deoxycholate	0.7 – 1.0 mg/kg IV daily	B	III
Preferred Maintenance	Itraconazole	200 mg PO 2-3 times a day	A	III
Alternate Maintenance	Voriconazole	400 mg PO twice daily for day 1, then 200 mg PO twice daily	B	III
	Fluconazole	800 mg PO once daily	C	II
Preferred Long-Term Suppressive Therapy	Itraconazole	200 mg PO once daily	A	III
Alternative Long-Term Suppressive Therapy	Fluconazole	400 mg PO once daily	C	II
	Voriconazole	200 mg PO twice daily	B	III
	Posaconazole	300 mg PO daily	B	III
Treatment in Pregnancy				
Preferred 1st trimester Therapy	Amphotericin B	Dose not given	A	III
Preferred 2nd/3rd trimester Therapy	Itraconazole	Dose not given	C	III
Abbreviations: IV = intravenous; kg = kilogram; mg = milligram; PO = by mouth				

After review, one guideline was excluded due to poor quality.[24]

New Formulations or Indications:

Cresemba® (isavuconazonium): A new indication for isavuconazonium 372 mg injection was approved in December 2023 for use in pediatric patients 1 year of age and older for the treatment of IA and IM.[2] The isavuconazonium 74.5 mg and 186 mg capsules also received approval for the treatment of IA and IM in pediatric patients 6 years of age and older who weigh at least 16 kg.[2] Evidence used to obtain the approval in pediatric patients (n=31) was from a phase 2, open-label, noncomparative study in patients 1 to less than 18 years with probable or definitive IA or IM.[25] The primary endpoint was all-cause mortality at day 42. All-cause mortality was 6.5% on day 42. Successful response rates were 54.8% at the end of treatment.[25]

New FDA Safety Alerts:

Table 4. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Itraconazole[3]	Sporanox®	October 2024	Warnings	Risk of pseudoaldosteronism characterized by new onset of hypertension or worsening hypertension and abnormal lab values (i.e., hypokalemia, low serum renin and aldosterone and elevated 11-deoxycortisol). Blood pressure and potassium levels should be monitored and discontinuing itraconazole may be appropriate.
Itraconazole[3]	Sporanox®	October 2023	Precautions	Finerenone, voclosporin, mobocertinib, entrectinib and pemigatinib were added to the drug interaction precautions section.
Itraconazole[3]	Sporanox®	December 2024	Adverse Reactions	Bradycardia has been reported in post-marketing reports.
Metronidazole[5]	Flagyl®	March 2024	Warnings	Risk of severe cutaneous adverse reactions (SCARs) and hearing impairment have been reported. Metronidazole should be discontinued immediately if signs of SCARs develop, including skin rash, blisters, fever or other signs of hypersensitivity.
Posaconazole[4]	Noxafil®	October 2024	Warnings	Risk of pseudoaldosteronism characterized by new onset of hypertension or worsening hypertension and abnormal lab values (i.e., hypokalemia, low serum renin and aldosterone and elevate 11-deoxycortisol). Blood pressure and potassium levels should be monitored and discontinuing itraconazole may be appropriate.
Voriconazole[6]	Vfend®	March 2025	Contraindications and drug interactions	Concomitant use of voriconazole and finerenone is contraindicated. Coadministration may result in significant increases in finerenone exposure and risk for serious adverse reactions.

Randomized Controlled Trials:
A total of 128 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

Antifungals, Oral

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

Antifungals, Topical

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

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

tolnaftate	ATHLETE'S FOOT	AERO POWD	N
tolnaftate	TOLNAFTATE	AERO POWD	N
tolnaftate	ANTIFUNGAL CREAM	CREAM (G)	N
tolnaftate	TOLNAFTATE	CREAM (G)	N
tolnaftate	TRITOLNACIDE C	CREAM(ML)	N
tolnaftate	TOLNAFTATE	POWDER	N
tolnaftate	ANTIFUNGAL	SOLUTION	N
tolnaftate	MICOMITIN	SOLUTION	N
tolnaftate	MICOTRIN AL	SOLUTION	N
tolnaftate	MYCOZYL AL	SOLUTION	N
tolnaftate	TOLNAFI-AL	SOLUTION	N
tolnaftate	TRITOLNACIDE S	SOLUTION	N
undecylenic ac/zinc undecylena	ANTIFUNGAL CREAM	CREAM (G)	N
undecylenic ac/zinc undecylena	UNDEX-25	OINT. (G)	N
undecylenic acid	TRIPENICOL C	CREAM(ML)	N
undecylenic acid	TRIPENICOL S	SOLUTION	N

Antifungals, Vaginal

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

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to June 19, 2025
Search Strategy:

#	Searches	Results
1	clotrimazole.mp. or Clotrimazole/	3432
2	Fluconazole/ or fluconazole.mp.	17714
3	nystatin.mp. or Nystatin/	5723
4	flucytosine.mp. or Flucytosine/	4168
5	griseofulvin.mp. or Griseofulvin/	4167
6	ibrexafungerp.mp.	161
7	isavuconazonium.mp.	110
8	itraconazole.mp. or Itraconazole/	12662
9	ketoconazole.mp. or Ketoconazole/	10169
10	miconazole.mp. or Miconazole/	3624
11	oteseconazole.mp.	58
12	posaconazole.mp.	3938
13	terbinafine.mp. or Terbinafine/	3846
14	voriconazole.mp. or Voriconazole/	9592
15	acetic acid.mp. or Acetic Acid/	58997
16	butenafine.mp.	117
17	ciclopirox.mp. or Ciclopirox/	752
18	clotrimazole.mp. or Clotrimazole/	3432
19	econazole.mp. or Econazole/	1075
20	efinaconazole.mp.	270
21	ketokonazole.mp.	24

22	luliconazole.mp.	238
23	naftifine.mp.	233
24	oxiconazole.mp.	124
25	sertaconazole.mp.	171
26	tavaborole.mp.	160
27	tolnaftate.mp. or Tolnaftate/	310
28	undecylenic.mp.	404
29	terconazole.mp.	268
30	tioconazole.mp.	260
31	butoconazole.mp.	72
32	terconazole.mp.	268
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	119823
34	limit 33 to (english language and humans and yr="2023 -Current")	3546
35	limit 34 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	128

Appendix 4: Key Inclusion Criteria

Population	Patients with active fungal infections
Intervention	Oral, topical, or vaginal antifungal therapies
Comparator	Placebo or active treatment
Outcomes	Mycological cure
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Antifungals

Goal(s):

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

Length of Authorization:

- See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Table 1: Examples of FUNDED indications (07/08/2025~~10/19/23~~)

ICD-10	Description
B37.1	Candidiasis of the lung
B37.3	Candidiasis of vulva and vagina (vaginitis and cervicitis)
B37.42, B37.49	Candidiasis of other urogenital sites
B37.5-37.6, B37.81-37.84, B37.89	Candidiasis of other specified sites
B37.7	Disseminated Candidiasis

B38.0-B38.4, B38.7, B38.9	Coccidiomycosis various sites
B39.0-39.5, B39.9, G02, I32, I39, J17	Histoplasmosis, subacute meningitis, acute bacterial meningitis
B40.9, B41.0, B41.9, B48.0	Blastomycosis
B42.0-42.9, B43.9, B44.9-45.0, B45.7, B45.9, B46.9, B48.1-48.2, B48.8, B49	Rhinosporidiosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycosis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Opportunistic Mycosis, Mycoses Nec and Nos
B44.81	Bronchopulmonary Aspergillus, Allergic
L03.019, L03.029, L03.039, L03.049	Cellulitis and abscess of finger and toe
L30.4	Severe intertrigo (see HERC guideline note 21 for definition of severe inflammatory skin disease)
N73.9-75.1, N76.0-N77.1	Acute inflammatory pelvic disease
P37.5	Neonatal Candida infection

Table 2: Examples of NON-FUNDED indications (07/08/2025~~12/16/21~~)

ICD-10	Description
B36.0	Pityriasis versicolor
B36.2	Tinea blanca
B36.3	Black piedra
B36.8, B36.9	Mycoses, superficial
B37.2	Cutaneous candidiasis
B37.9	Candidiasis, unspecified
L20.0-20.84, L20.89-20.9	Other atopic dermatitis and related conditions
L21.0-21.1, L21.8-21.9,	Erythematosquamous dermatosis
L22	Diaper or napkin rash
L23.0, 23.81, L24.0-24.2, L24.81, L25.0, L25.1-25.5, L25.8-L25.9. L55.1-L55.2, L56.8, L57.8, L57.9, L58.9	Contact dermatitis and other eczema
L26, L30.4, L49.0-L49.9, L51.0, L51.8-L51.9, L52, L53.0-L53.2, L53.8, L53.9, L71.0-L71.1, L71.8, L92.0, L93.0, L93.2, L95.1, L98.2	Erythematous conditions

L43.8, L44.1-44.3, L44.9,L66.1	Lichen Planus
L70.0-70.2, L70.8	Rosacea or acne
R21	Rash and other nonspecific skin eruption

Table 3: Diagnosis funded by OHP if criteria are met (7/081/2524)

ICD-10	Description
B35.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
B35.1	Tinea unguium (onychomycosis)
B35.2	Dermatophytosis of hand (tinea manuum)
B35.3	Dermatophytosis of foot (tinea pedis)
B35.5	Dermatophytosis of body (tinea corporis / tinea imbricate)
B35.6	Dermatophytosis of groin and perianal area (tinea cruris)
B35.8-B35.9	Deep seated dermatophytosis; dermatophytosis of other specified sites - unspecified site
B36.1	Tinea nigra
B37.83	Candidiasis of mouth

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by OHP? (See examples in Table 1)	**Yes:** Go to #3	**No:** Go to #8
3. Is the request for oteseconazole?	**Yes:** Go to #4	**No:** Go to #7
4. Does the patient have a diagnosis of recurrent vulvovaginal candidiasis (RVVC) defined as a history of 3 or more episodes of acute vulvovaginal candidiasis (VVC) in the previous 12 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Has the patient failed to have benefit with, or have contraindications or intolerance to, a course of oral fluconazole for recurrent vulvovaginal candidiasis?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient of reproductive potential?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 18 capsules for 12 months
7. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Approve for 3 months or course of treatment.
8. Is the prescriber a hematology, oncology or infectious disease specialty prescriber requesting voriconazole or posaconazole?	**Yes:** Approve for 3 months or course of treatment.	**No:** Go to #9
9. Is the diagnosis not funded by OHP? (see examples in Table 2).	**Yes:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #10	**No:** Go to #10
10. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	**Yes:** Go to #11	**No:** Go to #16

Approval Criteria		
11. Is the patient immunocompromised (examples below)? • Does the patient have a current (not history of) diagnosis of cancer **AND** is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment. **OR** • Does the patient have a diagnosis of HIV/AIDS? **OR** • Does the patient have sickle cell anemia? • Poor nutrition, elderly or chronically ill? • Other conditions as determined and documented by a RPh.	**Yes:** Record ICD-10 code. Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Go to #12

Approval Criteria		
12. Is the patient currently taking an immunosuppressive drug? Document drug. **Pass to RPh for evaluation if drug not in list.** Immunosuppressive drugs include but are not limited to: azathioprine / leflunomide basiliximab / mercaptopurine cyclophosphamide / methotrexate cyclosporine / mycophenolate etanercept / rituximab everolimus / sirolimus hydroxychloroquine / tacrolimus infliximab	**Yes:** Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Go to #13

Approval Criteria		
13. Is the request for treatment of a foot condition and does the member meet criteria for high-risk foot care? Antifungals are funded when all of the following criteria are met: 1) The patient is at high risk for nail/foot complications due to severe circulatory insufficiency and/or areas of desensitization OR resides in an institutional setting (e.g., skilled nursing/rehabilitation facility, group home, etc.) AND 2) There is clinical evidence of mycosis of the toenail; AND 3) The patient has documented marked limitation of ambulation, pain, and/or secondary bacterial infection resulting from the thickening and dystrophy of the infected toenail plate.	**Yes:** Approve as follows: ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #14
14. 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 #15	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
15. Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class and process appropriate PA.
16. RPh only: All other indications need to be evaluated to see if it is an OHP-funded diagnosis: • If funded: may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only. • If not funded: ○ If 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.)? ▪ If yes, may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only. ▪ If No, deny (medical necessity) ○ If the member is not eligible for EPSDT, Deny; not funded by the OHP. ▪ Deny non-fungal diagnosis (medical appropriateness) ▪ Deny fungal ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP). ▪ Forward any fungal ICD-10 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.		

P&T Review: *10/25 (KS); 12/23;12/22; 2/22; 11/19; 7/15; 09/10; 2/06; 11/05; 9/05; 5/05*
Implemented: *TBD; 1/1/24; 1/1/23; 4/1/22; 5/1/16; 8/15; 1/1/11; 7/1/06; 11/1/0; 9/1/0*

Drug Use Research & Management Program
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New Drug Evaluations: Epidermolysis bullosa

Date of Review: December 2025
Generic Name: beremagene geperpavec, topical gel
Generic Name: prademagene zamikeracel, topical gene-modified cellular sheets
Generic Name: birch triterpenes, topical gel

End Date of Literature Search: 09/12/2025
Brand Name (Manufacturer): Vyjuvek (Krystal Biotech, Inc)
Brand Name (Manufacturer): Zevaskyn (Abeona Therapeutics, Inc)
Brand Name (Manufacturer): Filsuvez (Lichtenheldt GmbH)

Dossier Received: No

Plain Language Summary:

- Epidermolysis bullosa is a condition associated with very fragile skin. In people with epidermolysis bullosa, small bumps and scrapes can cause chronic wounds that do not heal.
- The Food and Drug Administration (FDA) has approved 3 medicines to help wounds heal in people with epidermolysis bullosa. There are many different genetic mutations that cause epidermolysis bullosa, and these therapies have been mostly studied in people with mutations in the collagen type VII alpha 1 chain (COL71A) gene. People with this genetic mutation generally have many long-lasting, non-healing wounds.
    - Birch triterpenes is a medicine that patients apply to non-healing wounds every 1 to 4 days when wound dressings are changed. About 41% of people who applied birch triterpenes had wounds that healed over 45 days compared to 29% of people who had usual wound care. When wound healing was measured at 90 days or with other definitions, birch triterpenes was no different than usual wound care.
    - Beremagene geperpavec is a medicine that is approved by the FDA for people with at least one mutation in the COL71A gene. Providers can apply this medicine to the surface of non-healing wounds. This medicine is designed to correct the underlying genetic mutation that causes the wound, but it must be reapplied every week. In clinical studies, 65% of wounds treated with beremagene geperpavec were completely healed by 6 months compared to 26% of wounds treated with usual care.
    - Prademagene zamikeracel is a medicine that is approved by the FDA for people with at least two mutations in the COL71A gene. It is made from healthy skin cells that are collected from the patient and modified in the lab to correct the underlying genetic mutation. These modified cells are grown into sheets that are sewn onto non-healing wounds. After about 6 months, 16% of wounds treated with these modified skin cells were completely healed compared to 0% of wounds treated with usual care. Unlike other medicines, prademagene zamikeracel was studied in people who had very large and old wounds which could have influenced study results. The average age of non-healing wounds was 5 years (range 6 months to 21 years).
- There is not enough information to determine if one medicine is better than another. Differences in the studied populations (such as wound duration and size) make it difficult to determine if one particular medicine works better than another.
- During clinical studies, the number of people who had serious side effects was generally small for all 3 medicines. However, these medicines have not been studied in very many people, and there are many things that are not known about their long-term safety.

Author: Sarah Servid, PharmD

- We recommend that the Oregon Health Authority pay for birch triterpenes, beremagene geperpavec, or prademagene zamikeracel when the provider documents why someone needs these medicines. This process is called prior authorization.

Research Questions:

1. In people with epidermolysis bullosa (EB), what is the evidence for recent FDA-approved therapies to improve wound healing or symptoms and how does efficacy compare to current standard of care for wound treatment?
2. What is the evidence for safety of FDA-approved treatments for EB?
3. Are there subgroups of patients (based on genetic variation, disease severity, type of EB, or comorbid conditions) for whom these treatments are more effective or associated with more harms?

Conclusions:

- There is low certainty evidence from a single randomized controlled trial (RCT; n=223) that birch triterpenes gel has a small benefit for complete wound closure compared to standard wound care in people with junctional or dystrophic EB with about 45 days of therapy (41.3% vs. 28.9%; difference 12.4%; number-needed-to-treat [NNT] 9; relative risk [RR] 1.44; 95% confidence interval [CI] 1.01 to 2.05; p=0.013).[1] In the subgroup of people with junctional EB, wounds treated with birch triterpenes had less healing compared to standard of care, but the overall number of people with junctional EB was small and the study was not powered to detect differences between subgroups.[1]
- There is insufficient evidence to determine whether birch triterpenes affects EB complications (e.g., skin cancer, infection), quality of life, total wound burden, or re-opening of wounds. When wound closure and severity was evaluated using a variety of other outcomes including time to first complete wound closure, complete wound closure at 90 days, change in total wound burden, and percent of body surface area affected, the differences between groups were not statistically significant.[1] There is no data on efficacy in wounds older than 9 months.[1] For people enrolled in the trial, median wound duration was about 1 month, and 65% of wounds were less than 20 cm^2 in size.[1]
- There in low certainty evidence from a single small trial (n=31) that beremagene geperpavec improves complete wound healing in patients with dystrophic EB compared to usual care over 6 months (65% vs. 26%; difference 39%; 95% CI 14% to 63%; p=0.012; NNT = 3).[2] People enrolled in this trial generally had recessive dystrophic EB (97%) and a wound size less than 20 cm^2 (71%).[2] There is insufficient data to determine whether beremagene geperpavec impacts other symptoms including itching or pain, EB complications (e.g., skin cancer, infection), or quality of life. There is currently insufficient evidence on efficacy beyond 6 months. A long-term extension study documented that some people had wounds remain closed over a median treatment duration of 1.5 years, but evidence is limited by a significant amount of missing data, risk for selection bias, and lack of control groups.[3]
- There is insufficient evidence from a small trial (n=11) that prademagene zamikeracel improves wound healing in patients with recessive dystrophic EB and chronic non-healing wounds compared to usual care.[4] After 24 weeks, more people had treated wounds that were at least 50% healed (81% vs. 16%; difference 67%; 95% CI 50 to 89%) and completely healed (16% vs. 0%; difference 13%; 95% CI 2 to 26%) compared to standard of care.[4] In this trial the median wound age was 5 years (range 6 months to 21 years) and all wounds were larger than 20 cm^2.[4] There is insufficient evidence that prademagene zamikeracel improves pain compared to standard of care, and other clinically relevant outcomes have not been evaluated including total wound burden, complications (e.g., skin cancer, infection), or impacts on quality of life. Prademagene zamikeracel has not been studied in people with an immune response to type VII collagen or people who are more likely to develop an immune response to type VII collagen.[4]
- All 3 therapies were generally well tolerated in short-term studies. The incidence of serious side effects was generally infrequent and not attributed to therapy. Available safety data is limited by small trials, intra-patient study designs, and lack of controlled long-term data. For the gene therapies, it is currently unclear how immunogenicity against viral vectors or collagen type VII might impact long-term safety or efficacy of therapy. Studies of beremagene geperpavec documented development of antibodies for collagen type VII without impacts on short-term efficacy, and studies of prademagene zamikeracel

excluded people who had baseline antibodies for collagen type VII or were likely to develop antibodies. The long-term durability of treatment effects for these gene therapy is currently unknown.

Recommendations:

- Implement prior authorization for high cost treatments for epidermolysis bullosa including birch triterpenes, beremagene geperpavec and prademagene zamikeracel.

Background:

Epidermolysis bullosa (EB) is a condition affecting skin integrity in which minor trauma can cause blistering and chronic, non-healing wounds. It can be inherited (i.e., caused by genetic mutations in proteins essential to skin structure) or autoimmune-mediated.[5] Inherited forms of EB are broadly categorized into 4 types based on the location blisters form in the skin. In epidermolysis bullosa simplex, blisters originate in the epidermis; in junctional epidermolysis bullosa, blisters originate within part of the basement membrane called the lamina lucida; in dystrophic epidermolysis bullosa, blisters originate within the sublamina densa; and in Kindler epidermolysis bullosa blisters can originate at any layer of the epidermis.[5] Both junctional and dystrophic disease can be associated with severe symptoms, whereas EB simplex typically has more mild symptoms. Dystrophic epidermolysis bullosa can be further categorized as autosomal dominant or recessive depending on the inheritance pattern of mutations in the COL7A1 gene.[5] This gene is responsible for formation of the collagen type VII protein which forms anchoring fibrils that hold the epidermis and dermis together. In dominant dystrophic EB the amount of functional collagen VII protein is reduced, whereas recessive dystrophic EB is usually associated with absence of functional collagen VII and more severe symptoms.[5] Without collagen VII, when a blister forms, it is easier for skin layers to separate creating chronic non-healing wounds. It is estimated that 1 in 125,000 people live with some form of EB in the United States, and about 5-25% of patients have dystrophic EB.[5].

Diagnosis is based on clinical presentation of symptoms, evaluation of family history, skin biopsy to determine the level at which blisters form, and genetic testing. Laboratory diagnosis is typically recommended to rule out other skin conditions such as bullous pemphigoid, other inherited skin conditions, skin infections, and friction blisters. Inherited disease typically presents in neonates as skin blistering, most commonly on extremities or from diapers.[5] Blisters can be associated with pain, itching, scarring, and milia (e.g., small cysts caused by build-up of keratin in the skin).[5] More severe forms of the disease can be associated with nail dystrophy or loss, infection, alopecia, mucosal involvement resulting in growth failure or malnutrition, and scaring causing partial fusion of fingers and toes.[5] Long-term repeated blistering and scarring can increase risk for severe infections and squamous-cell carcinoma.[2] Both junctional and recessive dystrophic EB are associated with early mortality. Junctional EB has an estimated mortality of 50% by 2 years of age. In people with recessive dystrophic epidermolysis bullosa, squamous cell carcinoma is the most common cause of death with an estimated cumulative risk of 70% by 45 years of age.[5]

Management of EB is primarily supportive and focuses on wound management, skin care, and treatment of complications. Until recently, there have been no targeted treatments for EB. Pain and itching are some of the most common symptoms associated with open or partially healed wounds. Pain treatments could include cognitive behavioral therapy, topical analgesics and systemic analgesics.[5] Common treatments for pruritus could include antihistamines, tricyclic antidepressants, and gabapentinoids.[5] Wound care includes lancing and draining blisters, using soft, non-traumatic dressings with adhesive removers to remove adherent dressings, and monitoring for infection.[5,6] Because of the rarity of the conditions, much of the evidence for specific topical medications for wound management is based on case reports and expert opinion.[6] Choice of topical therapies and dressings should address specific wound characteristics considering need for wound debridement to remove dry or necrotic skin cells, infection or critically colonized wounds, or need moisturizers and exudate management.[6] Since 2023, the FDA has approved 3 therapies for treatment of wounds in people with certain types of EB (**Table 1**).

Table 1. FDA-approved indications for newer EB therapies

Generic Name (Brand)	Mechanism	FDA Indication	Gene mutation	Route and Frequency	How Supplied
birch triterpenes (FILSUVEZ)[7]	Decreases inflammation and promotes wound healing	Junctional and Dystrophic EB	Junctional: LAMA3, LAMB3, LAMC2, ITGB4, ITGA6, COL17A1, ITGA3 Dystrophic: COL7A1	Topical gel applied with dressing changes every 1-4 days	Single-use, sterile tubes
beremagene geperpavec (VYJUVEK)[8]	Gene therapy that delivers a functional COL7A1 gene to cells in existing wounds; COL7A1 is not incorporated into cellular DNA	Dystrophic EB	COL7A1	Topical gel applied weekly	Single-use vials of cryopreserved drug product intended to be mixed with excipient gel immediately before administration
prademagene zamikeracel (ZEVASKYN)[9]	Gene therapy in which the patient's cell have been collected and modified to produce a functional COL7A1 gene	Recessive Dystrophic EB	COL7A1	Topical sheets applied during surgery	Skin cells collected from biopsy, modified with retrovirus, and grown into sheets
Abbreviations: COL71A = collagen type VII alpha 1 chain; DNA = deoxyribonucleic acid; EB = epidermolysis bullosa					

Clinically relevant outcomes for patients with EB include improvements in wound healing, pain, or itching and prevention of complications like infection, scarring, and skin cancer. For patients with severe disease, wound management can present a significant burden and impact on quality of life. There is no broadly accepted definition for clinically meaningful differences in these outcomes.[10] For adults, wound closure for at least 3 months may represent a clinically significant benefit, and for people with severe disease, more than a 50% improvement in wound burden may be needed to lead a more normal life.[10] However, even closure of a small number of wounds may result in clinically meaningful improvement in pain, itching, or quality of life.[10]

Beginning in January 2026, the Oregon Health Authority is proposing that high cost, rarely used medications be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

The medications listed in **Table 1** are currently included in the list of medications proposed to be carved-out of CCO budgets. Over a 1 year period from 4/1/24 to 3/31/25, 7 members had a diagnosis of dystrophic EB in their medical claims.

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:

Filsuvez (birch triterpenes)

FDA approval for birch triterpenes was based on a single, phase 3 RCT evaluating topical application of birch bark extract with vehicle control in people with dystrophic or junctional EB (**Table 2**). The exact mechanism of triterpenes is unknown but it is thought to decrease inflammation and promote wound healing.[1] People enrolled in the clinical trial were primarily pediatric patients with recessive dystrophic EB with partial thickness wounds that had been present for at least 21 days.[1] At the initial treatment visit, one wound meeting eligibility criteria was selected as the target wound. Patients were excluded if they had local skin infections, recent antibiotic use, or EB simplex (which generally has less severe symptoms), and wounds older than 9 months.[1,11] The median wound size was 15.6 cm^2 and average age was 35.5 days.[1] The primary outcome was complete closure of the target wound within 45 days defined as re-epithelialization without drainage. In alignment with FDA guidance for wound outcomes, the first evaluation of wound closure was re-confirmed by a second observation within 7 days.[1] More patients treated with birch triterpenes had complete wound closure before 45 days compared to vehicle control (41.3% vs. 28.9%; RR 1.44; 95% CI 1.01 to 2.05; p=0.013).[1] However, data was limited by large and differential amounts of missing data for the follow-up observational visit (33% in treatment and 61% in placebo lacked confirmation after 7 days).[1] Additionally, none of the secondary outcomes evaluating wound healing or symptom improvement achieved statistical differences between groups. Secondary outcomes included the time to first complete closure of the target wound, complete wound closure at 90 days, incidence and severity of wound infection, change in total wound burden, percent of body surface area affected, pain and itch intensity.[1]

Evidence limitations and unknowns:

- Evidence from the phase 3 trial has risk for selection bias based on differences between groups in baseline characteristics (e.g., wound age and subtype of EB) and risk for attrition bias (with differential attrition between groups). FDA analyses to account for missing data using multiple imputation methods indicated high risk for attrition bias.[12] The treatment group enrolled more people with recessive dystrophic EB (83.5% vs. 73.7% with placebo).[1] Treatment effects were also more prominent in this subtype, and people with junctional or dominant dystrophic EB did not have trends favoring treatment over control.[1] In people with junctional EB, wound closure was more common in people treated with placebo (26.7%) compared to treatment (18.2%), but the total number of people treated was small (n=26) and the trial was not designed to detect differences between subgroups.[1]
- There is insufficient evidence to evaluate efficacy of birch triterpenes in specific subtypes of EB, and no data evaluating birch triterpenes in EB simplex (a less severe form of the disease).
- There is inadequate evidence to evaluate whether birch triterpenes improves sustained wound closure compared to placebo or assists with healing of chronic wounds. People with EB have inherently fragile skin, and it is common to have minor trauma re-open wounds after partial or complete healing. At 90 days, the difference between groups was smaller and not statistically significant.[1] While initially patients with wounds older than 9 months were eligible for trial enrollment, they were subsequently excluded from the study, and FDA analyses suggest that clinical activity of birch triterpenes is more relevant to promoting closure of acute wounds compared to healing older, chronic wounds.[12] There is no evidence that birch triterpenes prevents wounds from re-opening.
- There is insufficient evidence to evaluate other outcomes including total wound burden, other symptoms (like pain and itch severity), and prevention of infections or other long-term complications.

Beremagene geperpavec

Beremagene geperpavec is a topically administered gene therapy composed of a herpes simplex virus-type 1 (HSV-1) vector. It is intended to deliver a non-mutated copy of COL7A1 gene to the nucleus of skin cells without integration of DNA into the host cell chromosome. The delivered DNA results in formation of functional COL7 protein, but because the DNA is not integrated into the host genome, re-application is needed for ongoing efficacy. The drug was FDA approved based on results of a phase 3 trial which enrolled people with dystrophic EB (primarily recessive) caused by mutations in the COL7A1 gene (**Table 2**).[2] For each

enrolled patient, 2 matching wounds were identified and randomized to either treatment or placebo. Wounds were matched based on size, region and appearance. Median size was 10.6 cm^2 and most wounds were less than 40 cm^2 in size.[2] Age of wounds at baseline was not reported. Patients with active infection or history of squamous cell carcinoma were excluded. The primary endpoint was complete wound healing at 6 months defined as skin re-epithelialization without drainage for at least 2 weeks.[2] A key secondary endpoint was complete wound healing at 3 months. Compared to placebo, more wounds treated with beremagene geperpavec were completely healed by 3 months (68% vs. 23%; difference 45%; 95% CI 23 to 69%) and 6 months (65% vs. 26%; difference 39%; 95% CI 14 to 63%).[8,13] Pain severity during dressing changes for wounds receiving treatment or placebo was also evaluated as a secondary endpoint. However, changes from baseline were generally small for both groups (<1 point change on a 0-10 point visual analogue scale),[2] and methodological limitations make interpretation of these results unclear.[13] There was no pre-specified statistical analysis plan for pain severity endpoints, no methods documented to handle missing data, and rescue pain medication use was not documented.[13]

Data is limited by unclear risk of selection bias as randomization methods were not reported. The trial also included 5 patients (16%) who were previously enrolled in earlier trials for beremagene geperpavec which is a population likely to have had benefit from beremagene geperpavec based on prior treatment experience. There is insufficient data to evaluate differences in specific subgroups or populations. The trial was adequately blinded and enrolled a wide variety of races. The majority of data is applicable to people with recessive dystrophic EB who have wounds smaller than 40 cm^2. Wound age was not reported which make indirect comparisons to other treatment options difficult. Most people either tested positive for HSV antibodies at baseline or developed antibodies over the course of the study.[2] However, post-hoc subgroup analyses did not identify any differences in efficacy among people who tested seropositive or seronegative for anti-HSV-1 or anti-COL7 antibodies for the duration of the study.[2] Long-term data are needed to confirm these findings, and there is currently insufficient data to evaluate long-term efficacy and durability of response. Of the 24 patients in the phase 3 trial who enrolled in the long-term extension study, there was available efficacy data for 16 to 18 members who had consistent follow-up visits after 12 to 18 months of treatment.[3] In these members, 10 to 14 had complete wound closure (41.6% to 58.3%) after a treatment duration of 1 to 1.5 years.[3] However, long-term efficacy data is limited by a significant amount of missing data, risk for selection bias, and lack of control groups.

<u>Prademagene zamikeracel</u>

Prademagene zamikeracel is FDA approved for people with recessive dystrophic EB. It is manufactured from autologous skin cells collected from the patient, modified with a retrovirus to contain the COL7A1 gene, and grown in the laboratory into cellular sheets which are then sewn onto wounds.[9] Each cellular sheet is about 41 cm^2 and up to 12 sheets can be made from 2 skin biopsies.[9] All manufactured sheets are intended to be applied during a single surgery. In the phase 3 clinical trial, the average time between skin biopsy and application of cellular sheets was about 25 days.[4]

Prademagene zamikeracel was evaluated in an open-label, phase 3, intra-patient trial containing 11 people.[4] The study included people with recessive dystrophic EB and at least 2 large (≥20 cm^2) chronic (≥ 6 month) wounds.[4] Median wound duration was 5 years (range 6 months to 21 years).[4] Wounds were matched based on size, location and duration whenever possible and randomized to treatment or standard of care. After 24 weeks, more people had treated wounds that were at least 50% healed compared to standard of care (81% vs. 16%; difference 67%; 95% CI 50 to 89%).[4] The trial also reported pain improvement using 11-point visual analogue scale in treated wounds compared to untreated wounds (-3.07 vs. -0.9; MD -2.23; 95% CI -3.45 to -0.66) and more wounds with complete healing at 24 weeks (16% vs. 0%; difference 13%; 95% CI 2 to 26%).[4]

Due to the nature of the intervention, blinding was not possible. Data are limited by the open-label study design which increases risk of performance and detection bias, particularly for subjective outcomes like pain reduction. Wound healing was not evaluated by blinded assessors, and differences in treatment between groups (such as debridement and cauterization of wounds in the treatment arm) may account some of the differences between groups. Very few

patients were enrolled, and it is unclear whether 50% of wound healing represents a clinically meaningful outcome for patients. Only 16% of treated wounds were completely healed after 24 weeks.[4] However, unlike other drugs evaluated to promote wound healing in EB, the people enrolled in this trial had wounds that were generally larger and older than other trials of drugs to treat EB, making comparisons between agents difficult. There is insufficient data to determine if treated wounds continued to heal beyond 24 weeks, or if this gene therapy prevents wounds from re-opening or reforming. Re-treatment with prademagene zamikeracel has not been evaluated. People enrolled in the trial had to lack an immune response to type VII collagen and have expression of the amino-terminal NC1 fragment of type VII collagen, which decreases risk of developing an immune response. Because there is no data in other populations, it is unclear how an immune response to collagen VII would impact efficacy of prademagene zamikeracel.

In conclusion, there is no direct data to evaluate comparative efficacy or safety of therapies recently approved by the FDA for treatment of EB. All three therapies demonstrated improvements in wound healing compared to standard of care, though none of the trials described the specific interventions provided as standard of care. Studies of birch triterpenes enrolled the largest number of patients with a variety of EB subtypes, but studied wounds for the shortest duration. By comparison, both beremagene geperpavec and prademagene zamikeracel were studied in a much smaller population with primarily recessive dystrophic EB. The median wound size was smallest in patients treated with beremagene geperpavec and largest in patients treated with prademagene zamikeracel.

	Birch triterpenes[1]	Beremagene geperpavec[2]	Prademagene zamikeracel[4]
EB type	Recessive dystrophic (79%) Junctional (12%) Dominant dystrophic (9%)	Recessive Dystrophic (97%)	Recessive dystrophic (100%)
Number of patients enrolled	223	31	11
Median wound size	15.6 cm^2	10.4 cm^2	Not reported; all were ≥ 20 cm^2
Median wound age	35 days	Not reported	5 years
Trial duration	45 days	24 weeks	24 weeks
Study design	RCT	Intra-patient RCT	Intra-patient RCT

Abbreviations: cm = centimeters; EB = epidermolysis bullosa; RCT = randomized controlled trial.

Clinical Safety:

Filsuvez (birch triterpenes)

During the phase 3 study and open-label extension period, 223 people with inherited EB were exposed to birch triterpenes for a duration of 24 months.[7] The most common adverse event was application site reactions (e.g., pain, pruritus) which occurred at similar rates as placebo gel (7.3% vs. 6.1%).[7] Squamous cell carcinoma, which is a common complication in recessive dystrophic EB, was reported for 4 people, 2 of whom had applied birch triterpenes to the area that developed carcinoma.[7] However, animal studies do not indicate carcinogenic risk and overall systemic absorption is low.[7] There is no data on use in specific populations including those that are pregnant or lactating. Birch triterpenes was studied in people as young as 6 months of age but has not been evaluated in people over 65 years. Local hypersensitivity reactions have been reported in post-marketing data including urticaria and dermatitis.[7]

Beremagene geperpavec

During the phase 3 clinical trial, 31 people with dystrophic EB were exposed to beremagene geperpavec for a median duration of 25 weeks. The most common adverse events observed in 2 or more patients in the phase 3 study were itching (n=3; 10%), chills (n=3; 10%), redness, rash, cough, and runny nose (n=2; 6%).[8]

The intra-patient design of the phase 3 trial confounds the systemic safety evaluation, and the exact location of localized skin reactions was not documented.[13] However, only 3 patients experienced serious adverse events during the treatment period (e.g., asymptomatic bacteremia, cellulitis, diarrhea, and anemia) and none of the adverse events appeared to be related to treatment. There were no discontinuations due to adverse events. FDA-approved labeling includes warnings for accidental exposure. While beremagene geperpavec is not designed to be integrated into cellular DNA, general precautions include avoiding direct contact with treated wounds for 24 hours following application, wearing gloves during dressing changes, and flushing eyes or mucous membranes for 15 minutes in the case of accidental exposure.[8] There is insufficient long-term data to evaluate the impact of developing immunogenicity on adverse events related to treatment.

Prademagene zamikeracel

Package labeling for prademagene zamikeracel includes potential for retroviral vector-mediated insertional oncogenesis, and lifelong monitoring is recommended for the development of malignancies.[9] It is also manufactured using human and bovine-derived products which, like all human and animal-derived products, carry risk for infectious disease transmission or hypersensitivity reactions.[9] The most common adverse event in the phase 3 trial was procedural pain (n=3; 27%).[9]

None of the patients in the phase 3 trial developed antibodies against collagen type VII over the 6 month study.[9] However, the trial was small and excluded people at risk for development of antibodies. There is overall insufficient data evaluating the incidence or clinical importance of anti-collagen type VII antibodies in people treated with prademagene zamikeracel.[9]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Complete wound closure
2) Total wound burden (e.g., number, frequency, or severity of wounds)
3) Pain or Itching
4) Quality of life, missed work or school days
5) Skin infection or skin cancer
6) Serious adverse events
7) Study withdrawal due to an adverse event

Primary Study Endpoint(s):
1) Complete wound closure
2) 50% wound closure
3) Pain improvement

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. Kern, et al. 2022.[1] DB, PC, phase 3 RCT NCT03068780	1. birch triterpenes 10% gel applied at least every 4 days 2. Placebo vehicle gel Administered in conjunction with standard of care dressings Duration: 90 day double-blind phase followed by 24 month open-label extension study	Demographics: - Median patient age: 12 years (95% CI 14.8-18.5) - Dystrophic EB Recessive: 79% 1. 83.5% 2. 73.7% Dominant: 9% 1. 5.5% 2. 12.3% - Junctional EB: 12% 1. 10.1% 2. 13.2% - Wound Size 10 to <20 cm^2: 65% 20 to <30 cm^2:21% 30-50 cm^2: 14% - Median wound age: 1. 39 days 2. 32 days Key Inclusion Criteria: - Dystrophic, junctional, Kindler EB - Partial-thickness wound lasting between 21 days and 9 months - Wound size 10-50 cm^2 Key Exclusion Criteria: - EB Simplex - Signs of local infection or antibiotic use within 7 days - Systemic or topical steroids - Immunosuppressive or cytotoxic chemotherapy - Prior gene therapy or stem cell transplant - Basal or squamous cell carcinoma	ITT: 1. 109 2. 114 PP: 1. 100 2. 99 Attrition 1. 9 (8%) 2. 15 (13%)	Primary Endpoint: Complete wound closure in 45 days 1. 45 (41.3%) 2. 33 (28.9%) Difference: 12.4% (95% CI 0.8 to 25.6%); RR 1.44 (95% CI 1.01 to 2.05); p=0.013 Secondary Endpoints: Time to first complete closure of target wound 1. 37.7 days (95% CI 31.9 to 43.6) 2. 44.5 days (95% CI 37.1 to 51.9) P=0.302 Complete wound closure in 90 days 1. 50.5% 2. 43.9% RR 1.16 (95% CI 0.88 to 1.52); P=0.296 All secondary endpoints were non-significant and considered exploratory based on the pre-specified testing plan	12.4%/ 9 NA NA	Serious AE: 1. 7 (6.4%) 2. 6 (5.3%) Withdrawal due to AE: 1. 3 (2.8%) 2. 2 (1.8%) Overall Infections & infestations: 1. 37 (33.9%) 2. 36 (31.6%) Wound-related infection: 1. 8 (7.3%) 2. 10 (8.8%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: HIGH. Randomized using blinded and computer-generated allocation tables with concealment for treatment group. Stratification included EB subtype and size of the target wound. More patients randomized to treatment had recessive dystrophic subtype (83.5% vs. 73.7%) and median wound age was 7 days older in the treatment group. Performance Bias: LOW. Blinded with identical vehicle control made from sunflower oil, cera flava/yellow wax and carnauba wax. Detection Bias: UNCLEAR. Blinding of assessors not reported. Blinded patients initially notified clinic of wound closure which was confirmed by clinic assessment upon the next visit. Unblinded interim analysis was conducted to determine whether estimated sample size was sufficient. Attrition Bias: HIGH. All patients randomized were included in the analysis. Differential attrition (5%) between groups. Missing data was defined as not achieving complete closure for the primary endpoint and censored at the date last known to have not achieved complete closure for the key secondary endpoint. Patients (n=2 in control arm) were withdrawn from the study because the target wound worsened or developed infection. Analyses to account for missing data using multiple imputation and tipping point analyses show that results "were fragile to these sensitivity analyses".[12] Reporting Bias: UNCLEAR. Primary and secondary outcomes reported as pre-specified. Multiple subgroup analyses and secondary outcomes evaluated at a variety of time-points. Other Bias: UNCLEAR. Funded by Amryt Research Limited. **Applicability**: Patient: Subgroup analyses indicate improvement was primarily driven by changes in people with recessive dystrophic EB, though the proportion of people with other types of EB was small. Rate of wound closure was higher in people with junctional EB who were prescribed placebo. Intervention: Applied in 1 mm layer to wound dressing at least every 4 days. At baseline, 43% changed dressings daily and 41% applied dressings every 2 days. Frequency of dressing changes decreased slightly in the treatment group over the course of the study. Comparator: Placebo gel appropriate to determine efficacy. Specifics Outcomes: Wound healing is a clinically relevant outcome. None of the secondary outcomes evaluating wound closure achieved differences from placebo; and magnitude of benefit is likely small. Re-opening of wounds is common in EB and re-confirmation within 7 days of initial assessment was planned. These results are supportive of the primary analysis but were limited by a significant amount of missing data; 33% in treatment and 61% in placebo lacked confirmation after 7 days.

								Setting: April 2017 to June 2020 in 26 countries (Asia, Europe, Americas)
2. Guide, et al. 2022.[2] FDA Clinical Review[13] DB, phase 3, PC, intra-patient RCT NCT04491604 For each patient, 2 wounds were matched based on size, region and appearance and randomized to treatment or placebo	1. Beremagene geperpavec applied topically weekly (at a dose of $4x10^8$ to $1.2x10^9$ plaque forming units depending on baseline wound size) 2. Placebo Duration: 26 weeks Dose was determined by size of the wound at baseline and applied in drops about 1 cm apart; any remaining dose could be applied to up to 4 additional wounds.	Demographics: - Median patient age: 16 years - Recessive dystrophic EB: 97% - Male: 65% - White: 65% - Asian: 19% - American Indian/Alaskan Native: 16% - Hispanic: 52% - Median wound size: 10.6 cm^2 (range 2.3-57.3) <20cm^2: 71% 20 to <40 cm^2: 26% Key Inclusion Criteria: - Patient age ≥ 6 months - Clinical and genetically confirmed dystrophic EB - 2 wounds of similar size, location, appearance Key Exclusion Criteria: - Current immuno- or chemotherapy - Active infection or current or historical squamous cell carcinoma in the treatment area - Active substance use disorder - Skin graft in the past 3 months	ITT: 1. 31 PP: 1. 28 Attrition 1. 3 (10%)	Primary Endpoint: Complete wound healing for at least 2 weeks at ~24 weeks (6 months) 1. 20 (65%) 2. 8 (26%) Difference: 39%; 95% CI 14 to 63%; p=0.012 Secondary Endpoints: Complete wound healing at ~12 weeks (3 months) 1. 21 (68%) 2. 7 (23%) Difference 45%; 95% CI 22 to 69%; p=0.003	NA	Serious AE: 1. 3 (10%) Withdrawal due to AE: 1. 0 Pruritus: 1. 3 (10%) Chills: 1. 3 (10%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Primary wound pair matched based on size, region, appearance and randomized to treatment or placebo. Randomization method was not reported. Pairing only controls for known confounding factors, and the similarity between wounds was not reported. Intra-patient design limits ability to evaluate systemic AEs. Wound age was not reported. Performance Bias: LOW. Patients, investigators, site staff and sponsor were blinded with matching placebo (with the same viscosity, appearance and volume). Open-label treatment was allowed for up to 4 additional wounds which may increase risk of potential unblinding. Detection Bias: LOW. Site staff evaluating wound closure were blinded with use of matching placebo. Attrition Bias: LOW. Overall attrition 10% (n=3) with ITT analysis. Missing data were imputed with a mixed model approach assuming data was missing at random and using a worst case scenario strategy with similar magnitude of effect. Reporting Bias: HIGH. Pain scores were reported at multiple time points and other secondary outcomes were not reported. Because the primary outcome was assessed over 2 consecutive weeks, it was evaluated twice for each patient (e.g., at 22 and 24 weeks or 24 and 26 weeks), leading to potential bias if the outcome was not consistent for all 3 weeks. However, the number of wounds in each group that had closed wounds that reopened at 26 weeks was similar between groups.[13] Other Bias: UNCLEAR. Funded by Krystal Biotech. Study sponsor was involved in data collection, monitoring, statistical analyses, and writing the manuscript. **Applicability**: Patient: Data is most applicable to patients with recessive dystrophic EB; only 1 patient had dominant dystrophic EB. Potentially enriched study population; 5 patients (16%) had been enrolled in the phase 1/2 trial for this treatment. Intervention: Cryopreserved drug product is mixed with excipient gel immediately before administration and applied to the wound in drops 1 cm apart each week until wound closure. Five wounds that closed at weeks 22 to 24 re-opened at week 26 indicating that weekly administration is needed to maintain treatment effects. Comparator: Placebo controlled appropriate to determine efficacy. Outcomes: Wound healing is a clinically relevant outcome. Only wounds that remained closed for at least 2 weeks were defined as completely healed. Setting: Three sites in the United States from August 2020 to April 2021.

Tang, et al. 2025.[4] Open-label, phase 3, intra-patient RCT NCT04227106	1. prademagene zamikeracel 2. standard of care Duration: 24 weeks Maximum of 6 wounds could be treated per patient. Non-matched wounds could receive open-label treatment Long-term follow-up is planned for a total of 15 years in NCT05708677	<u>Demographics</u>: - Median patient age: 21 years - Female: 64% - White 91% - Hispanic/Latino: 18% - Median wound duration: 5 years (range 0.5 to 21) - Subtype Severe: 36% Intermediate: 64% <u>Key Inclusion Criteria</u>: - Patient age ≥ 6 years - Clinical and genetically confirmed recessive dystrophic EB - At least 2 chronic wounds present for ≥6 months & ≥ 20 cm^2 - Expression of the amino-terminal NC1 fragment of type VII collagen - No immune response to type VII collagen <u>Key Exclusion Criteria</u>: - Current or historical squamous cell carcinoma - Hypersensivity to vancomycin or amikacin	<u>ITT</u>: 11 enrolled 1. 43 wounds 2. 43 wounds <u>Attrition</u> 0	<u>Primary Endpoint</u>: Proportion of wounds with ≥ 50% healing at week 24 1. 35 (81%) 2. 7 (16%) difference 67%; 95% CI 50 to 89%; p<0·0001 Pain reduction at week 24 (range 0-10 VAS) 1. -3.07 2. -0.90 MD -2.23; 95% CI -3.45 to -0.66; p=0.0002 <u>Secondary Endpoints</u>: Complete wound healing at 12 weeks 1. 6 (14%) 2. 0 (0%) Difference 19%; 95% CI 3 to 42; p=0·032 Complete wound healing at 24 weeks 1. 7 (16%) 2. 0 (0%) Difference 13%; 95% CI 2 to 26; p=0·016	NA	<u>Serious AE:</u> 2 (18%) <u>Withdrawal due to AE:</u> 0 <u>Wound infection</u> Patients 8 (73%) Wounds 1. 12/57 (21%) 2. 4/43 (9%) <u>Procedural pain</u> Patients 6 (55%) Wounds 1. 10/57 (18%) 2. 3/43 (7%)	NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: HIGH. Wounds were paired based on chronicity, location and size and wound pairs were randomized to treatment or standard of care with a computer randomization and an electronic data capture system. No allocation concealment. Pairing only accounts for known confounding factors and there is potential for mismatched wounds and selection bias. More control wounds were located on the back. <u>Performance Bias</u>: HIGH. Open-label design without blinding as wounds had visible sheets sutured to wounds. Lack of blinding could have influenced frequency of wound dressing changes impacting healing and incidence of wound infections. Treated wounds were debrided and cauterized under general anesthesia and untreated wounds were not debrided. In the absence of treatment, debridement may increase wound size. <u>Detection Bias</u>: HIGH. Outcomes for wound healing were not conducted by independent or blinded assessors. Open-label design without blinding increases risk of bias particularly for subjective outcomes like pain in which there is typically a large placebo response. <u>Attrition Bias</u>: UNCLEAR. Amount of missing assessments was not reported. ITT analysis with use of last observation carried forward for missing data. Responses for each wound pair were averaged to get a single measure per patient, then averaged for the population. <u>Reporting Bias</u>: LOW. Protocol available. Outcomes reported as prespecified. <u>Other Bias</u>: UNCLEAR. Funded by Abeona therapeutics who was involved in study design, data review, interpretation, analysis and writing the manuscript. **Applicability**: <u>Patient</u>: Applicable to members with recessive dystrophic EB and large, chronic non-healing wounds that have been present for at least 6 months (with a median duration of 5 years). Enrolled patients had no immune response to type VII collagen and were unlikely to form an immune response based on expression of amino-terminal NC1 fragment of type VII collagen. <u>Intervention</u>: Non-blistered skin was collected from two 8 mm punch biopsies. Isolated keratinocytes were transduced with retrovirus carrying COL7A1 gene and cultured to form autologous 40 cm^2 sheets. About 25 days after the biopsy under general anesthesia, treated wounds were debrided and cauterized to fit the size of the 40 cm^2 sheet. Sheets were sutured onto wounds and covered with non-adhesive protective dressings. Patients remained hospitalized for 7 days to protect sheets from pressure and friction. Median number of sheets administered was 6 (range 3-6). <u>Comparator</u>: Supportive standard of care appropriate to determine efficacy.

								Outcomes: Unclear whether 50% improvement in wound healing is clinically significant. Complete wound healing defined as re-epithelization without visible drainage or erosions and with only the presence of minor crusting, confirmed on a subsequent visit. Setting: Two sites in the United States from January 2020 to March 2022.
Abbreviations: AE = adverse events; ARR = absolute risk reduction; DB = double blind; CI = confidence interval; cm2 = square centimeters; EB = epidermolysis bullosa; FDA = Food and Drug Administration; ITT = intention to treat; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; RR = relative risk; VAS = visual analog scale								

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VYJUVEK® (beremagene geperpavec-svdt) biological suspension mixed with excipient gel for topical application
Initial U.S. Approval: 2023

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	09/2025
Dosage and Administration, Dose (2.1)	09/2025

INDICATIONS AND USAGE

VYJUVEK is a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy indicated for the treatment of wounds in adult and pediatric patients with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene. (1)

DOSAGE AND ADMINISTRATION

For topical application only.

Age Range	Maximum Weekly Dose (PFU)	Maximum Weekly Volume (mL)*
<3 years old	2×10^9	1
≥ 3 years old	4×10^9	2

PFU=plaque forming unit; mL=milliliter
*Maximum weekly volume is the volume after mixing VYJUVEK biological suspension with excipient gel.

Apply VYJUVEK gel to the selected wound(s) in droplets spaced evenly within the wound, approximately 1cm-by-1cm apart. (2.3)

- Apply VYJUVEK gel on wounds once a week. (2.1)
- See full prescribing information for instructions on preparation and handling, (2.2) and administration. (2.3).

DOSAGE FORMS AND STRENGTHS

VYJUVEK is a biological suspension, mixed into excipient gel, for topical application. VYJUVEK biological suspension is supplied as a 1 mL extractable volume in a single dose vial at a nominal concentration of 5×10^9 PFU/mL. The excipient gel is supplied as a 1.5 mL fill volume in a separate single use vial. VYJUVEK biological suspension (1 mL) is mixed into the excipient gel vial prior to administration as VYJUVEK gel. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Accidental Exposure to VYJUVEK: Avoid direct contact with treated wounds and dressings of treated wounds until the next dressing change, following application. Clean the affected area if accidental exposure occurs. (5.1)

ADVERSE REACTIONS

The most common adverse drug reactions (incidence >5%) were itching, chills, redness, rash, cough, and runny nose. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Krystal Biotech, Inc. at 1-844-557-9782 or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2025

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZEVASKYN (prademagene zamikeracel), gene-modified cellular sheets, for topical use
Initial U.S. Approval: 2025

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

ZEVASKYN is an autologous cell sheet-based gene therapy indicated for the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB). (1)

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

For autologous topical application on wounds only

- The recommended dose of ZEVASKYN is based on the surface area of the wound(s). One sheet of ZEVASKYN covers an area of 41.25 cm^2. (2.1)
- Up to twelve ZEVASKYN sheets may be manufactured from the patient biopsies and supplied for potential use. (2.1)
- Verify the patient's identity prior to ZEVASKYN application. (2.2)
- See full prescribing information for ZEVASKYN preparation, and administration instructions. (2.2, 2.3)

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

ZEVASKYN is supplied as a single-dose of up to twelve cellular sheets each measuring 41.25 cm^2 (5.5 cm x 7.5 cm) and consisting of patient's own, viable, gene-modified cells that contain functional copies of the *COL7A1* gene, which express collagen 7 (C7) protein. (3)

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

None.

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

- Hypersensitivity reactions to vancomycin, amikacin, or product excipients may occur with ZEVASKYN application. (5.1)
- Retroviral vector (RVV)-mediated insertional oncogenesis may potentially occur after treatment with ZEVASKYN. (5.2)
- Transmission of Infectious Agents may occur because ZEVASKYN is manufactured using human- and bovine-derived reagents. (5.3)

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

The most common adverse reactions (incidence ≥5%) were procedural pain and pruritus. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Abeona Therapeutics Inc. at 1-844-888-2236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2025

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

FILSUVEZ® (birch triterpenes) topical gel
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

FILSUVEZ topical gel is indicated for the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa in adult and pediatric patients 6 months of age and older. (1)

DOSAGE AND ADMINISTRATION

- Apply a 1 mm layer of FILSUVEZ to the affected wound surface and cover with wound dressing or apply FILSUVEZ directly to dressing so that the topical gel is in direct contact with the wound. Do not rub in the topical gel. (2)
- Apply FILSUVEZ at wound dressing changes until the wound is healed. (2)
- Each tube of FILSUVEZ is for one-time use only. (2)
- For topical use; not for oral, intravaginal, intra-anal, or ophthalmic use. (2)

DOSAGE FORMS AND STRENGTHS

Topical gel: 10% birch triterpenes w/w supplied in 25 mL sterile tubes (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- *Hypersensitivity Reactions:* If signs or symptoms of hypersensitivity occur, discontinue use immediately and initiate appropriate therapy. (5.1)

ADVERSE REACTIONS

The most common (incidence ≥2%) adverse reactions are application site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amryt Pharmaceuticals DAC at 1-855-303-2347 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 12/2023

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	Birch triterpenes	Beremagene geperpavec-svdt	Prademagene zamikeracel
Mechanism of Action	Unknown; contains various triterpenes refined from birch bark including betulin (72-88%). Triterepenes are thought to decrease inflammation and enhance keratinocyte migration and differentiation.	HSV-1 viral vector delivers a copy of the COL7A1 gene to the nucleus of both keratinocytes and fibroblasts. This DNA is transcribed to form the collagen type VII protein which is secreted and forms anchoring fibrils that hold the epidermis and dermis together.	A retroviral vector is used to insert a functional COL7A1 gene in skin cells collected from the patient. Modified cells are grown into cellular sheets and applied topically to wounds during surgery.
Distribution and Protein Binding	protein binding >99.9%	N/A	N/A
Elimination	Following topical administration, 68% of people had undetectable betulin blood levels. The average exposure was a mean 12% BSA treated or wound surface area of 0.11m^2 over 90 days.	N/A. No systemic exposure of viral vector following topical application	N/A
Half-Life	N/A	About 61% of patients had skin swabs that were positive for viral vector following treatment. Negative shedding from skin swabs was achieved in 16 of the 19 patients (84%) within six weeks following treatment.	N/A
Metabolism	Not fully characterized; primarily metabolized via CYP3A enzymes	N/A	N/A

Abbreviations: BSA = body surface area; COL7A1 = collagen type VII alpha 1 chain; DNA = deoxyribonucleic acid; HSV = herpes simplex virus; m^2 = square meters; N/A = not applicable; ng/mL= nanograms per milliliter

Epidermolysis Bullosa

Goal(s):

- Approve wound treatments in people with epidermolysis bullosa when supported by the evidence

Length of Authorization:

- Up to 12 months

Requires PA: pharmacy or provider administered claims

- Birch triterpenes (Filsuvez)
- Beremagene geperpavec (Vyjuvek)
- Prademagene zamikeracel (Zevaskyn)

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

Covered Alternatives:

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

Table 1. FDA-approved indications and dose

Drug	Maximum dose	Indication	Pathogenic gene mutation
Birch triterpenes (Filsuvez)	1 tube (25 mL) per day	Junctional or dystrophic epidermolysis bullosa	Junctional: LAMA3, LAMB3, LAMC2, ITGB4, ITGA6, COL17A1, ITGA3 Dystrophic: COL7A1
Beremagene geperpavec (Vyjuvek)	1 mL weekly for ages < 3 years 2 mL weekly for ages ≥ 3 years	Dystrophic epidermolysis bullosa	At least one pathogenic mutation in COL7A1
Prademagene zamikeracel (Zevaskyn)	12 sheets total per lifetime	Recessive dystrophic epidermolysis bullosa	2 pathogenic mutations in the COL7A1 gene with recessive inheritance pattern (biallelic)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a patient with a prior FFS approval for the requested drug?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3

Approval Criteria		
3. Is this an FDA approved indication and age (Table 1)?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there documentation of genetic testing to support the diagnosis?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request prescribed by, or in consultation with, a dermatologist or provider with experience in epidermolysis bullosa management or wound care?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for birch triterpenes in a patient with junctional epidermolysis bullosa? Note: In junctional epidermolysis bullosa, people treated with standard of care had better wound healing compared to people who used birch triterpenes.	**Yes:** Pass to RPh. Refer request to medical director for manual review, assessment of clinical severity, and goals of therapy.	**No:** Go to #7
7. Is request for concurrent use of more than one of the medications in Table 1?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is there documentation of current open chronic wounds including baseline wound size and estimated duration?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the request for an FDA-approved quantity (Table 1)?	**Yes:** Approve: Filsuvez for 3 months. Vyjuvek for 3 months. Zevaskyn for up to 12 months. Notify DMAP of approved Zevaskyn requests for care coordination.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for an FDA-approved quantity (Table 1)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Is there documentation that treated wound(s) have improved (e.g., decrease in size, closed, or healed)?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/2025
Implementation: TBD

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

New Drug Evaluation: Carbaglu® (carglumic acid) tablets for oral suspension

Date of Review: December 2025
Generic Name: carglumic acid

End Date of Literature Search: 09/10/2025
Brand Name (Manufacturer): CARBAGLU (Recordati Rare Diseases Group)
Dossier Received: No

Plain Language Summary:

- This review looks at evidence for carglumic acid, a medicine used to treat urea cycle disorders, which are conditions that are caused when a person cannot remove waste ammonia from their body.
- People with urea cycle disorders get sick when there is too much ammonia in the blood. Too much ammonia can lead to confusion, permanent brain damage, and death. Many people with urea cycle disorders become sick as newborns or very young babies.
- People with urea cycle disorders are treated by monitoring food (protein) intake and taking certain amino acids (protein is made of amino acids) supplements. CARBAGLU (carglumic acid) is used to manage a condition called N-acetyl glutamate synthetase (NAGS) deficiency, which is one kind of urea cycle disorder.
- Carglumic acid is also approved to treat a rare group of disorders called organic acidemias. In these conditions, the body does not have the enzymes needed to break down amino acids which results in a buildup of acids in the blood. Symptoms include poor feeding, vomiting, weak muscle tone, and lack of energy. Studies have shown that propionic acidemia and methylmalonic acidemia can be treated with carglumic acid.
- The Drug Use Research and Management group recommends that the Oregon Health Authority pay for carglumic acid in patients with NAGS deficiency or organic acidemias that are indicated by the Food and Drug Administration after their provider documents medical appropriateness through a process called prior authorization.

Research Questions:

1. What is the efficacy and effectiveness of carglumic acid in managing specific urea cycle disorders, including n-acetyl glutamate synthetase (NAGS) deficiency, propionic acidemia (PA), and methylmalonic acidemia (MMA)?
2. What are the harms of carglumic acid for the management of NAGS, PA, and MMA?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which carglumic acid is more effective or associated with fewer adverse events?

Conclusions:

- Carglumic acid is FDA-approved as adjunctive therapy for the acute and chronic treatment of acute hyperammonemia due to NAGS deficiency and as adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to PA or MMA.[1]

Author: Deanna Moretz, PharmD, BCPS

- The efficacy of carglumic acid in the treatment of acute and chronic hyperammonemia due to NAGS deficiency was evaluated in an unpublished, retrospective case series of 23 NAGS deficiency patients treated with carglumic acid over a median duration of 7.9 years (range 0.6 to 20.8 years).[1] Short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3.[1] Persistence of the effect was evaluated using long-term mean and median change in plasma ammonia level.[1] By day 3 of treatment with carglumic acid mean plasma ammonia levels had normalized (43.3 micromol/L; 95% CI, 0.5 to 86.2) and remained within or near normal range during long-term treatment, which ranged from 7 to 249 months (51.9 micromol/L; 95% Confidence Interval [CI], 11.4 to 92.1; low-quality evidence).[1]
- A randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated the efficacy of carglumic acid in the treatment of hyperammonemia in patients with PA and MMA (NCT01599286).[1] The study is not published, and study details are limited to the prescribing information issued by the manufacturer. Participants with an eligible hyperammonemic episode, defined as an admission to the hospital with a plasma ammonia level 70 micromol/L or higher, were randomized 1:1 to receive either carglumic acid or placebo for 7 days or until hospital discharge, whichever occurred first.[1] The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level of 50 micromol/L or less (normal range) or hospital discharge.[1] The median time to reach the primary endpoint was 1.5 days in the carglumic acid group compared to 2.0 days in the placebo group, a difference of 0.5 days (95% CI, -1.2 to 0.1; not significant; low-quality evidence).[1] Throughout the first 3 days of treatment, a higher proportion of carglumic acid-treated episodes reached the primary endpoint compared to placebo-treated episodes.[1]
- In the retrospective case series of 23 NAGS deficiency patients treated with carglumic acid, 17 of the 23 patients reported an adverse reaction.[1] The most common adverse reactions (occurring in ≥ 13% of patients) were vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, decreased hemoglobin, and headache.[1] **Table 1** summarizes adverse reactions that occurred in 2 more patients who received carglumic acid in the retrospective case series.
- In a randomized, double-blind, placebo-controlled clinical trial, 24 patients (15 with PA and 9 with MMA) at least 1 adverse reaction was reported during the course of hyperammonemic episodes in 42% of hyperammonemic episodes.[1] The most common adverse reactions (≥ 5%) during hyperammonemic episodes were neutropenia, anemia, vomiting, electrolyte imbalance, decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy and pancreatitis/lipase increased.[1] **Table 2** summarizes adverse reactions reported during hyperammonemic episodes in patients with PA or MMA treated with carglumic acid or placebo.[1]
- There is insufficient evidence to determine if there are subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which carglumic acid is more effective or associated with fewer adverse events.

Recommendations:
- Make one carglumic acid product preferred on the Preferred Drug List with clinical prior authorization (PA) criteria to ensure use in appropriate populations (**Appendix 3**).
- Review drug costs in the executive session.

Background:
The urea cycle consists of a series of enzymes that function interdependently to convert ammonia, a product of protein catabolism, into urea, a molecule that can be excreted into the urine.[2] Urea cycle disorders result from a deficiency of any of the following enzymes: N-acetylglutamate synthase (NAGS), carbamyl phosphate synthetase 1 (CPS 1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), argininosuccinate lyase (AL), or arginase (ARG).[3] These disorders are autosomal recessive diseases with the exception of OTC deficiency, which is an X-linked disorder.[2] Urea cycle disorders have an overall prevalence

of approximately 1 in 30,000 live births.[2] Ornithine transcarbamylase deficiency is the most common urea cycle disorder, while NAGS deficiency is one of the rarest.[2]

Hyperammonemia is the primary pathophysiologic consequence of NAGS deficiency and other urea cycle disorders.[2] Hyperammonemia leads to multiple biochemical and structural changes in the brain, and is thought to cause swelling of astrocytes in the brain as well as pleomorphic changes in the mitochondria.[2] The brain lacks a complete urea cycle and relies on the synthesis of glutamine to remove excess ammonia and to store temporary nitrogen.[2] This process is primarily localized in the astrocytes, such that hyperammonemia leads to accumulation of glutamine from glutamate and ammonia via glutamine synthetase.[2] Excess glutamine is released into the extracellular space, altering astrocyte-neuronal transmission.[2] This creates an imbalance of excitatory versus inhibitory neurotransmission because of increased glutamate production combined with decreased synaptic uptake of glutamate.[2] It is thought that acute hyperammonemia leads to changes in astrocyte protein expression, glutamine synthetase, glial fibrillary acidic protein, glutamate transporter, nitric oxide synthase, and peripheral benzodiazepine receptors.[2] These changes alter the brain's ability to remove additional ammonia, to regulate cerebral blood flow, to maintain energy homeostasis and neurotransmission.[2]

NAGS deficiency is an extremely rare disease, with about 50 known cases reported worldwide.[4] N-acetyl glutamate synthase is an enzyme that is essential for the function of the urea cycle.[2] It is located in the liver and intestine.[2] Patients with NAGS deficiency are unable to synthesize urea from ammonia.[2] Inherited NAGS deficiency results from one or more mutations in the NAGS gene, which causes an absence or a decrease in the enzyme activity.[2] Without the co-factor NAG, CPS 1 is catalytically inactive.[2]

The autosomal recessive disorder expresses phenotypes that range from acute neonatal onset to late-onset disease in adults.[2] The neonatal-onset phenotype has a destructive clinical course, and usually reflects complete absence of NAGS activity.[2] Symptoms result primarily from hyperammonemia.[2] Newborns who have hyperammonemia may present with respiratory alkalosis, hypotonia, lethargy, and vomiting.[2] Symptoms may progress to include cerebral edema, seizures, and death. If newborns survive the acute hyperammonemic episode, they usually tend to exhibit significant development delays, residual neurologic impairments and seizure disorder.[2]

Late-onset NAGS deficiency has a variable age of onset, and the degree of residual enzyme activity is heterogeneous.[2] Patients with partial NAGS deficiency may present with their initial symptoms anywhere from the first year of life to adulthood.[2] In infants, they may become symptomatic following weaning from breast milk or a change from a lower protein infant formula to cow's milk.[2] In children and adults, events such as acute infection, a high dietary protein load, or a combination of the two may lead to hyperammonemia.[2] Symptoms result primarily from hyperammonemia, and the most common clinical findings include central nervous system symptoms such as lethargy, irritability, or somnolence.[2] These symptoms may progress to agitation, disorientation, combativeness, ataxia, and amblyopia.[2] Children with partial enzymatic defects tend to have better outcomes than the ones with complete absence of NAGS activity.[2] Children with partial NAGS deficiency may exhibit cognitive dysfunction such as learning disabilities and attention deficit hyperactivity disorders.[2]

Organic acidemias are a rare class of inborn errors of metabolism characterized by accumulation of organic acid metabolites and a poor prognosis.[5] Most organic acidemias become apparent during the newborn period or in early infancy.[5] Hyperammonemia in patients with MMA and PA is caused by accumulation of propionyl-CoA which decreases the synthesis of NAG the natural activator of CPS 1.[6] The overall incidences of PA and MMA in Western populations have been estimated at up to 1/150,000 and 1/50,000 births, respectively, although the incidences are much higher in some countries.[7] Patients present either shortly after birth with acute deterioration, metabolic acidosis and hyperammonemia or later at any age with a more heterogeneous clinical picture, leading to early death or to severe neurological handicap in many survivors.[7] Mental outcome tends to be worse in PA. Late complications include chronic kidney disease almost

exclusively in MMA and cardiomyopathy mainly in PA.[7] The treatment of these conditions is focused on managing acute hyperammonemia.[5] First-line medications, range from nitrogen scavengers, carglumic acid, and carnitine to continuous hemodiafiltration.[5] Long-term management focuses mainly on a protein-restricted diet while monitoring the patients' daily needs for normal growth and development and administration of l-carnitine and metronidazole.[8]

Beginning in January 2026, the Oregon Health Authority is proposing that high cost medications for rare conditions be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

In the past year (September 2024 to September 2025), 11 patients enrolled in OHP CCOs and 2 patients in the FFS population had claims for the NAGS diagnosis. There are 2 patients in the CCO population with a diagnosis of PA, while 31 CCO patients have a diagnosis of MMA. For the FFS population, no patients had claims for a diagnosis of PA, while 4 patients had claims for MMA.

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:

Carglumic acid is FDA-approved in pediatric and adult patients as: 1) adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to NAGS deficiency; 2) maintenance therapy for the treatment of hyperammonemia due to NAGS deficiency; and 3) adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to PA or MMA.[1]

The efficacy of carglumic acid in the treatment of acute and chronic hyperammonemia due to NAGS deficiency was evaluated in an unpublished, unblinded, uncontrolled, retrospective case series of 23 NAGS deficiency patients treated with carglumic acid over a median duration of 7.9 years (range 0.6 to 20.8 years).[1] For acute treatment, patients received carglumic acid at 100 mg/kg/day to 250 mg/kg/day orally administered in 2 to 4 divided doses.[1] For maintenance treatment, the dosage was reduced over time based on plasma ammonia level and clinical response.[1] Fourteen males (61%) and 9 females (39%) received carglumic acid in the case series.[1] The mean age at initiation of carglumic acid therapy was 2 years (range 0 to 13 years).[1] The 23 patients were treated with carglumic acid at 14 sites that were either hospitals or outpatient clinics located in the Netherlands, Germany, France, United Kingdom, Sweden, Italy, Spain, and Austria.[2] Most patients were treated in France.[2]

The clinical and biochemical data in the case series could not be formally analyzed using statistical testing.[1] Short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3.[1] Persistence of the effect was evaluated using long-term mean and median change in plasma ammonia level.[1] Of the 23 patients with NAGS deficiency in the case series, 13 patients had documented plasma ammonia levels prior to, and after long-term treatment with, carglumic acid.[1] All 13 patients had increased plasma ammonia levels at baseline (mean 271 micromol/L; normal range: 5 to 50 micromol/L).[1] By day 3 of treatment with carglumic acid, mean plasma ammonia levels had normalized (43.3 micromol/L; 95% CI, 0.5 to 86.2) and remained within or near normal range during long-term treatment, which ranged from 7 to 249 months (51.9 micromol/L; 95% CI, 11.4 to 92.1; low-quality evidence).[1]

A randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated the efficacy of carglumic acid in the treatment of hyperammonemia in 24 patients with PA or MMA (NCT01599286).[1] This study is not published, and study details are limited to the prescribing information issued by the manufacturer. Eligible hyperammonemic episodes, defined as an admission to the hospital with a plasma ammonia level 70 micromol/L or greater, were randomized 1:1 to receive either carglumic acid or placebo for 7 days or until hospital discharge, whichever occurred earlier.[1] All patients received standard of care, including a combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine; the use of alternative pathway medications (e.g., sodium benzoate and medications with phenylacetate as an active metabolite) was prohibited.[1] Carglumic acid was dosed orally at 150 mg/kg/day for patients who weighed 15 kg or less, or 3.3 g/m^2 /day for patients who weighed more than 15 kg. The daily dose was divided into 2 equal doses administered 12 hours apart by NG tube, G-tube, or oral syringe.[1] Plasma ammonia testing was performed at pre-randomization and at post-dosing intervals of every 6-12 hours for the first 48 hours and every day thereafter if the ammonia level was 50 micromol/L or higher.[1]

The efficacy evaluation was based on 90 hyperammonemic episodes (42 treated with carglumic acid and 48 with placebo) in 24 patients (12 male and 12 female) with PA (n = 15) or MMA (n = 9).[1] The median patient age was 8 years (range 4 days to 29 years).[1] The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level of 50 micromol/L or less (normal range) or hospital discharge.[1] The median time to reach the primary endpoint was 1.5 days in the carglumic acid group compared to 2.0 days in the placebo group, a difference of 0.5 days (95% CI, -1.2 to 0.1; not significant; low-quality evidence).[1] In the first 3 days, a higher proportion of carglumic acid-treated episodes reached the primary endpoint compared to placebo-treated episodes.[1]

An additional, prospective, randomized, open-label study funded by the manufacturer compared the efficacy of adding carglumic acid (50 mg/kg/day in divided doses, twice daily) to standard treatment in patients with PA and MMA.[5] Standard treatment followed the most recent guidelines of l-carnitine (150 mg/kg/day divided and given every 8 h), metronidazole (15 mg/kg/day divided and given every 8 h for one week each month), and a protein-restricted diet.[8] The study was conducted in 2 tertiary care centers in Saudi Arabia. The study was open-label as patients might present to the ER with acute crises, where the attending physicians would need the details of their treatment regimens.[5] Additionally, according to the emergency protocol for the management of PA and MMA, carglumic acid is considered a rescue medication and should be used in all patients with hyperammonemia, even for those in the standard treatment arm.[5] The primary outcome was long-term effectiveness (2 years) of carglumic acid in reducing the number of emergency department (ED) admissions due to hyperammonemia in patients with PA or MMA.[5] Secondary outcomes included comparing effects on plasma ammonia levels from baseline to the end of the study, time to the first episode of hyperammonemia, levels of relevant biochemical biomarkers including plasma amino acids, acylcarnitine profile, and urine organic acids.[5]

Thirty-eight patients were enrolled in the study, 21 were randomized to carglumic acid plus standard therapy and 17 were allocated to the standard therapy arm.[5] The study included patients aged ≤ 15 years whose parents or legal guardians had provided written consent and were not participating in any other trial.[5] PA was confirmed by measuring acylcarnitine profile, urine organic acid, propionyl-CoA carboxylase in leukocytes or cultured fibroblasts, or by DNA molecular testing of the PCCA or PCCB genes.[5] MMA was confirmed by measuring acylcarnitine profile, urine organic acid, methyl malonyl-CoA mutase in cultured fibroblasts, or DNA molecular testing of the MUT gene.[5] Only patients with an expected survival of ≥ 6 months were included in the study.[5] These were defined as those not admitted to the pediatric intensive care unit (PICU) for > 2 times/year because of hyperammonemia, asymptomatic patients diagnosed by newborn screening, or stable chronic patients who were followed up at the outpatient clinic.[5] Genotyping was performed on all participants to confirm the diagnosis.[5]

The patients included 27 boys and 11 girls, almost equally distributed between the two arms.[5] Of the 21 patients allocated to receive carglumic acid, 5 did not return after the screening visit and were excluded from the analysis.[5] During the trial, two patients in the carglumic acid arm underwent liver transplantation and discontinued the follow-up visits; however, their data were included in the final analysis.[5] Although one patient from the standard treatment arm was lost to

follow-up after four visits, their data were included in the final analysis.[5] Sixteen patients were analyzed in the carglumic acid plus standard therapy cohort and 17 patients were analyzed in the standard therapy only cohort.[5] The mean age of the participants in the standard treatment arm was approximately 36 months, while the mean age in the carglumic acid arm was approximately 40 months.[5] All other demographic characteristics between the two arms were evenly distributed.[5]

The total number of ED admissions was 12.76 in the standard treatment group and 6.31 in the carglumic acid group over 24 months.[5] Results of the Poisson regression analysis suggest that carglumic acid achieved a 51% significant reduction in the number of ED admissions compared to standard therapy (rate ratio, 0.4945; 95% CI, 0.2904 to 0.8422; p = 0.0095).[5] The plasma ammonia levels from the baseline and at the end of the study did not show any significant difference between the arms.[5] When the times of the first episode of hyperammonemia were compared using the Kaplan–Meier curve, both arms had a comparable course.[5] For the biochemical markers, there was a significant difference in the level of plasma glycine favoring the carglumic acid arm (p = 0.046).[5] There were no significant differences in the levels of other plasma amino acids.[5]

Clinical Safety:

In a retrospective case series of 23 NAGS deficiency patients treated with carglumic acid, 17 of the 23 patients reported an adverse reaction.[1] The most common adverse reactions (occurring in ≥ 13% of patients) were vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, decreased hemoglobin, and headache.[1] **Table 1** summarizes adverse reactions that occurred in 2 more patients who received carglumic acid in the retrospective case series.

Table 1. Adverse Reactions Reported In Patients With NAGS Deficiency Treated With Carglumic Acid In A Retrospective Case Series[1]

Adverse Reaction	Number of Patients (%)
Vomiting	6 (26)
Abdominal Pain	4 (17)
Pyrexia	4 (17)
Tonsillitis	4 (17)
Anemia	3 (13)
Diarrhea	3 (13)
Ear Infection	3 (13)
Infections	3 (13)
Nasopharyngitis	3(13
Decreased Hemoglobin	3 (13)
Headache	3 (13)
Dysgeusia	2(9)
Asthenia	2 (9)
Hyperhidrosis	2 (9)
Influenza	2 (9)
Pneumonia	2 (9)
Decreased Weight	2 (9)
Anorexia	2 (9)

Somnolence	2 (9)
Rash	2 (9)
Abbreviations: NAGS = N-acetylglutamate synthetase	

In a randomized, double-blind, placebo-controlled clinical trial, 24 patients (15 with PA and 9 with MMA) at least 1 adverse reaction was reported during the course of hyperammonemic episodes in 42% of hyperammonemic episodes.[1] The most common adverse reactions (≥5%) during hyperammonemic episodes were neutropenia, anemia, vomiting, electrolyte imbalance, decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy and pancreatitis/lipase increased.[1] **Table 2** summarizes adverse reactions reported during hyperammonemic episodes in patients with PA or MMA treated with carglumic acid or placebo.[1]

Table 2: Adverse Reactions During Hyperammonemic Episodes in Patients with PA or MMA Treated with Carglumic Acid or Placebo[1]

Adverse Reaction	**Carglumic Acid (n = 42 episodes) N (%)**	**Placebo (n = 48 episodes) N (%)**
Neutropenia	6 (14)	4 (8)
Anemia	5 (12)	4 (8)
Vomiting	3 (7)	1 (2)
Electrolyte Imbalance	3 (7)	1 (2)
Decreased Appetite	2 (5)	1 (2)
Hypoglycemia	2 (5)	1 (2)
Lethargy/Stupor	2 (5)	1 (2)
Encephalopathy	2 (5)	0
Pancreatitis/Increased Lipase	2 (5)	0
Cardiomyopathy	1 (2)	0
Increased Alanine Aminotransferase	1 (2)	0
Increased Aspartate Aminotransferase	1 (2)	0
Infusion Site Extravasation	1 (2)	0
Increased White Blood Cell Count	1 (2)	0
Behavior Disorder	1(2)	0
Sleep Disorder	1 (2)	0
Apnea	1 (2)	0
Hyperventilation	1 (2)	0
Abbreviations: MMA = methylmalonic acidemia; PA = propionic acidemia		

No dosage adjustment is warranted in patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2).[1] The dose of carglumic acid in patients with moderate or severe renal impairment must be modified according to the specific indication as outlined by the manufacturer in the prescribing information.

References:

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8. Fraser JL, Venditti CP. Methylmalonic and propionic acidemias: clinical management update. *Curr Opin Pediatr*. Dec 2016;28(6):682-693. doi:10.1097/mop.0000000000000422

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CARBAGLU® (carglumic acid) tablets for oral suspension
Initial U.S. Approval: 2010

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

CARBAGLU is a carbamoyl phosphate synthetase 1 (CPS 1) activator indicated in pediatric and adult patients as:

- Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency. (1.1)
- Maintenance therapy for the treatment of chronic hyperammonemia due to NAGS deficiency. (1.1)
- Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA). (1.2)

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

Acute Hyperammonemia due to NAGS deficiency (2.2)

- The recommended dosage in adult and pediatric patients is 100 mg/kg to 250 mg/kg orally daily. Divide the daily dosage into 2 to 4 doses.

Chronic Hyperammonemia due to NAGS deficiency (2.2)

- The recommended dosage in adult and pediatric patients is 10 mg/kg to 100 mg/kg orally daily. Divide the daily dosage into 2 to 4 doses.

Therapeutic Monitoring for NAGS Deficiency (2.2)

- Closely monitor plasma ammonia and titrate dosage to maintain the ammonia level within normal range for the patient's age, taking into consideration their clinical condition.

Acute Hyperammonemia due to PA or MMA (2.3)

- The recommended dosage in adult and pediatric patients is:
  - 150 mg/kg orally daily for patients less than or equal to 15 kg
  - 3.3 g/m^2 orally daily for patients greater than 15 kg
- Divide the daily dosage into 2 doses.
- Continue treatment until ammonia level is less than 50 micromol/L and for a maximum duration of 7 days.

Patients with Renal Impairment (2.4)

- See Full Prescribing Information for Instructions on Dosage Adjustment.

Preparation and Administration (2.5)

- Disperse CARBAGLU tablets in water. Do not swallow whole or crushed.
- Take immediately before meals or feedings.
- For additional instructions on preparation and administration orally or through a nasogastric tube or gastrostomy tube, see Full Prescribing Information.

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

Tablets for oral suspension: 200 mg, functionally scored. (3)

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

None. (4)

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

- NAGS deficiency: Most common adverse reactions (≥13%) are vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, hemoglobin decreased, and headache. (6.1)
- PA and MMA: Most common adverse reactions (≥5%) are neutropenia, anemia, vomiting, electrolyte imbalance, decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy and pancreatitis/lipase increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 1/2024

Appendix 2. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Carbamoyl phosphate synthetase 1 (CPS 1) activator
Oral Bioavailability	10%
Distribution and Protein Binding	Volume of distribution: 15 \L/kg (after IV infusion). Not bound to plasma proteins.
Elimination	9% of products is excreted by the kidneys as unchanged product and 60% is recovered unchanged in the feces.
Half-Life	25 hours
Metabolism	A proportion of carglumic acid may be metabolized by intestinal bacterial flora. Likely end product of metabolism is carbon dioxide, eliminated through the lungs.

Abbreviations: kg = kilograms; L = Liters

Carglumic Acid (CARBAGLU)

Goal(s):
- Ensure appropriate utilization of carglumic acid in FDA-approved indications

Length of Authorization: Up to 12 months

Requires PA:
- CARBAGLU (carglumic acid) tablets for oral suspension for FFS and CCO patients

Covered Populations: FFS and CCO enrolled patients starting 1/1/26

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy?	**Yes:** Go to Renewal Criteria	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes:** Go to # 4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for therapy to treat hyperammonemia due to N-acetyl glutamate synthetase (NAGS) deficiency treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA)?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the diagnosis been confirmed by genetic testing?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient on a protein restricted diet?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Have baseline ammonia levels been documented?	**Yes:** Go to #8 Document date and results _____	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the medication prescribed by or in consultation with a provider with expertise in managing urea cycle disorders or organic acidemias?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the request for a preferred product?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request to renew therapy for treatment of hyperammonemia due to NAGS deficiency, or treatment of acute hyperammonemia due to PA or MMA?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Has the patient's condition improved as assessed by the prescribing provider and the provider attests to patient's improvement ?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/25 (DM)
Implementation: TBD

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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New Drug Evaluations: Miplyffa™ (arimoclomol) capsules, Aqneursa™ (levacetylleucine) oral suspension
Medications for Niemann-Pick Disease Type C

Date of Review: December 2025
Generic Name: arimoclomol
Generic Name: levacetylleucine

End Date of Literature Search: 10/08/25
Brand Name (Manufacturer): Miplyffa (Zevra Therapeutics)
Brand Name (Manufacturer): Aqneursa (IntraBio)

Dossier Received: MIPLYFFA (yes); AQNEURSA (no)

Plain Language Summary:

- Niemann-Pick Disease type C is a rare condition passed down in families that causes many different symptoms. Many people have trouble walking due to loss of muscle control, or other problems such as seizures or dementia. Symptoms can start anytime from infancy to adulthood and get worse over time. There is no cure.
- The Food and Drug Administration has approved 2 medicines to treat Niemann-Pick disease type C. These medicines have been studied in a small number of people. Most had the diagnosis confirmed with genetic testing.
    - Arimoclomol is a medicine that people take 3 times a day by mouth or feeding tube. After 12 months, people taking arimoclomol with another medicine called miglustat had a small improvement in symptoms compared to people taking placebo with miglustat. Arimoclomol was only studied in people who developed symptoms as babies or during childhood.
    - Levacetylleucine is a medicine that people take 2 to 3 times a day by mouth or feeding tube. After 12 weeks, people taking levacetylleucine had a small improvement in some symptoms compared to people who took a placebo. The survey doctors used to evaluate symptoms was different from the survey people took with arimoclomol. Most people were also taking miglustat.
- There is not enough information to determine if one medicine is better than another or if arimoclomol and levacetylleucine are work better or are safe to take at the same time.
- These medicines have not been studied in very many people, and their long-term safety beyond 12 months compared to placebo is unknown.
- We recommend that the Oregon Health Authority pay for arimoclomol and levacetylleucine when the provider documents why someone needs these medicines. This process is called prior authorization.

Research Questions:

1. What is the evidence for efficacy and safety for medications for Niemann-Pick disease type C (NPC)?
2. Are there any differences in efficacy and harms for the medications for NPC for certain demographic subtypes (e.g., age of onset, concomitant miglustat, symptom types, or other demographic differences)?

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Conclusions:

- Evidence for arimoclomol and levacetylleucine safety and efficacy in patients with NPC was evaluated in one phase II/III trial and one phase III trial. Arimoclomol is approved by the Food and Drug Administration (FDA) in combination with miglustat for neurological manifestations of NPC in patients 2 years of age and older. Levacetylleucine is FDA-approved for neurological manifestations of NPC in adult and pediatric patients weighing at least 15 kg.[1,2]
- Miglustat is an off-label therapy for NPC that has some evidence for improving symptoms and is recommended for many patients with NPC by experts.[3,4]
- There is low-certainty evidence from one 12-month, double-blind, phase II/III, randomized controlled trial (RCT) of patients age 2 to 19 years (n=50) that, when combined treatment with miglustat, arimoclomol improves symptoms of NPC compared to placebo combined with miglustat.[5] There was a statistically significant difference in the baseline to 12-month change in 4-domain NPC Clinical Severity Scale (NPCCSS; range 0 to 20, higher scores indicate more severe impairment) in those taking baseline miglustat and arimoclomol (change -0.2) compared to patients taking placebo and miglustat (1.9; difference -2.2, 95% confidence interval [CI] -3.8 to -0.6).[5] The FDA determined the subgroup without miglustat had insufficient evidence to support use of arimoclomol monotherapy for NPC.[6] This trial had methodological concerns with the endpoint which underwent alteration by the FDA as well as concerns with the standardization of procedures across trial sites which may reduce reliability of the results.[6,7]
- There is low-certainty evidence from one randomized, double-blind, phase III, crossover trial that levacetylleucine improves ataxia symptoms over 12 weeks in patients 4 years of age and older with NPC (n=60) weighing at least 15 kg.[8] Using the Scale for the Assessment and Rating of Ataxia (SARA; range 0 to 40, with lower scores indicating better neurologic status), mean change from baseline in the SARA total score was −1.97 points after 12 weeks of levacetylleucine and −0.60 points after 12 weeks of receiving placebo (least-squares mean (LSM) difference, −1.28 points; 95% CI, −1.91 to −0.65; P<0.001).[8] Using the functional SARA (fSARA) as an alternative, FDA requested endpoint, mean fSARA score was statistically significantly lower for levacetylleucine (fSARA 5.1) compared to placebo (fSARA 5.6; difference -0.4, 95% CI -0.7 to -0.2; P<0.001), though it is unclear if this is clinically meaningful.[8] This trial had methodological concerns with the endpoint which underwent alteration at FDA request and is of short duration for assessment of a chronic progressive condition.[4]
- There is no comparative data between treatments of arimoclomol with miglustat versus levacetylleucine.
- There is insufficient evidence of the efficacy and safety of combination therapy of arimoclomol used with levacetylleucine.
- There is insufficient evidence arimoclomol with miglustat is effective for adolescent- or adult-onset NPC. It is unclear if there are differences in efficacy and safety of either drug for other subtypes of NPC based on age of onset or specific mutation.
- There were no significant safety signals with either medication, but data is limited by small sample sizes and short study durations of placebo control. Both are thought to be embryo-fetal toxic and should be avoided in patients who may become pregnant.[1,2]

Recommendations:

- Make arimoclomol and levacetylleucine non-preferred on the Oregon Health Plan (OHP) Preferred Drug list (PDL).
- Implement prior authorization (PA) for high cost treatments for Niemann-Pick disease type C.
- Implement separate miglustat PA for 100 mg formulation with corresponding updates to PA criteria for Pompe Disease and Gaucher disease.
- Evaluate costs in executive session.

Background:

Niemann-Pick disease is an autosomal recessive disease with three distinct pathologies of type A, B, and C. Type A and B are acid sphingomyelinase deficiencies caused by mutations on the SMPD1 gene.[9] Type C affects roughly 1 in 100,000 to 150,000 people, though it may be underrecognized.[3,9] It is a neurological

disorder which results from mutations on NPC1 and NPC2 genes with the C1 subtype affecting more than 90% of those with NPC.[10] It is most common in populations from Nova Scotia.[10] Different types of mutations are possible, including missense, splicing, frameshift, or premature stop mutations.[5] Presence of stop mutations on both alleles is associated with severe disease progression and early onset, while other genotype/phenotype relationships have not been consistently described.[5] These mutations result in abnormal cholesterol trafficking and esterification. Toxic cholesterol accumulates in the lysosome and results in cell damage.[10] There is no cure for NPC. The disease symptoms vary by type and age of onset. Those developing symptoms as infants often have more aggressive disease than those presenting later in life as adolescents or adults.[5]

NPC may present anytime between the neonatal period and adulthood, and patients with later onset may live up to 70 years.[9] It is associated with a number of signs and symptoms. Common symptoms include inability to look up and down, difficulty walking, difficulty swallowing, and progressive loss of vision and hearing.[10] Liver involvement is common and may include neonatal cholestasis, hepatosplenomegaly, acute liver failure, cirrhosis, and hepatocellular carcinoma.[10] Neurologic involvement with neurodegeneration results in cerebellar ataxia, dysarthria, dysphagia, and progressive dementia.[9] Patients may have seizures, cataplexy, narcolepsy, and dystonia. Adult-onset patients may be misdiagnosed with other hereditary ataxic disorders.[9] Other organs may also be affected including bone marrow and lungs, though direct lung involvement is more common with other types of Niemann-Pick disease.[9] Aspiration pneumonia is a problematic complication as the disease progresses.

Patients can be divided into four phenotypic forms: fetal and early infantile, late infantile, juvenile, and adolescent/adult-onset.[9] The fetal and early infantile form often presents with fetal hydrops and ascites and is usually fatal within 5 years. The late infantile form usually presents with seizures and other neurological manifestations; lifespan is generally 7 to 12 years. The juvenile form of mid to late childhood is most common and may begin with school difficulties, ataxia, and loss of motor abilities. Seizures and dementia develop later, and splenomegaly is common. Prognosis ranges from late teen years to 30 years old, sometimes longer. Those with the adolescent/adult-onset form typically have a gradual onset of disease. Patients may have psychosis, mild ataxia, dystonia, dysarthria, cognitive dysfunction. Epilepsy is possible but rare in adult-onset patients.[9] Diagnosis can be difficult due to the varying presentations and similarities with other conditions (e.g., Huntington disease, Wilson disease, Friedreich ataxia, etc.). Biomarkers can be used to aid with diagnosis, which should be confirmed with genetic testing and possibly a filipin test.[3]

Miglustat is approved as treatment for neurological manifestations of NPC in Europe, Japan, and Canada.[4,5] It works as a substrate reduction treatment to reduce accumulation of glycosphingolipid in the lysosome.[9] Miglustat has United States (US) approval for some forms of Gaucher disease in adults (100 mg formulation) and in certain patients with Pompe disease (65 mg formulation).[11] Itis considered off-label in the US for NPC.[5] Miglustat has been studied in several trials in people with NPC, including RCTs and multiyear long-term longitudinal cohorts. Efficacy may be improved in those with juvenile and adult-onset NPC compared to infantile onset.[9] Guidelines from 2018 developed by NPC experts from Europe, Australia, and North America made a weak recommendation that all NPC patients be considered for miglustat therapy based on low-quality evidence.[3] There was significant disagreement amongst the experts making this recommendation.[3] There was more uniformity among experts that pre-symptomatic patients or those who only have spleen/liver enlargement should not be offered miglustat (weak recommendation, low-quality evidence), that it should not be started in those with advanced neurological disease/dementia (weak recommendation, low-quality evidence), and that it should not be started in NPC patients with another life threatening illness with estimated life span of less than 1 year (weak recommendation, low-quality evidence).[3] The FDA has stated miglustat is considered standard of care in adult and pediatric patients with NPC by experts.[4] Dosing ranges from 100 mg daily to 200 mg given three times daily, based on age and body surface area.[11] Most other options are supportive in nature such as mobility aids and rehabilitation for strength and balance, or medications to treat symptoms such as spasticity, hypersalivation, epilepsy, and cataplexy.[9] Epilepsy should be treated by a specialist as some medications, including carbamazepine and vigabatrin, may aggravate the disease.[3]

There are several scales used globally for NPC clinical care. The NPCCSS is a clinician-reported outcome measure which was based on a 4-domain NPC specific disability scale. It was broadened to a 17-domain severity scale to characterize and quantify disease severity and progression for ongoing patient monitoring and was validated for clinical assessment of disease over a one year time period NPC patients (range 0 to 54).[6,8] It includes 9 major domains (ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, and swallowing) and 8 minor domains (auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, and respiratory problems). Major domains include a clinically reported 0 to 5 ordinal scale; minor domains have a 0 to 2 response scale. Higher numbers indicate greater clinical severity. The FDA has noted several concerns with this instrument.[6] The cognition domain response options may be dependent on a patient's educational and employment services, and the overlapping clinical presentations cannot be interpreted as distinct states of cognitive function.[6] The FDA does not consider the cognition score fit-for-purpose for use in regulatory decision making.[6] Additionally, the response categories may not be fully linear with several domains having no response category for certain values. For example, a score of 3 for ambulation is not a possible response option (**Appendix 3**).[6]

The Scale for the Assessment and Rating of Ataxia (SARA) is an 8-domain rating scale (range 0-40) reported to be reliable and valid with high internal consistency when used for patients with cerebellar ataxias but has not been validated in NPC. It measures symptom and ataxia severity where higher numbers correspond to worsening disease. SARA domains include gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, heel-shin slide, stance, and sitting.[12] Different domains account for different total points (e.g., gait has 9 points, speech has 7 points).[4] The modified SARA (mSARA; range 0-30) omits the stance and sitting domains. During clinical trials for levacetylleucine, the FDA requested rescoring of categories to allow all domains to have equal points, and recommended use of the functional SARA (fSARA, range 0 to 16) as a trial endpoint.[2,4] The fSARA includes only the domains of gait, stance, sitting, and speech.[4] A minimally clinically important difference (MCID) for NPCCSS was not identified, a 1 point difference in SARA may be clinically significant.[8] Modified versions of this assessment tool (mSARA and fSARA) are not validated.

Beginning in January 2026, the Oregon Health Authority is proposing that high cost medications for rare conditions be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

Both arimoclomol and levacetylleucine are currently included in the list of medications proposed to be carved-out of CCO budgets. Over a 1 year period from 4/1/24 to 3/31/25, there were 8 Oregon Health Plan members with a diagnosis indicating NPC in their medical claims.

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:

<u>Arimoclomol</u>

Arimoclomol is FDA-approved in combination with miglustat for the treatment of neurological manifestations of NPC in patients 2 years of age and older.[1] It is a small molecule given orally that is able to cross the blood brain barrier with detectable levels in the cerebrospinal fluid.[5] While the mechanism of action is not fully understood,[1] it is thought to affect the heat shock response and prevent misfolding of proteins which may preserve cellular function and prevent cell death in cells with lysosomal stress.[5]

Arimoclomol originally received a complete response letter (i.e., denial of approval) from the FDA in June 2021.[6] This denial was based on questions about the inclusion and validity of the cognition domain in the primary efficacy endpoint, change in NPCCSS, of the pivotal trial.[6] Additionally, there were scoring concerns around the swallow domain ("*whether the response options overlapped, were ordered to reflect increasing disease severity, and allowed for comprehensive assessment of swallowing, including silent aspiration*"), standardization of procedures used to administer the NPCCSS, and the concerns regarding if scoring of speech, fine motor, and ambulation domains were non-linear with overlapping scoring of adjacent responses.[6] The application was resubmitted in December 2023, where it was approved based on additional information provided and a public advisory committee (i.e., Genetic Metabolic Diseases Advisory Committee) meeting.[6] In the resubmission, the cognitive domain was excluded from the primary efficacy endpoint and swallow scoring was revised.[6,7] The FDA noted that lack of standardized procedures for this symptom assessments reduces confidence in reliability of results and scoring consistency between clinicians and within the same clinician over time.[6] The speech, fine motor, and ambulation domains were accepted in the resubmission, though it was noted that the NPCCSS would be improved by creating linear severity scoring with non-overlapping options.[6]

The trial used for both FDA approval submissions (NCT02612129) was a 12-month, randomized, placebo-controlled, double-blind, phase 2/3 trial using the 5-domain NPCCSS score as the primary endpoint.[5] As described above, a 4-domain version was used in the revised submission leading to FDA approval after omission of the cognitive domain (range 0 to 20, higher scores indication more severe impairment).[6] The full 17-domain NPCCSS was administered during trial visits.[5] Clinical Global Impression-Improvement scale (CGI-I) scores were used to assess overall health.[5] After stratification by baseline miglustat use, patients were randomized to weight-adjusted arimoclomol (n=34) or matching placebo (n=16) given orally three times a daily, in addition to routine clinical care.[5] Just over half of the patients (n=27) were previously enrolled in an observational study of natural disease course.[5] Patients attended 6 trial visits over 12-months.[5] Most patients (n=41) then opted to enroll in the open-label extension study through month 36.[5] Sample size and trial duration were informed by feasibility rather than sample size calculation.[5]

Predefined subgroup analyses were included for those above or below 4 years old, and those with or without baseline miglustat.[5] There was a statistically significant difference in the baseline to 12-month change in 4-domain NPCCSS in those taking baseline miglustat and arimoclomol (change -0.2), while the placebo group on miglustat score worsened (1.9; difference -2.2, 95% CI -3.8 to -0.6).[5] The FDA determined the subgroup without miglustat had insufficient evidence to support use of arimoclomol monotherapy for NPC.[6] The 5-domain NPCCSS in the original protocol showed similar results to the 4-domain NPCCSS for the full treatment population (**Table 3**), while the CGI-I responder rate showed no difference.[5]

In addition to the concerns raised by the FDA review regarding the NPCCSS tool and assessment procedures, other bias was noted (**Table 3**). Attrition was different between groups (arimoclomol 20.6% vs. 6.3% placebo) and there was an "early escape clause" allowing unblinding of patients with rapid progression.[5] Two arimoclomol patients were unblinded and further evaluations at study visits were not included in the analysis.[5] Missing data imputation was not done for the primary efficacy analysis.[5] There were some baseline differences in the initial NPCCSS score with higher scores in the arimoclomol group in all 5 domains.[5] There were no patients with adolescent-adult onset disease included in the study.[5]

<u>Levacetylleucine (N-acetyl-L-leucine)</u>

Levacetylleucine has an FDA indication for treatment of neurological manifestations of NPC in adults and pediatric patients weighing at least 15 kg.[2] It is the L-enantiomer of an acetylated amino acid and is the prodrug of leucine, an essential amino acid.[12] While the mechanism of action is unknown,[2] it crosses the blood-brain barrier and is thought to enter enzyme-controlled pathways that correct metabolic dysfunction and improve energy production of adenosine triphosphate.[8] This may improve lysosomal dysfunction and potentially reduce storage of unesterified cholesterol and sphingolipids.[8]

Approval was primarily based on a 12-week, double-blind, placebo-controlled, randomized, crossover trial in patients 4 years and older with NPC.[8,12] The trial was originally designed to assess total score on the SARA (range 0 to 40) where lower scores indicate better neurological status.[8,12] The authors report a modified SARA (mSARA) score was requested by the FDA, excluding sitting and stance domains and including the remaining 6 domains (range 0 to 30).[8,12] However, the FDA review reports that the tool modification request for was the fSARA (range 0-16) to be used, including the domains of gait, stance, sitting, and speech and rescored for each domain to include the same score weight.[2,4] The Agency stated that the excluded "*neurological exam findings do not directly assess the patient's ability to function, nor do they reflect clinically meaningful change in a patient's ability to perform daily functions, making them unsuitable for inclusion in a primary efficacy endpoint to convey clinical benefit.*"[4] The Agency responded by rescoring the desired response categories *"to create the same number of response categories across each domain… to ensure equal representation of each domain in the total score and interpretability of a 1-point change as clinically meaningful".*[4] The trial was powered at 80% to detect a 1.0 point difference in total SARA score.[8] Most patients opted to continue in the open-label extension study after completion of the initial trial.[8]

A total of 60 total patients with NPC and baseline SARA scores of 7 to 34 were randomized to each treatment sequence with immediate crossover at 12 weeks.[8] Patients ranged from 5 to 67 years of age and weighed at least 15 kg.[8] The LSM difference from baseline was improved after 12 weeks for the levacetylleucine period (Change -1.97) compared to the placebo period (Change -0.6; LSM difference -1.28, 95% CI -1.91 to -0.65).[8] The mean fSARA score was also improved for levacetylleucine (fSARA 5.1) compared to placebo (fSARA 5.6) with a small difference between groups (LSM difference -0.4, 95% CI -0.7 to -0.2; P<0.001).[8] The NPCCSS was included as an exploratory endpoint and showed no statistically significant difference in score change (Levacetylleucine -0.3, Placebo 0.1; difference -0.5, 95% CI -1.2 t 0.2), though NPCCSS is validated for changes over a 1-year period rather than 12 weeks.[8] The FDA subgroup analysis of patients based on miglustat at baseline did not identify a statistical difference in fSARA compared to those not on baseline miglustat. However, the patient group was extremely small (n=4 first trial period, n=5 second trial period after crossover) and the study was not powered to show differences between subgroups.[8]

It is unclear if the crossover design, with no washout between crossover, is most appropriate for a progressive disease. Trial duration was short in setting of a long-term, progressive condition. While statistically significant, it is unclear if the less than 1.0 point difference in the fSARA between treatment groups is clinically significant.

Clinical Safety:

Arimoclomol

Three patients withdrew due to adverse events (urticaria, angioedema, increased serum creatinine).[5] One death occurred in the active treatment group.[5] One placebo treated patient withdrew due to worsening epilepsy, which was considered part of disease progression.[5] Six arimoclomol treated patients had serum creatinine increases of more than 1.5-fold, with 2 patients with levels more than double the baseline value.[5] Arimoclomol is known to cause a reversible rise in serum creatinine by inhibiting a transporter and reducing creatinine secretion into the kidneys.[5] While there are no listed contraindications, there are warnings about hypersensitivity reactions (e.g., urticaria, angioedema), risk for embryo-fetal toxicity due to high anticipated fetal exposure and increased rates of post-implantation loss noted in animal studies, and risk for increased creatinine without effect on glomerular function (mean increase 10-20% above baseline).[1]

Adverse events occurring more often than placebo in the subgroup receiving both arimoclomol and miglustat are found in **Table 1**. The study population was limited to 19 years and younger, any differences in safety in the adult population are unknown.

Table 1. Adverse Events Occurring in at Least 8% of Patients on Arimoclomol and Miglustat[1]

Adverse event	Arimoclomol and miglustat N=26 n (%)	Placebo and miglustat N=13 n (%)
Upper respiratory tract infection	8 (31)	2 (15)
Diarrhea	6 (23)	3 (23)
Decreased weight	4 (15)	0
Decreased appetite	3 (12)	0
Tremor	3 (12)	0
Urticaria (with or without angioedema)	3 (12)	0
Headache	3 (12)	1 (8)
Lower respiratory tract infection	3 (12)	1 (8)
Seizure	3 (12)	1 (8)

Levacetylleucine (N-acetyl-L-leucine)

One patient withdrawal and death occurred after complications of gastrostomy tube placement followed by aspiration pneumonia, unrelated to treatment.[8] Four patients experienced thrombocytopenia during the trial.[8] All were on concomitant miglustat and 2 had thrombocytopenia present at baseline. One patient experienced an exacerbation of rosacea during therapy that responded to treatment.[8] The composite rate of infections and infestations was more than 5% higher for levacetylleucine (16/60, 26.7%) than placebo (12/59, 20.3%).[8] Concomitant use with the racemic mixture or isolated D-enantiomer (e.g., N-acetyl-D-leucine or N-acetyl-DL-leucine) would compete for binding sites and be expected to reduce efficacy.[2] Levacetylleucine is a p-glycoprotein inhibitor; concomitant use of p-glycoprotein transport substrates may also cause altered drug levels and increased risk for adverse reactions.[2]

The crossover design without washout and small overall trial size limits interpretation of some safety data. **Table 2** presents adverse events from the first trial period before crossover. There are no labeled contraindications, and labeling includes a warning regarding risk of embryo-fetal toxicity based on higher rates of embryo-fetal death and skeletal malformations in animal studies.[2]

Table 2. Adverse Events Occurring in at Least 5% of Patients on Levacetylleucine During the First Half of The Trial[2]

Adverse event	Levacetylleucine N=30 n (%)	Placebo N=30 n (%)
Upper respiratory tract infection	5 (17%)	1 (3%)
Abdominal pain	2 (7%)	0 (0%)
Dysphagia	2 (7%)	0 (0%)
Vomiting	2 (7%)	0 (0%)

Look-alike / Sound-alike Error Risk Potential: N-acetyl-D-leucine or N-acetyl-DL-leucine; Migalastat

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Mortality
2) Quality of Life
3) Functional status
4) Neurologic function
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in NPCCSS 4- or 5- domain scale over time
2) Change in SARA or fSARA scale over time

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mengel et al. NCT02612129[5,6] DB, PC, RCT, MC Phase 2/3 2:1 randomization Stratified by miglustat use at baseline	1. Arimoclomol weight adjusted orally/feeding tube three times daily (16 mg, 31 mg, 62 mg capsules; dose 93 to 372 mg/day) 2. Placebo orally/feeding tube 3 times daily 12 m duration	Demographics: -Female: 52% -NPC1 mutation on both alleles: 100% -Miglustat use at baseline: 78% -Mean age: 11.1 y (range 2-19) -White: 90% -Age at first neurologic symptoms ◊ Prenatal: 2% ◊ Early-infantile: 16% ◊ Late-infantile: 48% ◊ Juvenile: 34% ◊ Adolescent/Adult: 0% -H/O Seizure: 28% Key Inclusion Criteria: -NPC diagnosis (molecularly confirmed) -2 to 19 years old -stable miglustat dosing x 6m (if prescribed) -Minimum 1 neurologic sign of disease -Walk independently or with assistance Key Exclusion Criteria: -Other trial participation (exception: non-interventional registries) -Severe liver or renal insufficiency -Other investigational product within 4 weeks -Severe, uncontrolled epileptic seizures -Neurologically asymptomatic	ITT: 1. 34 2. 16 PP: 1. 27 2. 15 Attrition: 1. 7 (20.6%) 2. 1 (6.3%) Miglustat subgroup: 1. 22 2. 12	Primary Endpoint: 4-domain NPCCSS from baseline at 12 m in miglustat subgroup (FDA) 1. -0.2 2. 1.9 Difference -2.2 (95% CI -3.8 to –0.6) 5-domain NPCCSS change from baseline at 12 m (original protocol) 1. 0.76 (95% CI, -0.05 to 1.56) 2. 2.15 (95% CI, 1.05 to 3.25) Difference -1.4 (95% CI, -2.76 to -0.03) p-value=0.046 Secondary Endpoint: CGI-I at 12 m responder (stable or improved) 1. 20/34 (58.8%) 2. 9/16 (56.3%) Difference 2.6% (95% CI, -26.8 to 32.0) P=1.000	NA	Any TEAE: 1. 30/34 (88.2%) 2. 12/16 (75.0%) Serious TEAE*: 1. 5/34 (14.7%) 2. 5/16 (31.3%) Vomiting: 1. 8/34 (23.5%) 2. 4/16 (25.0%) Withdraw due to AE 1. 3 2. 1 Death 1. 1 (NPC progression) 2. 0	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized via interactive response technology stratified by age and baseline miglustat use.. Some unbalance in baseline NPCCSS score with higher scores in the active drug group (NPCCSS full scale median difference 6 points, median difference 5-domain NPCCSS score 3.5 points. Performance Bias: (Low) Placebo capsules matched composition, texture, appearance, solubility, smell, and flavor of active drug. Unblinded DSMB allowed for "early escape clause" for rapid disease progression and use of "rescue" arimoclomol treatment initiation with exclusion from future efficacy assessment. Serum creatinine reviewed by independent expert to avoid accidental unblinding as arimoclomol causes reversible increase in SCr due to transport inhibition. Detection Bias: (High) Clinicians provided with NPCCSS scoring manual and training. Caregivers were not trained but caregiver reports were often used to provide assessments. Caregivers did not have daily diaries. There were no instructions on the order of assessments of NPCCSS and SARA assessments and certain NPCCSS domains were notably higher on visits when SARA was also given. Most (84%) baseline CGI-I scores were completed retrospectively. Sample size and trial duration informed by feasibility rather than sample size calculation. Attrition Bias: (High) Uneven attrition. Option for "early escape clause" unblinding used for 2 arimoclomol patients with rapid progression. Missing data not imputed for primary analysis but included in sensitivity analysis. Reporting Bias: (Unclear) Unclear given outcome changes after trial initiation and data lock, though varying NPCCSS versions generally had similar findings Other Bias: (Unclear) Funding by Orphazyme A/S (original manufacturer) **Applicability**: Patient: No adolescent-adult onset patients (who typically have slower disease progression) included. All patients had preexisting neurological signs of disease. Most on miglustat at baseline and all were ambulatory. Roughly half of study population recruited from preceding observational study of disease progression, potentially indicating they had NPC forms with slower overall disease progression than overall infantile and juvenile NPC population.

								Intervention: Dosing appropriate based on prior studies. Product acceptable for administration via feeding tube. Miglustat dosing not reported. Comparator: Placebo appropriate with allowance of miglustat co-administration. Outcomes: Significant concerns around appropriateness of endpoint voiced by FDA and modifications mandated. MCID unclear. Setting: 14 sites in 9 countries (Europe and US) from June 2016 to June 2018
2. Bremova-Ertl et al. NCT05163288[4,8,12] DB, PC, crossover, RCT, MC Phase 3 1:1 randomization	1. N-acetyl-L-leucine then crossover to placebo 2. Placebo then crossover to N-acetyl-L-leucine Weight based dosing: - ≥ 13 y or 4 to 12 y and ≥35 kg: 2g AM, 1g afternoon, 1g PM - 4 to 12y and 25 to < 53 kg: 1g AM, 1 g afternoon, 1g PM - 4 to 12y and 15 to 25 kg: 1 g AM, 1g PM Granules for oral suspension in a sachet suspended in 40 mL water, orange juice, or almond milk given using study provided measuring cup.	Demographics: -Age Range 5 to 67 y -Age < 18 y: 38% -Female 45% -White 90% -Age at diagnosis: <2y 15% 2 to <6y 23% 6 to <15y 38% ≥ 15y 23% -Mean NPC duration 171 months -Miglustat Use 85% -Baseline SARA 1. 15.88 2. 15.68 Key Inclusion Criteria: -NPC diagnosis (US: confirmed with genetic testing. Non-US: Clinical features plus genetic test, or positive biomarker screen and/or filipin test without genetic test, or positive biomarker screen and/or filipin test with genetic test identifying only one NPC mutation.) -Age 4 y or more -performed washout of other agents x 42 d (miglustat allowed) -SARA score 7 to 34 (out of 40) PLUS EITHER	N=60, crossover design ITT: 1. 60 2. 59 ITT with score at end of treatment period: 1. 59 2. 58	Primary Endpoint: SARA at end of each 12-week period Mean (SD) 1. -1.97±2.43 2. -0.6±2.39 LSM difference -1.28 (95% CI, -1.91 to -0.65) P<0.001 Mean fSARA at end of each 12-week period 1. 5.1 2. 5.6 Difference -0.45 (95% CI, -0.7 to -0.19) P<0.001		TEAE: 1. 36 (60.0%) 2. 30 (50.8%) Withdrawal/ Death 1 patient during first half of trial (PEG tube placement complication with aspiration pneumonia)		**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Centrally randomized with Medpace ClinTrack Interactive Response Technology web-based system with permuted block design. Baseline demographics by treatment order not reported. Performance Bias: (Low) Matching placebo granules for oral suspension. Double-blind assignment maintained until database lock. Compliance assessed with review of unused sachets returned by patients. Detection Bias: (High) Crossover design may not be appropriate for progressive disease, though overall treatment period was short and progression may be minimal. No washout period occurred between different treatment periods of trial which could affect results from second half of trial. Modifications to primary endpoint after data collection. Attrition Bias: (Low) Mixed-effects model with 'missing at random' assumption used for missing data. Reporting Bias: (Unclear) Protocol published. Differing information regarding requests for endpoint adjustment between FDA and trial authors/manufacturer. Other Bias: (Unclear) Funded by IntraBio (trial design, drug supply, contracted out data analyses [Cetara]) **Applicability**: Patient: Subtype by age mixed, unclear if treatment more effective in any specific subtype of NPC. Baseline scores ~15-16 on 40 point scale Intervention: Dosing appropriate based on prior studies. Product acceptable for administration via feeding tube. Comparator: Placebo appropriate with allowance of miglustat. Dosing appropriate based on prior studies. Product acceptable for administration via feeding tube. Outcomes: Significant concerns around appropriateness of endpoint voiced by FDA and modifications mandated. The clinical significance of a 0.45 improvement on n fSARA is unclear. Setting: 13 sites (Australia, Europe, US)

	12-week duration for each treatment then crossover	2-7 of SARA gait subtest OR able to perform 9HPT-D in 20 to 150 seconds (SCAFI subtest) -Weight ≥ 15 kg -If childbearing/siring potential, using defined effective birth control. Key Exclusion Criteria: -Allergy to Acetyl-leucine or derivatives or known excipients used in research product. -Participation in other medication research trial within 42 days -Severe, uncorrectable vision, hearing impairment, arthritis, or other musculoskeletal disorder which interferes with assessments						

Abbreviations: AE = adverse event; AM = morning; ARR = absolute risk reduction; CGI-I = Clinical Global Impression-Improvement scale; CI = confidence interval; DSMB = data safety monitory board; FDA = Food and Drug Administration; fSARA = functional Scale for Assessment and Rating of Ataxia; H/O = history of; ITT = intention to treat; LSM = least squared mean; m= month; MCID = minimum clinically important difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NPC = Niemann- Pick disease type C; NPCCSS = 5-domain NPC clinical severity scale; PEG = percutaneous endoscopic gastrostomy; PM = evening; PP = per protocol; R4DNPCCSS = rescored 4-domain NPC Clinical Severity Scale; SARA = Scale for Assessment and Rating of Ataxia; SCAFI = Spinocerebellar Ataxia Functional Index; SCr = serum creatinine; SD = standard deviation; TEAE = treatment emergent adverse events; US = United States; y=year; 9HPT-D = 9-Hole Peg Test with dominant hand.
*All considered related to NPC except those leading to discontinuation

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Appendix 1: Prescribing Information Highlights

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

MIPLYFFA (arimoclomol) capsules, for oral use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
MIPLYFFA is indicated for use in combination with miglustat for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended MIPLYFFA oral dosage, in combination with miglustat, for patients with actual body weight of (2.1):
  - 8 kg to 15 kg, is 47 mg three times a day
  - > 15 kg to 30 kg, is 62 mg three times a day
  - > 30 kg to 55 kg, is 93 mg three times a day
  - > 55 kg, is 124 mg three times a day
- Administer with or without food. (2.1)
- See full prescribing information for recommended dosage in patients with an eGFR ≥ 15 to < 50 mL/minute. (2.2)
- See full prescribing information for instructions on preparation and administration. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 47 mg, 62 mg, 93 mg and 124 mg of arimoclomol. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- *Hypersensitivity Reactions*: Urticaria and angioedema have been reported. Discontinue MIPLYFFA in patients who develop these adverse reactions. (5.1)
- *Embryofetal Toxicity*: May cause fetal harm. Advise pregnant females of the potential risk to the fetus and consider pregnancy planning and prevention. (5.2)
- *Increased Creatinine without Affecting Glomerular Function:* Mean increases in serum creatinine of 10-20% have been reported. Use alternative measures to assess renal function which are not based on creatinine. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥15%) are: Upper respiratory tract infection, diarrhea, and decreased weight. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zevra Therapeutics, Inc. at toll-free phone 1-844-600-2237 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Substrates of the Organic Cationic Transporter 2 (OCT2 substrates)*: Monitor for adverse reactions and reduce the dosage of the OCT2 substrate. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- *Females and Males of Reproductive Potential*: Based on animal findings, MIPLYFFA may impair fertility. (8.3)

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

Revised: 9/2024

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

AQNEURSA™ (levacetylleucine) for oral suspension
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
AQNEURSA is indicated for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing ≥15 kg. (1)

----------DOSAGE AND ADMINISTRATION----------
- For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment. (2.1)
- Recommended dosage (2.2)

Patient Body Weight	Morning Dose	Afternoon Dose	Evening Dose
15 to <25 kg	1 g	No Dose	1 g
25 to <35 kg	1 g	1 g	1 g
35 kg or more	2 g	1 g	1 g

- See the full prescribing information for administration instructions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For oral suspension: 1 gram levacetylleucine in a unit-dose packet. (3)

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

----------WARNINGS AND PRECAUTIONS----------
Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 days after the last dose if AQNEURSA is discontinued. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and greater than placebo) are abdominal pain, dysphagia, upper respiratory tract infections, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact IntraBio Inc. at 1-833-306-9677 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *N-acetyl-DL-leucine or N-acetyl-D-leucine*: Avoid concomitant use with AQNEURSA. (7.1)
- *P-glycoprotein (P-gp) Transporter Substrates*: Monitor for adverse reactions if used with AQNEURSA. (7.2)

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

Revised: 9/2024

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	Arimoclomol	Levacetylleucine
Mechanism of Action	unknown	unknown
Oral Bioavailability	Not determined; Tmax ~ 0.5 hours	NR
Distribution	Mean apparent volume of distribution of arimoclomol at steady state in healthy adult subjects is 211 L	Apparent (oral) volume of distribution is 253 L
Protein Binding	10%	NR
Elimination	Mean apparent clearance of arimoclomol at steady state is 34 L/hr in healthy adult subjects. 12% of the dose was recovered in feces and 77.5% in urine (42% unchanged)	Apparent (oral) clearance is 139 L/h
Half-Life	4 hours	Estimated half-life is around 1 hour
Metabolism	Arimoclomol is predominantly metabolized through glutathionation, O-glucuronidation and NO-oxime cleavage	Metabolized into acetate and L-leucine by ubiquitously expressed enzymes, which are used endogenously in catabolic and metabolic pathways. Cytochrome P450 enzymes are not involved in the metabolism.

Abbreviations: h = hour; L = liter; NR = not reported.

Appendix 3: NPCCSS assessment for Ambulation, Speech, Swallowing, Fine Motor, and Cognition from NCT02612129[6]

Ambulation	Score =
Normal	0
Clumsy	1
Ataxic unassisted gait or not walking by 18 months	2
Assisted ambulation or not walking by 24 months	4
Wheelchair dependent	5
Speech	**Score =**
Normal speech	0
Mild dysarthria (easily understood)	1
Severe dysarthria (difficult to understand)	2
Non-verbal/functional communication skills for needs	3
Minimal communication	5
Swallow	**Score =**
Normal, no dysphagia	0
Cough while eating	1
Intermittent dysphagia with liquids*	(+1)
Intermittent dysphagia with solids*	(+1)
Dysphagia with liquids*	(+2)
Dysphagia with solids*	(+2)
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5
Fine Motor Skills	**Score =**
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	2
Moderate dysmetria/Dystonia (limited fine motor skills, difficulty feeding self)	4
Severe dysmetria/Dystonia (gross motor limitation, requires assistance for self-care activities)	5
Cognition	**Score =**
Normal	0
Mild learning delay, grade appropriate for age	1
Moderate learning delay, individualized curriculum or modified work setting	3
Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function	4
Minimal cognitive function	5

Medications for Niemann-Pick disease Type C

Goal(s):
- Ensure medically appropriate use of medications for Niemann-Pick disease Type C
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- Miplyffa™ (arimoclomol)
- Aqneursa™ (levacetylleucine)

Covered populations: FFS and CCO patients beginning 1/1/26

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for arimoclomol or levacetylleucine in a patient already taking the other agent (i.e., combination therapy without documentation of planned therapeutic switch)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4

Approval Criteria		
4. Has the diagnosis of Niemann-Pick disease type C been confirmed by genetic testing or a filipin test?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request being made by or in consultation with an expert in metabolic or genetic disease or experienced in treating Niemann-Pick disease type C?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there documentation that the patient has developed at least one neurological manifestation of disease?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has baseline severity been documented using NPCCSS, SARA, or some other appropriate tool for assessing Niemann-Pick disease type C? Examples: • Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS) • Scale for the Assessment and Rating of Ataxia (SARA)	**Yes**: Go to #8 Record tool and value:_____	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Go to #11
9. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10
10. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Has the provider documented patient-specific goals for this therapy over the next 6 to 12 months? Note: Goals of therapy can vary from intent to cure, disease burden reduction, disease stabilization and control of symptoms.	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
12. Has the provider defined objective criteria to evaluate unsuccessful treatment or lack of response based on individual patient goals and current symptoms (i.e., when would the provider consider discontinuing therapy)? To qualify for treatment coverage, the patient and provider must have a documented discussion about when risks of the therapy outweigh the benefits and a knowledge of the realistic expectations of treatment efficacy. Care must always take place in the context of the patient's support systems, overall heath, and core values.	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Is the request for arimoclomol in a patient who is at least 2 years old and ambulatory (with or without assistance)?	**Yes**: Go to #14	**No:** Go to #15
14. Is patient taking concomitant miglustat or starting miglustat therapy with arimoclomol initiation?	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness Arimoclomol is only approved for use in combination with miglustat.
15. Is the request for levacetylleucine in a patient weighing at least 15 kg?	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been adherent to current therapy?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Is there documentation that the patient's goals of therapy established prior to treatment have been met?	**Yes**: Approve for 12 months	**No:** Go to #3
3. Is there documentation that pre-established criteria for unsuccessful treatment or lack of response have been met?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Have the patient and provider had a documented discussion about when benefits of the therapy outweigh the potential risks?	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/25 (SF)
Implementation: TBD

Miglustat 100 mg capsule (Zavesca, Yargesa, generic)

Goal(s):
- Ensure medically appropriate use of miglustat for Niemann-Pick disease Type C and Gaucher disease.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- Miglustat (ZAVESCA, YARGESA, generic 100 mg capsules). For OPFOLDA see Pompe disease criteria.

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

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a patient with a prior FFS approval for the requested drug?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the drug prescribed by made or in consultation with an expert in metabolic or genetic disease or experienced in treating Niemann-Pick disease type C or Gaucher disease?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the drug being prescribed for Niemann-Pick disease type C?	**Yes**: Go to #5	**No:** Go to #7
5. Is that patient at least 2 years old?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product?	**Yes**: Inform prescriber of covered alternatives in class. Approve preferred therapy for up to 6 months.	**No:** Approve for up to 6 months
7. Is the drug being prescribed for mild to moderate type 1 Gaucher disease in an adult (18 years or older)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have current symptoms characteristic of bone involvement such as: a. Low platelet count b. Low hemoglobin and hematocrit levels c. Radiologic bone disease, T-score less than -2.5 or bone pain d. Delayed growth in children (<10th percentile for age) OR e. Splenomegaly or hepatomegaly?	**Yes:** Go to #9 Document baseline labs and symptoms	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the request for combination treatment with more than one targeted therapy for Gaucher disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the patient have a documented contraindication, intolerance, inadequate response, or inability to access or adhere to enzyme replacement therapy?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product?	**Yes**: Inform prescriber of covered alternatives in class. Approve preferred therapy for up to 6 months.	**No:** Go to #12
12. Does the patient have either: • A documented failure (either therapeutic or due to adverse events) with the preferred version of this product OR • Documentation of inability to access product to due to national/regional shortage?	**Yes**: Approve therapy for up to 6 months.	**No:** Pass to RPh. Deny; cost effectiveness.

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to miglustat?	**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. Has the patient been adherent to current therapy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Is there objective documentation of benefit based on improved labs or patient symptoms?	**Yes:** Approve for up to 12 months Document labs and patient symptoms	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/25
Implementation: TBD

Gaucher Disease

Goal(s):
- Ensure medically appropriate use of drugs for Gaucher disease

Length of Authorization:
- Up to 12 months

Requires PA:
- Drugs for Gaucher disease (pharmacy and provider administered claims)

  Note: See Agents for Pompe Disease criteria if miglustat is being prescribed for Pompe Disease

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

Table 1. FDA-Approved Minimum Ages

Drug	Age
Eliglustat	18
Imiglucerase	2
~~Miglustat~~	~~18~~

Taliglucerase alfa	4
Velaglucerase alfa	4

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request from a provider experienced in the treatment of Gaucher disease?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness ~~See other criteria if miglustat is prescribed for Pompe Disease.~~ ~~Approve if requested for Niemann-Pick disease type C in a patient with an active PA or treatment with arimoclomol~~.
4. Is the request for treatment of Type 1 Gaucher Disease? Note: Type 1 disease is characterized predominately by bone involvement without CNS symptoms.	**Yes**: Go to #6	**No:** Go to #5
5. Is the request for treatment of Type 3 Gaucher Disease? Note: Drugs are not FDA-approved for Type 2 or 3 Gaucher disease. Type 3 disease is characterized by both bone involvement and CNS symptoms.	**Yes:** Refer requests to the medical director for review. Provide relevant chart notes and literature documenting medical necessity.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the request for an FDA-approved age in Table 1?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have current symptoms characteristic of bone involvement such as: a. Low platelet count b. Low hemoglobin and hematocrit levels c. Radiologic bone disease, T-score less than -2.5 or bone pain d. Delayed growth in children (<10th percentile for age) OR e. Splenomegaly or hepatomegaly?	**Yes:** Go to #8 Document baseline labs and symptoms	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for combination treatment with more than one targeted therapy for Gaucher disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Is the request for enzyme replacement therapy?	**Yes:** Go to #10	**No:** Go to #11
10. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: 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. Approve preferred therapy for up to 6 months.	**No:** Approve for up to 6 months
11. Does the patient have a documented contraindication, intolerance, inadequate response, or inability to access or adhere to enzyme replacement therapy?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the request for eliglustat?	**Yes:** Go to #13	**No:** Approve for up to 6 months

Approval Criteria		
13. Does the patient have cardiac disease, long-QT syndrome, or is currently taking a Class IA or Class III antiarrhythmic medication?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Does the patient have moderate to severe hepatic impairment?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Does testing for CYP2D6 metabolizer status indicate extensive, intermediate or poor CYP2D6 metabolism?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Is the dose consistent with FDA labeling based on CYP2D6 metabolism and use of concomitant CYP inhibitors (see FDA labeling for full details)?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment for Gaucher disease?	**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. Has the patient been adherent to current therapy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Is there objective documentation of benefit based on improved labs or patient symptoms?	**Yes:** Approve for up to 12 months Document labs and patient symptoms	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/25 (SF); 11/19 (SS)
Implementation: TBD; -1/1/2020

Pompe Disease Agents

Goal(s):
- Ensure medically appropriate use of approved agents for the treatment of Pompe disease

Length of Authorization:
- Up to 12 months

Requires PA:
- Alglucosidase alfa (pharmacy and provider administered claims)
- Avalglucosidase alfa (pharmacy and provider administered claims)
- Cipaglucosidase alfa (pharmacy and provider administered claims)
- Miglustat (OPFOLDA) (pharmacy and provider administered claims)

Covered Populations:
- Opfolda (miglustat): FFS and CCO patients beginning 1/1/26
- All others: FFS only

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

Table 1: FDA-approved Dosage and Administration

Agent	Indication	Age Minimum	Dosing Regimen
Alglucosidase alfa	Early Onset Pompe Disease (EOPD) Late Onset Pompe Disease (LOPD)	None	20 mg/kg IV once every 2 weeks
Avalglucosidase alfa	Late Onset Pompe Disease (LOPD)	≥ 1 year	< 30 kg: 40 mg/kg IV once every 2 weeks ≥ 30 kg: 20 mg/kg IV once every 2 weeks
Cipaglucosidase alfa*	Late Onset Pompe Disease (LOPD)	18 years or older	<40 kg: not indicated ≥40 kg: 20 mg/kg IV once every 2 weeks **-plus-** Miglustat 260 mg orally (≥ 50 kg) -or- 195 mg orally (≥40 kg to <50 kg) (administer 1 hour before cipaglucosidase infusion)

*must be administered with miglustat according to FDA labeled dosing parameters

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the requested agent for an approved indication and dosed appropriately based on age and weight taken within the past month? (**see Table 1**)	**Yes:** Document patient weight and go to #3. Weight: _____	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is there documentation that the provider has assessed the patient for signs or susceptibility to the following? • Fluid volume overload • Acute underlying respiratory illness • Compromised cardiac or respiratory function necessitating fluid restriction	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the treatment for the diagnosis of Pompe disease confirmed by either DNA testing or enzyme assay (e.g. acid alpha-glucosidase activity test)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is this request from a metabolic specialist, biochemical geneticist, or has provider documented experience in the treatment of Pompe disease?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for treatment of late-onset Pompe disease (LOPD)?	**Yes:** Go to #11	**No:** Go to #8
8. Has the provider documented a baseline value for ALL the following assessments? • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status (e.g. FEV, FVC, or other age-appropriate test of pulmonary function)? • Cardiac imaging (e.g. chest x-ray, echocardiography)? • CRIM status?	**Yes:** Document baseline results and go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient CRIM-negative?	**Yes:** Go to #10	**No:** Approve for 3 months If approved, a referral will be made to case management by the OHA.
10. Is there documentation that concomitant immune tolerance induction (ITI) therapy will be initiated with enzyme replacement therapy (ERT)?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Is the request for cipaglucosidase alfa or miglustat for Pompe Disease?	**Yes:** Go to #12	**No:** Go to #13
12. Does the provider plan to order combination treatment as outlined in Table 1?	**Yes:** Approve miglustat as combination treatment. Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient 5 years of age or older?	**Yes:** Go to #14	**No:** Go to #15
14. Is there a baseline documentation for both of the following? • Pulmonary function test (PFT) with spirometry including baseline percent predicted forced vital capacity (FVC) • Demonstration of completed 6-minute walk test (6MWT) -OR- Muscle weakness in the lower extremities?	**Yes:** Approve for 6 months Document baseline results. If approved, a referral will be made to case management by the OHA.	**No:** Pass to RPh. Deny; medical appropriateness
15. Has the provider documented a baseline value for both of the following assessments: • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status (e.g. FEV, FVC, or other age-appropriate test of pulmonary function)?	**Yes:** Approve for 3 months Document baseline results. If approved, a referral will be made to case management by OHA.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documented evidence of adherence and tolerance to the approved infusion therapy regimen through claims history and/or provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh, Deny; medical appropriateness

Renewal Criteria		
2. Is this a request for **al**glucosidase alfa?	**Yes:** Go to #3	**No:** Go to #5
3. Is this the first renewal for **al**glucosidase alfa?	**Yes:** Go to #4	**No:** Go to #5
4. Is there documentation that the patient has recently been tested* for IgG antibody formation? ** Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter per manufacturer labeling.*	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Compared to baseline measurements, is there documented evidence of improvement or stabilization in muscle, motor, and/or respiratory function?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is patient under 5 years old? Note: Approve therapy per Table 1 (including miglustat if appropriate)	**Yes:** Approve for 3 months	**No:** Go to #7
7. Has the patient received the requested therapy for at least 6 months? Note: Approve therapy per Table 1 (including miglustat if appropriate)	**Yes:** Approve for 12 months	**No:** Approve for 3 months

P&T/DUR Review: 12/25; 6/24 (DE); 2/22; 4/21;
Implementation: TBD; 7/1/24; 4/1/22; 5/1/21

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: zopapogene imadenovec-drba (PAPZIMEOS)

Date of Review: December 2025
Generic Name: zopapogene imadenovec-drba

End Date of Literature Search: 10/14/25
Brand Name (Manufacturer): Papzimeos (Precigen, Inc.)

Dossier Received: No

Plain Language Summary:

- Recurrent respiratory papillomatosis (RRP) is a rare disease caused by the human papillomavirus (HPV). RRP causes wart-like growths (papillomas) in the airways, such as the windpipe and vocal cords. Most of the growths do not cause cancer but can block the airway.
- Symptoms of RRP are hoarseness, trouble breathing, and voice changes.
- There are two forms of RRP, juvenile-onset and adult-onset. The juvenile-onset occurs in childhood and is often passed from the mother to the baby during childbirth. Adult-onset occurs later and is usually associated with milder symptoms but is often reoccurring.
- The main treatment is surgery to remove the growths. Surgery often needs to be repeated because growths return. Until recently, there were no medications specifically approved by the Food and Drug Administration (FDA) for RRP.
- The FDA approved a new therapy called zopapogene imadenovec, or PAPZIMEOS, for adults with RRP. It is given as 4 injections given under the skin, spaced over 12 weeks.
- Evidence from one small study in 38 patients shows that zopapogene imadenovec decreased the number of surgeries needed for patients with RRP.
- The most common side effects were pain related to the injection, fever and chills.
- The Drug Use Research and Management Group recommends that the Oregon Health Authority pay for zopapogene imadenovec in patients with RRP who need repeated surgeries after their provider documents medical appropriateness through a process called prior authorization.

Research Questions:

1. What is the evidence for efficacy of the zopapogene imadenovec in the treatment of RRP?
2. What is the evidence for the safety of zopapogene imadenovec in the treatment of RRP?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender, disease severity), for whom zopapogene is more effective or associated with less harm?

Conclusions:

- Zopapogene imadenovec is an orphan drug approved for the treatment of RRP. FDA approval was based on one phase 1/2 trial.
- There is low quality evidence that zopapogene imadenovec reduces the number of interventions (i.e., surgical resection or laser ablation) to remove recurrent papillomas in patients with RRP.[1]

Author: Kathy Sentena, PharmD

- Zopapogene imadenovec was studied in 38 adults diagnosed with RRP who required 3 or more interventions in the year before treatment .[1] Patients received 4 doses of zopapogene imadenovec over 12 weeks after receiving a debulking procedure prior to administration. The primary outcome was complete response rate, defined as patients who did not require an intervention (i.e., surgery or laser ablation) to control RRP symptoms in the 12 months following treatment. Eighteen of 35 patients (51%) had a complete response.[1] Recurrent respiratory papillomatosis is a very heterogenous disease and there is not a predictable disease course following surgery to remove papillomas. The median number of interventions required in patients in the study in the previous 12 months prior to treatment was 4.
- Zopapogene imadenovec was well tolerated with no discontinuations due to adverse effects. Injection site reactions were the most common adverse event occurring in 97% of patients.[1] Fatigue, chills and fever were also common adverse events.
- There is insufficient evidence to evaluate efficacy or safety of zopapogene imadenovec in specific subgroups based upon age, gender, or disease severity.

Recommendations:
- Make zopapogene imadenovec nonpreferred on the preferred drug list (PDL).
- Implement prior authorization (PA) to allow coverage for adult patients when other RRP treatments have failed.

Background:
Recurrent respiratory papillomatosis is a chronic, variable disease with an incidence of 4.3 per 100,000 children and 1.8 per 100,000 adults in the United States.[2] It is rare disease caused by HPV type 6 or 11 which results in recurrent growth of papillomas in the upper and lower respiratory tracts. The most common sites of infection are the larynx, trachea, and lungs.[1] Adult onset is usually occurs between 20 and 40 years and is typically transmitted through sexual contact. Disease patterns are variable from spontaneous remission to aggressive persistent disease.[3] Presentation in those under 5 years of age can occur and is usually acquired via transmission from mother to child during birth. HPV acquired during birth is the most common benign laryngeal tumor in children.[4] Infection in younger populations is decreasing due to increased rates of preventative HPV vaccination.[1] The clinical symptoms of RRP are dysphonia, stridor, dyspnea, chronic cough and airway occlusion.[5] Recurrent airway lesions can lead to loss of lung volume, post-obstructive pneumonia or respiratory failure and occasionally can cause malignant disease.[6]

Until recently, there were no approved medical therapies for treatment of RRP. Vaccination is effective for prevention but does not consistently provide benefit in those already infected with RRP.[1] Low quality evidence suggests vaccination may decrease the rates of papillomas and need for surgery. The current standard of care for RRP is repeated endoscopic debulking of lesions by ablation or surgical excision.[6] However, debulking surgery does not address the underlying HPV infection, and papillomas can reoccur. Adjuvant treatment is recommended for patients requiring 3 or more surgical removals of papilloma in a year, rapid recurrence of the papilloma with airway compromise, or distal multisite spread.[6] Up to 20% of patients may require adjuvant treatments. Adjuvant treatments studied for RRP include off-label use of immunomodulators (e.g., imiquimod), disruption of HPV replication (e.g., cidofovir), inflammation control (e.g., celecoxib) or prevention of angiogenesis (e.g., bevacizumab).[6] Adverse reactions and variable effectiveness prevent routine use of adjuvant therapies for RRP. Bevacizumab has the most evidence for reducing requirement for surgeries but requires chronic use which can be associated with toxicity.[6]

Due to the rarity of RRP there are no outcome measures or biomarker of disease to reliably track treatment efficacy. The Derkay score is a staging system used for RRP with scores that range from 0-30.[7] Higher scores indicate severe disease. Scoring is based on the number of sites and bulkiness of papillomas in the pharynx, larynx and trachea as well as subjective clinical symptoms (i.e., voice and breathing symptoms).[1] There is no official minimal clinically important difference (MCID), but reductions of 50% or more are considered clinically meaningful .[7] The Voice Handicap Index-10 (VHI-10) is a validated patient-reported

tool to measure the extent that a voice disorder interferes with a patient's daily life.[8] Scores range from 0 to 40 with higher scores suggestive of greater handicap. Scores above 11 are considered abnormal. The MCID is a 6 point or more decrease in scoring.[8]

In 2025, the FDA approved zopapogene imadenovec for treatment of RRP in adults.

Beginning in January 2026, the Oregon Health Authority is proposing that high cost, rarely used medications be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

Zopapogene imadenovec is currently included in the list of medications proposed to be carved-out of CCO budgets. Zopapogene imadenovec is a one-time treatment course with an estimated cost of $460,000.

Zopapogene imadenovec is a non-replicating adenoviral vector-based immunotherapy that enhances T-cell responses to detect and reduce cells infected with HPV.[9] The dose of zopapogene imadenovec is $5x10^{11}$ particles (1 mL) injected subcutaneously four times over a 12-week time period (at weeks 0, 2, 6 and 12).[9] Surgical debulking of visible papilloma is recommended prior to the initial dose of zopapogene. Removal of additional papilloma is recommended prior to the third and fourth doses if present. Zopapogene imadenovec is supplied as a frozen suspension that must be thawed prior to injection. The thawing process should not exceed 5 minutes, with injection required immediately once thawed.[9] Patients should be monitored for 30 minutes post-injection after initial treatment for local injection site reactions.

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:

Zopapogene imadenovec was studied in a 12-week single-center, single-arm phase 1/2 study in patients that were 18 years and older with a diagnosis of RRP.[1] Diagnosis was defined as histological diagnosis of papillomas, presence of laryngotracheal papillomas, and history of three or more clinically indicated interventions in the 12 months before treatment. A 30-day washout was required for patients prescribed systemic bevacizumab or any other systemic, adjuvant RRP therapy.[1] The use of corticosteroids or other immunosuppressants was held for 14 days prior to administration of zopapogene imadenovec. HPV vaccine within one year of zopapogene imadenovec was not permitted.[1] Patients received zopapogene as 4 subcutaneous doses at day 1, 15, 43 and 85 following a debulking procedure.[1] Patients with visible papilloma growth underwent additional surgery to maintain residual disease if present at days 43 and 85. Patients had to have an Eastern Cooperative Oncology Group performance score of 0 or 1 which indicates patients were fully active and ambulatory with the ability to carry out light work and are able to tolerate surgery. Higher scores on this scale indicate diminished ability to complete daily activities without assistance. The median age was 49 years, age diagnosis was 35 years, 43% were female and HPV 6 was the primary genotype (69% of patients).[1] The number of lifetime interventions (i.e., surgery) for RRP was 40 and the median number of interventions done in the previous 12 months was 4. The baseline Derkay score was 8, indicating mild disease with limited airway involvement and manageable symptoms. The baseline VHI-10 score was 24, suggestive of moderate handicap, in which the patient experiences significant limitations in daily activities due to their voice.[1] The primary outcome was complete response rate, which was the

percentage of patients with no clinically indicated interventions (i.e., surgical resection or laser ablation) during the 12 months after treatment. Clinically indicated interventions were based on documentation from patient's home care team.

For the primary outcome, 51% of patents had a complete response at 12 months after treatment with zopapogene imadenovec.[1] This response was maintained in 83% of patients up to 33 months after completing treatment.[1] A median of one debulking surgery was required to maintain residual disease in patients that were complete responders during treatment and a median of 2 debulking procedures were required in the non-complete responder group. An objective response (i.e., defined as patients with at least 50% decrease in the number of interventions in the 12 months after treatment compared to the 12 months before treatment) was achieved in 66% (n=23) of patients (95% CI, 48 to 81%).[1] The number of interventions 12 months after treatment was less in complete responders (median of 0) compared to non-complete responders, median of 2 (P<0.001).[1] Time to first intervention was not met because an intervention was not needed by those that had a complete response with follow up of 22 months. Subgroup analysis by the FDA found results to be consistent regardless of HPV type, number of surgeries prior to treatment, and age of disease onset.[6] Additional data analyses on complete responders demonstrated no surgical interventions in 15/18 patients studied out to 2 years and 6/6 patients evaluated at 3 years.[6]

The study had several limitations. Results were presented based on a complete response versus a non-complete response which increases the risk of reporting bias as some outcomes appear more improved compared to reporting results as a whole. There was a high risk of selection and performance bias since there was no randomization and a single-arm, open-label study design. Assessment of RRP was done by patient's home care team which could introduce significant variability in outcome evaluation and increase risk of detection bias. The study was conducted at a single center which reduces external validity. Since RRP is a heterogenous disease with fluctuations in disease severity over time, having a primary outcome evaluated over 12 months may not necessarily predict long-term durability or additional need for surgery.

Clinical Safety:
The most common adverse reactions associated with zopapogene imadenovec were injection-site reactions, fatigue, chills, fever and myalgia.[1,9] These common adverse events are due to the non-replicating adenovector-based immunotherapy mechanism of action which activates an immune response. No serious side effects were reported in the study. There were no discontinuations due to treatment related adverse reactions.[1] There is a risk of thrombosis with adenoviral vector-based therapies which may be caused by cytokine mediated coagulation, endothelial activation and platelet activation.[9]

There are no long-term studies to provide evidence on the chronic use of zopapogene imadenovec. The safety and efficacy of repeated doses, beyond the recommended 4 doses, has not been studied. Zopapogene imadenovec has not been studied in pregnant women. There are unknown safety effects in patients with more severe RRP disease and when the drug is given to a wider population.

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Prevention of recurring papillomas
2) Number of interventions to remove papillomas
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Complete response rate (i.e., no need for interventions to remove papillomas for 12 months following treatment)

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. Norberg, et al SA, SC, OL, Phase 1/2	1. Zopapogene imadenovec $5x10^{11}$ particle units subcutaneously on day 1, 15, 43, and 85* Treatment course: 12 weeks Study duration: 12 months	Demographics: Median age: 49 years Median age at diagnosis: 35 years Juvenile-onset RRP: 12 (34%) Adult-onset RRP: 23 (66%) Female: 15 (43%) Number of lifetime interventions for RRP: 40 HPV 6: 24 (69%) HPV 11: 11 (31%) Median Derkay score: 8 Median VHI-10 score: 24 Key Inclusion Criteria: - Ages 18 years and older - RRP diagnosis - Three or more interventions in the previous year - Eastern Cooperative Oncology Group performance score of 0 or 1. Key Exclusion Criteria: - Immunosuppressant use - History of previous systemic therapy for RRP within 3 half-lives from the previous drug	ITT: 35 PP: 35 Attrition: 0	Primary Endpoint: Complete Response Rate†: 1. 18 (51%) (95% CI, 34% to 69%) Secondary Endpoint: Objective Response Rate‡: 1. 23 (66%) Fewer number of interventions 12 months after treatment compared to 12 months before treatment: 1. 30 patients (86%) (95% CI 70% to 95%) Number of patients with a decrease in Derkay score after treatment compared to baseline: Complete responders: 90% Non-complete responders: 32% Number of patients with a decrease in VHI-10 score changes compared to baseline: Complete responders: 95% Non-complete responders: 14% Median number of clinically indicated interventions during treatment: Responders: 1 Non-complete responders: 2	NA for all	Injection-site Reaction: 34 (97%) Fatigue: 28 (80%) Chills: 25 (71%) Fever: 24 (69%) Serious AE: 0 Discontinuations due to AE: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Trial not randomized. Performance Bias: (High) Trial was open label with no comparison group. Detection Bias: (High) Assessments of primary outcome was based on patient's home care team (otolaryngologist, independent of study team1) which could vary between clinics and providers. Attrition Bias: (Low) None observed. Reporting Bias: (High) Timeframe of measurement of Derkay score and VHI-10 score was not prespecified. Other Bias: (Unclear) Trial was funded by manufacturer. **Applicability**: Patient: Patients Derkay scores indicative of mild impairment and VHI-10 scores indicating severe dysphonia. Patients required debulking surgeries prior to treatment. Intervention: Dose was based on phase 1 phase of the study which demonstrated efficacy and safety. Comparator: None which makes it difficult to determine if zopapogene imadenovec results in fewer interventions compared to standard of care. Outcomes: Number of interventions for papillomas is a clinically appropriate and relevant outcome. Setting: Single-center at National Institutes of Health.

Key: * Treatment started on day 1 following surgical debulking; † Complete response rate was defined as percentage of patients who did not require an intervention to control RRP in the 12 months after treatment; ‡ Percentage of patients with a complete response or partial response (defined as patients with at least 50% decrease in the number of interventions in the 12 months after treatment compared to the 12 months before treatment).
Abbreviations: AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; HPV = human papillomavirus; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; PP = per protocol; RRP = SA = single-arm; SC = single-center; VHI = Vocal Handicap Index 10.

References:

1. Norberg S, Valdez J, Napier S, et al. PRGN-2012 gene therapy in adults with recurrent respiratory papillomatosis: a pivotal phase 1/2 clinical trial. Lancet Respir Med 2025; 13:318-26.

2. Derkay C, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118(7):1236-47.

3. Fortes H, Ranke F, Escuissato D, et al. Recurrent respiratory papillomatosis: A state-of-the-art review. Respir Med . 2017 May:126:116-121. doi: 10.1016/j.rmed.2017.03.030. Epub 2017 Apr 1.

4. Palefsky J. Human papillomavirus infections: Epidemiology and disease associations - UpToDate. Accessed September 18, 2025. https://www.uptodate.com/contents/human-papillomavirus-infections-epidemiology-and-disease-associations?search=recurrent%20respiratory%20papillomatosis&sectionRank=1&usage_type=default&anchor=H15115461&source=machineLearning&selectedTitle=1~13&display_rank=1#H15115461

5. Derkay CS, Wiatrack B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118:1236-37.

6. Food and Drug Administration. BLA Clinical and Clinical Pharmacology Review Memorandum - Papzimeos. August 2025.

7. Derkay CS, Malis DJ, Zalzal G, et al. A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis. Laryngoscope. 1998;108(6):935-937.

8. Rosen CA, Lee AS, Osborne J, et al. Development and validation of the Voice Handicap Index-10. Laryngoscope. 2004;114(9):1549-1556.

9. Papzimeos (zopapogene imadenovec-drba) [prescribing information]. Germantown, MD; Precigen, Inc. August 2025.

Appendix 1: Prescribing Information Highlights

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

PAPZIMEOS (zopapogene imadenovec-drba) suspension for subcutaneous injection
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
PAPZIMEOS™ is a non-replicating adenoviral vector-based immunotherapy indicated for the treatment of adults with recurrent respiratory papillomatosis. (1)

----------DOSAGE AND ADMINISTRATION----------
PAPZIMEOS is for subcutaneous injection only. (2.1)

The recommended dose of PAPZIMEOS is 5×10^{11} particle units (PU) per injection administered by subcutaneous injection four (4) times over a 12-week interval. (2.1)

Prior to the initial administration of PAPZIMEOS, perform a surgical debulking of visible papilloma to establish minimal residual disease. To maintain minimal residual disease during treatment with PAPZIMEOS, remove visible papilloma, if present, prior to the third and fourth administration of PAPZIMEOS. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
PAPZIMEOS is supplied in a single-dose vial that contains 5×10^{11} PU in an extractable volume of 1 mL of suspension. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Injection-site reactions: Injection-site reactions, have been observed. Monitor patients for local site reactions for at least 30 minutes after the initial treatment. (5.1)
- Thrombotic events: Thrombotic events may occur following administration of adenoviral vector-based therapies. Monitor patients for signs and symptoms of thrombotic events and treat events according to clinical practice. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥5%) were injection site reactions, fatigue, chills, pyrexia, myalgia, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Precigen Inc. at 855-743-6777 and medinfo@precigen.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Non-replicating adenoviral vector-based immunotherapy
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Not studied
Elimination	Not studied
Half-Life	Not studied
Metabolism	Not studied

Appendix 3: Proposed Prior Authorization Criteria

Papzimeos™ (zopapogene imadenovec-drba)

Goal(s):

- To allow for the adjuvant treatment of recurrent respiratory papillomatosis (RRP) in patients who have persistent disease despite surgical intervention.

Length of Authorization:

Up to 12 months

Requires PA:

- All doses of Papzimeos™ (zopapogene imadenovec-drba) require PA

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

Covered Alternatives:

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

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

Approval Criteria		
2. Is this an FDA approved age? Note: Papzimeos is currently approved for adults.	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for a patient with recurrent respiratory papillomatosis (RRP)? * Note: Recurrent is defined as a need for 3 or more debulking procedures for papillomas related to RRP in the previous 12 months	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with Papzimeos?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for one treatment course; 4 doses over 12 weeks

P&T/DUR Review: 12/25 (KS)
Implementation: TBD

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

New Drug Evaluation: Palovarotene, oral capsules

Date of Review: December 2025
Generic Name: palovarotene

End Date of Literature Search: 10/01/25
Brand Name (Manufacturer): SOHONOS (Ipsen Biopharmaceuticals, Inc)

Dossier Received: yes

Plain Language Summary:

- Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease where muscles and connective tissue gradually turn into bone.
- Early signs of FOP include malformed big toes, painful "flare-ups" after minor injuries, and loss of mobility.
- There is no cure for FOP; care focuses on avoiding injury and using short steroid courses, such as prednisone, to ease flare-ups.
- Palovarotene (SOHONOS) is a medicine the Food and Drug Administration (FDA) approved to treat FOP in girls at least 8 years old and boys at least 10 years old. It is a medicine that may help slow new bone growth to allow normal repair of muscles and tissues.
- Common side effects of palovarotene are skin dryness and joint aches; serious risks include stunted growth in children and birth defects.
- Providers must explain to the Oregon Health Authority (OHA) why someone needs palovarotene before OHA will pay for it. This process is called prior authorization.

Research Questions:

1. What is the efficacy of palovarotene compared to placebo or currently available treatments for FOP?
2. What is the safety of palovarotene compared to placebo or currently available treatments for FOP?
3. Are there any subgroups (based on age, gender, race, ethnicity, socioeconomic status, comorbidities, disease duration or severity) that would particularly benefit or be harmed by treatment with a specific agent for FOP?

Conclusions:

- Data from one pivotal phase 3, multi-center, open-label, single arm study indicate that at 18 months, patients treated with palovarotene had a statistically significant reduction in new heterotopic ossification (HO) formation compared to the untreated natural history study (NHS) cohort used as a historical control (Mean new HO volume: -10.9 cm^3/year (95% confidence interval [CI] -21.2 to -0.6; p=0.039; quality of evidence (QoE): insufficient).[1] It is unclear whether a 10.9 cm^3/year reduction in new HO volume is clinically meaningful to patients with FOP as the outcome has not been associated with improvements in functional status.
- There is insufficient evidence comparing palovarotene to surgical interventions or agents used in the treatment of FOP such as glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX2) inhibitors as no head-to-head trials have been conducted.

Author: Dave Engen, PharmD

- Roughly 97% of participants experienced at least one retinoid-associated mucocutaneous adverse event; the most common adverse events (≥10%) were dry skin, lip dryness, arthralgia, pruritis, rash, alopecia, erythema, and headache.[1-3]
- Palovarotene has FDA warnings for increased risk of metabolic bone disorders, psychiatric disorders, and night blindness.[3]
- Palovarotene is contraindicated in pregnancy and has an FDA black-box warning for embryo-fetal toxicity.[3] For females of reproductive potential, prescribers should obtain a negative pregnancy test within one week prior to initiating and periodically during therapy.[3]
- Palovarotene has a boxed warning for premature epiphyseal closure.[3] In growing pediatric patients, assessment of skeletal maturity, hand and wrist bone age, and knee x-rays, is recommended at baseline and then every 6 to 12 months until skeletal maturity or final adult height is reached.[3]

Recommendations:
- Designate palovarotene as non-preferred on the preferred-drug list (PDL).
- Implement prior authorization (PA) criteria for palovarotene to ensure safe and appropriate use for children and adults with FOP (**Appendix 3**).

Background:
Fibrodysplasia ossificans progressiva is a rare genetic disorder where unrestrained, atypical growth of bone takes place in soft tissues (e.g. muscles, ligaments, tendons, etc.) which eventually become ossified.[4] FOP causes significant joint inflammation and pain that eventually results in permanent immobility and greatly reduces patient survival.[4-6] The disease is caused by a gain-of-function mutation in the activin receptor IA (ACVR1) gene that occurs randomly in reproductive cells or during early embryonic development.[7] FOP affects about 1 in 1.6 million newborns worldwide and is not of higher prevalence in any particular race, gender, or geographic region.[8]

Diagnosis of FOP is challenging as clinical presentation is heterogeneous which often leads to a missed or delayed diagnosis.[9,10] Malformed great toes at birth occur in roughly 90% of people with FOP which can be an early sign that further genetic testing is necessary.[9,10] The progressive, postnatal formation of extra-skeletal bone in muscle and soft tissues, or heterotopic ossification (HO), is the hallmark of FOP.[9] Flare-up episodes often occur in the first decade of life following trigger events such as trauma, intramuscular injections, surgery, or viral illness.[9,10] HO degeneration destabilizes joints which affect posture, gait, and mobility.[10] Over half the patients with FOP report progressive mobility constraints regardless of flare-ups.[9,10] Mobility restrictions are one of many complications that lead to a poor prognosis in patients with FOP.[9] FOP may also result in cardiopulmonary issues such as right-side heart failure, respiratory compromise, and pneumonia.[10] HO in the temporomandibular joint region may hamper eating and lead to malnutrition and weight loss.[10] By the age of 30, many patients with FOP are wheelchair bound and require lifelong assistance and rehabilitation with activities of daily living (ADLs).[9,10] The median life expectancy of patients with FOP is around 56 years of age with respiratory complications identified as the most common cause of death.[9,10] The accumulation of HO in patients with FOP is considered to be irreversible.[9,10]

Osteogenesis, or bone formation, is a complex process of progenitor cell differentiation into mineralized bone.[6,9-10] The ACVR1 gene codes for a bone morphogenic protein (BMP) type 1 receptor within the transforming growth factor beta (TGF-β) superfamily.[6,9-10] BMP ligands initiate a signaling cascade to promote tissue growth and repair as well as cell differentiation (e.g. myoblasts to osteoblasts) and proliferation.[6,9-10] However, variants of the ACVR1 gene can disrupt normal BMP signaling and lead to abnormal ACVR1 protein production.[6,9-10] Approximately 97% of the patients with FOS have the ACVR1 gene mutation identified as c.617G>A;R206H.[6,9-10] This mutation causes hyper responsiveness to Activin A and excessive signaling through the SMAD1/5/8 over activation of HO pathways.[6,9-10] Disproportionate receptor activity produces an overgrowth of bone and cartilage observed in patients with FOP.[6,9-10]

Although HO as a result of FOP follows a fairly consistent pattern, comprehensive data concerning the natural disease progression and its morbidity/mortality rates are insufficient.[11] There are specific regions of the body that tend to be early targets for HO.[6,9,10] HO typically begins in the axial/cranial and proximal areas of the body (e.g. neck, spine, shoulders) then radiates to the appendicular/caudal and distal bodily regions (e.g. hips, elbows, knees, wrists, and ankles).[6,9-10] There are no blood tests available to monitor disease activity, however, certain imaging techniques may be employed to assist.[5] Computed tomography (CT) imaging supports the initial diagnosis of FOP and helps monitor changes in fully formed bone.[5] Changes in HO volume may be estimated using low-dose whole body computed tomography (WBCT) and, when performed sequentially, may help detect heterotopic bone volume increases over time.[5] Some studies have converted WBCT observations into an analog scoring scale to assess outcomes of drug interventions.[1,2,4] While HO gradually accumulates over time and generally leads to worsening mobility, it remains unclear whether negative HO volumes are indicative of improvements in function and/or quality of life.[2]

Clinical staging of FOP is important because it allows clinicians to develop appropriate care plans as well as monitor and adjust interventions based on effectiveness.[10,12,13] There are 5 major stages of FOP identified with common features that help distinguish each stage.[10,12,13] The features of each clinical stage include affected body region and flare-up activity, thoracic insufficiency syndrome, functional assessments (ADLs, ambulation, and cumulative analog joint involvement scale CAJIS score), and other complications.[10,12,13] Some patients may present with additional atypical features such as mild cognitive impairment but this phenomenon is rare.[10,12,13] The staging and clinical features of each stage are summarized in **Table 1.**

Table 1. Clinical Stages of FOP (modified)[10,13]

	Clinical Stages				
Features	**Early/Mild**	**Moderate**	**Late/Severe**	**Profound**	**End-Stage**
Body regions affected	Neck, back, upper limbs	Neck, back, upper and lower limbs	Neck, back, upper and lower limbs; jaw	Neck, back, upper and lower limbs; jaw and distal limbs (wrists and ankles)	Ankyloses of most or all joints
Flare-ups	None or limited to scalp, neck or back	Limited to axial regions and upper limbs	Any location	Any location	Any location
Thoracic insufficiency	N/A	Limited chest expansion	Rigid chest wall; no chest expansion; diaphragmatic breathing	Symptomatic thoracic insufficiency syndrome	Symptomatic thoracic insufficiency syndrome
ADLs	No or minimal assistance required due to mild joint limitations or physical delay in developmental milestones	Some assistance required	Assistance needed for most activities	Dependent for all ADLs	Dependent for all ADLs
Ambulation	Unaffected or cannot evaluate due to very young age	Walks; Use wheelchair in extenuating circumstances (e.g. long distances)	Walks with assistive device and/or uses wheelchair	Wheelchair-bound	Mostly bed-bound

Other complications	N/A	N/A	N/A	Pneumonia; pressure ulcers	Recurrent respiratory infections
CAJIS score (range 0 to 30)	≤4	5–18	19–24	≥24	≥28
Abbreviations: ADLs=activities of daily living; CAJIS=cumulative analog joint involvement scale					

The cumulative analog joint involvement scale (CAJIS) and patient-reported mobility assessment (PRMA) are two scales commonly used to evaluate functional status and mobility in patients with FOP.[12,14] The CAJIS is a physician-derived scale that assesses limitation at 15 different body locations such as the jaw, neck, thoracic and lumbar spine, bilateral shoulders, elbows, wrists, hip, knees, and ankles.[12] Patients are given a score of 1 point for each affected location and receive an additional point if the site is functionally ankylosed.[12] The CAJIS scale has a maximum score of 30 points.[12] There is research to suggest that the CAJIS score increases by about 0.5 points per year in the typical patient with FOP.[12] The other common scale used to assess function is the patient-reported mobility assessment (PRMA).[13,14] The anatomical areas assessed with the PRMA are the same as CAJIS in which the patient evaluates whether movement is normal (0 points), partially impaired (1 point), or completely restricted (2 points).[13,14] The scoring for the PRMA ranges from 0 (no limitation) to 30 (severe limitation).[13,14]

Management of FOP is largely supportive as there are no available agents to cure the underlying cause.[13,15] Physical rehabilitation may be employed but must be carefully considered as excessive stress to joints may exacerbate lesions and potentially worsen disease.[13,15] Surgical intervention and invasive biopsies may also cause flare-ups and worsen ossification.[13,15] Flare-ups are usually managed by a short course of high-dose corticosteroids (e.g. prednisone) to provide temporary relief, but it does not completely resolve symptoms.[4,6,13] The anti-inflammatory effects of corticosteroids, specifically glucocorticoids, are most effective within 24 hours of a flare-up.[4,6,13] Non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX2) inhibitors may be used when prednisone is discontinued, but evidence of long-term efficacy in treating the symptoms of patients with FOP is limited.[4,6,13] Imatinib, a tyrosine kinase inhibitor, has been studied for its immunomodulatory and anti-proliferative effects in mast cells with the goal of decreasing flare-up intensity in patients with HO related to FOP.[6,13] With no cure for FOP, guidelines recommend prevention of injury as the most reasonable treatment.[13]

In 2023, the FDA approved palovarotene, a selective gamma retinoic acid receptor (RARγ) agonist, for patients with FOP.[3] Retinoids are derivatives of vitamin A and function in the regulation of tissue and organ development.[16] Progenitor cell differentiation into cartilage is greatly influenced by retinoid signaling.[16] Studies have shown that exogenous active retinoids may inhibit chondrogenesis.[17] Retinoic acid receptor gamma (RARγ) is a nuclear hormone receptor found in chondrogenic cells that regulates ectopic bone development and skeletal formation.[17] RARγ agonists are being explored in the treatment of various diseases such as FOP due to their anti-inflammatory and inhibitory effects on bone/cartilage production.[17,18] By binding to RARγ, it is believed that BMP/ACVR1 signaling may be decreased by blocking SMAD1/5/8, resulting in reduced chondrogenesis and osteocyte differentiation.[6,9,19] Whether RARγ agonists have a significant role in reducing HO volume or lesion activity remains unclear.[2] It is uncertain whether reductions in HO volume, lesions, or inflammation is of clinical benefit since these factors have not been associated with improvements in the functional status of patients with FOP.[2]

Beginning in January 2026, the Oregon Health Authority is proposing that high cost, rarely used medications be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

Palovarotene (SOHONOS) is a medication proposed to be carved-out of CCO budgets. Over a 1 year period from 10/1/24 to 9/30/25, one member had a diagnosis of fibrodysplasia ossificans progressiva in their medical claims.

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

Clinical Efficacy:
SOHONOS (palovarotene) was approved for the treatment of FOP in females at least 8 years old and in males at least 10 years old.[2,3] Approval by the United States FDA was granted on the basis of one pivotal trial (MOVE) which was a global, open label, single arm, phase 3 trial over 18 months in 97 patients at least 4 years of age with FOP (Study PVO-1A-301; NCT03312634; **Table 3**).[2,3]

Enrolled subjects received palovarotene 5 mg once daily for 24 months.[1,2] For flare-ups, palovarotene 20 mg was given once daily for 4 weeks followed by 10 mg once daily for 8 weeks.[1,2] The palovarotene dose was adjusted for skeletally immature patients, defined as patients less than 18 years of age with less than 90% skeletal maturity on hand/wrist x-rays at the time of screening.[1,2] The primary endpoint was the annualized change in new HO volume in nine body regions (chest, neck, shoulder, mid-torso, arms, hips, and legs) as assessed by whole body commuted tomography (WBCT) at months 12, 24, 36 and overall.[1,2] WBCT-imaging observations/measurements were converted into an analog scoring scale.[1,2] Clinicians measured the quantity and diameter of HO spicules or coalescing island/reticular complexes of bone and score accordingly with a 0 up to 6 (higher score = more severe).[2] A score of NE was used if the HO lesion was not evaluable.[2] The key secondary endpoint was the proportion of patients with new HO at month 12.[1,2] Results from the MOVE trial were compared to an external historical control of untreated participants with FOP who were enrolled in the 3-year global, observational, prospective, Natural History Study (NHS Study PVO-1A-001; NCT02322255).[1,2,20] In the NHS, patients used standard treatments such as NSAIDs and corticosteroids.[1,2] Disease progression was tracked via WBCT and other clinical assessments performed at different intervals in the two studies (scheduled every 6 months in study 301 and every 12 months in the NHS).[1,2,20] Study subjects had some notable differences between cohorts at baseline.[1,2] There were a higher proportion of adult (>18 years old) patients in the NHS group than the palovarotene group (roughly 50% vs 30%, respectively), a higher frequency of flare-ups in the past year (2.5 vs 1.4, respectively), and less time since their last flare-up (about 19 vs 25 months, respectively).[1,2,20] The study called for two prespecified formal interim analyses at 12 months and 18 months to assess both efficacy and futility.[1,2]

To measure changes from baseline in HO volume, a square root transformation of HO volume was used to account for the high variability in HO volume observed in the NHS.[1,2] With this method, the rate of growth in HO volume was to be estimated for each incremental change by body region between scans.[1,2] The prespecified futility analysis revealed that the trial was unlikely to meet its primary efficacy endpoints at 12 months.[2] After a study pause to reassess the trial design, endpoint definitions, and statistical methods, the manufacturer proposed that the study endpoint be modified to use annualized absolute change in HO volume rather than percent change in HO volume. This change was deemed necessary to better reflect reductions in HO volume by providing an ability to accommodate negative HO values.[2] The new post-hoc analysis at 18 months demonstrated a statistically significant reduction in new HO formation in patients treated with palovarotene compared to the untreated NHS cohort (Mean new HO volume: -10.9 cm^3/year (95% CI -21.2 to -0.6; p=0.039).[1-3] It is unclear whether a 10.9 cm^3/year reduction in new HO volume across 9 body regions is clinically meaningful to patients with FOP as the measurement has not been conclusively associated with improvements in functional status, health-related quality of life, or frequency of flare ups.[2]

There were limitations noted in the MOVE study. The study was not randomized so there were limits in the ability to control for unknown or undocumented confounding factors such as undocumented disease severity, incidence of injury, undocumented interventions, or changes in standard of care over time. In addition, there were no data on relevant clinical outcomes such as disease progression, function, symptom change, survival, or quality of life. Lastly, the method of analysis was changed post-hoc so there is a significant risk of reporting bias. Palovarotene was approved by Health Canada in January 2022, but was denied authorization for marketing after review by the European Medicines Agency (EMU) in May 2023.[21,22] The EMU cited concerns with post-hoc analysis of data, the clinical relevance of the study's main endpoint, and a lack of efficacy in functional areas.[22]

Clinical Safety:

Palovarotene safety was evaluated in 164 subjects with FOP, including 139 subjects in the indicated population of ages 8 years and above for females and 10 years and above for males.[2,3] Most of the palovarotene safety data comes from patients exposed to the 5 mg chronic dose or the 20/10 mg flare-up for 12 weeks regimen.[2,3] Doses were reduced according to weight in subjects who displayed <90% skeletal maturity.[1-3] Safety was evaluated over part A (24 months) and part B (24-month extension).[1-3] The mean duration of palovarotene exposure was 79 weeks for chronic dosing (N=131 subjects) and 35 weeks for flare-up dosing (N=105 subjects).[2] All patients treated with palovarotene experienced at least 1 adverse event, with the most frequent events summarized in **Table 2**.[3] About 97% of participants experienced at least one retinoid-associated mucocutaneous adverse event such as dry skin, arthralgia, pruritis, rash, and alopecia.[1-3] Serious adverse events occurred in approximately 29% of subjects treated with palovarotene with the most serious being premature epiphyseal closure in patients under 14 years of age (37%).[1-3] Other metabolic bone disorders associated with palovarotene use are decreased bone mineral density and increased fracture risk.[2,3]

Table 2. Summary of Adverse Reactions Reported at greater than 10% Frequency in FOP Subjects 8/10 years and older in Clinical Trials[3]

Adverse Reaction	Chronic Dosing 5 mg N=131 n (%)	Flare-up dosing 20/10 mg N=105 n (%)
Dry skin	80 (61)	60 (57)
Lip dry	62 (47)	40 (38)
Arthralgia	47 (36)	32 (31)
Pruritis	45 (34)	50 (48)
Pain in extremity	38 (29)	29 (28)
Rash	36 (28)	31 (30)
Alopecia	32 (24)	31 (30)
Erythema	25 (19)	34 (32)
Headache	25 (19)	20 (19)
Back pain	22 (17)	12 (11)
Skin exfoliation	20 (15)	30 (29)
Nausea	20 (15)	14 (13)

Musculoskeletal pain	18 (14)	14 (13)
Myalgia	15 (12)	9 (9)
Dry eye	13 (10)	23 (22)
Hypersensitivity	13 (10)	21 (20)
Peripheral edema	12 (9)	20 (19)
Fatigue	7 (5)	12 (11)

Low-dose WBCT revealed decreased bone mineral density and a trend toward increased vertebral fracture.[2,3] Palovarotene has a boxed warning for premature epiphyseal closure and also embryo-fetal toxicity/teratogenicity.[3] It is contraindicated in pregnancy and requires the use of strict contraception in patients of childbearing potential.[3] Night blindness has also been associated with palovarotene use.[3] Other safety risks associated with palovarotene and listed in the retinoid class product labels include psychiatric disorders, pseudotumor cerebri, pancreatitis, hepatotoxicity, hypertriglyceridemia, hearing impairment, inflammatory bowel disease, and hyperostosis.[2,3]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved survival
2) Functional Improvement
3) Use of mobility aids and personal care tools
4) Health related quality of life
5) Serious adverse events (e.g. hearing loss)
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total volume heterotopic ossification

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Pignolo R, et al. MOVE[1,2] NCT03312634 OL, MC, single-arm, study N=107	1. Chronic Dosing Palovarotene 5 mg once daily (or weight-based equivalent) x 24 months -and- Flare-up Dosing (if needed) Palovarotene 20 mg once daily (or wt-based equivalent) for 4 weeks, followed by palovarotene	Demographics: Male: 1. 53.5% 2. 54.1% Mean age: 1. 15.1 years 2. 17.8 years Race: White 1. 70.7% 2. 73% Black or African American 1. 1% 2. 0% Asian	ITT: 107 PP: 97 Attrition: 19/107 (18%) -per patient request (10.3%) -per sponsor request (1.9%)	Primary Endpoint: Annualized change in new HO volume 1. 9.4 cm^3/year 2. 20.3 cm^3/year MD 10.9 cm^3/year (95% CI, -21.1 to -0.6) Secondary Endpoints: Proportion of patients with new HO at month 12 1. 64% 2. 62%	NA	Important AEs SAEs 29.3% DC due to AE 9.1% Retinoid-associated TEAEs 97% Deaths none	NA	**Risk of Bias (low/high/unclear)**: *Risk of bias unable to be fully assessed as study was open-label and non-randomized. Confounding cannot be ruled out.* Selection Bias: HIGH. No information on patients screened but not included. No randomization or blinding. Baseline characteristics not fully reported; older age and more frequent flare-ups may indicate more severe disease in NHS patients compared to treated subjects; baseline imbalances were not adjusted or controlled. Intervention Bias: HIGH. Open label study design. Radiologists blinded to WBCT scan groups (MOVE study and NHS) but unblinded

	10 mg once daily (or wt-based equivalent) for 8 weeks -Total flare-up treatment duration: 12 weeks Total treatment duration: 48 mo. -Part A = 24 mo. -Part B = 24 mo. 2. Natural History (no treatment) N=101	1. 9.1% 2. 8.1% Unknown 1. 11.1% 2. 14.4% History of flare-ups 1. 100% 2. 97.3% Time since previous flare-up (mos) 1. 24.5 2. 18.9 Mean number of flare-ups past year 1. 1.4 2. 2.5 Mean WBHO volume, cm^{3*} 1. 208.0 2. 389.4 CAJIS score, mean* 1. 9.4 2. 13.1 Number of body regions with HO, mean* 1. 6 2. 6.8 <u>Key Inclusion Criteria</u>: -FOP Dx -R206H mutation • ≥4 years of age • <u>></u>2 acute symptomatic flare-ups in the past 2 years • no flare-up Sx within 4 wks • no prior palovarotene use • abstinence; use two forms of birth control <u>Key Exclusion Criteria</u>: • Weight < 10 kg • Refusal to d/c use of vit A or preps containing vit A • Synthetic oral retinoids last 4 wks • Concurrent Tx with TCN • Hx of allergy or hypersensitivity to retinoids, gelatin, or lactose • Use of strong inhibitors or inducers of cypP450 3A4 activity; or kinase inhibitors, such as imatinib	-due to AE (5.6%)	Mean number of body regions at month 12 with new HO since baseline 1. 1.3 2. 1.5 *Not statistically significant*		Common AEs <u>Skin and SC tissue disorders</u> 97% <u>GI disorders</u> 77.8% <u>Infection</u> 75.8% <u>Musculoskeletal and connective tissue disorders</u> 65.7%		to timing of image collection. Imaging protocols were inconsistent between groups. High variability in radiologist ability to detect HO. <u>Data Collection Bias</u>: UNCLEAR. Eligibility criteria and flare-up management modifications made mid-trial based on interim futility analysis. Changes detected from baseline used post-hoc analysis data. <u>Attrition Bias</u>: UNCLEAR. 17.8% of the 107 enrolled patients discontinued the study before data cutoff for the third interim analysis. <u>Reporting Bias</u>: HIGH Funded by Clementia Pharmaceuticals Inc., which was acquired by Ipsen in April 2019. **Applicability**: <u>Patient</u>: Eligible patients were subject to many exclusions including comorbidities and conditions such as liver dysfunction and hypertriglyceridemia which may not be representative of the OR Medicaid population. <u>Intervention</u>: Doses fixed or based on body weight and flare-up status. <u>Comparator</u>: Natural history study. Untreated patients may have had different disease severity. <u>Outcomes</u>: (Surrogate) - HO volume changes not directly linked to functional improvement. Long term impact on disease progression unknown. <u>Setting</u>: 16 sites in Argentina, Australia, Brazil, Canada, France, Italy, Japan, Spain, Sweden, the United Kingdom, and the United States of America.

		• Amylase or lipase > 2× ULN or a hx of chronic pancreatitis • Elevated AST or ALT > 2.5 × ULN • Fasting TGs > 400 mg/dL • Uncontrolled CVD, hepatic, pulmonary, GI, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease • SI/suicidal behavior previous month						

Abbreviations: AE = adverse event; ALT =alanine transaminase; ARR = absolute risk reduction; AST = aspartate transaminase; CAJIS = cumulative analog joint involvement scale; CI = confidence interval; cm = centimeters; CVD = cardiovascular disease; dL = deciliter; Dx = diagnosis; FDA = food and Drug Administration; GI = gastrointestinal; HO = heterotopic ossification; Hx = history; ITT = intention to treat; MC = multicenter; MD = mean difference; mg = milligrams; mITT = modified intention to treat; mo/mos = month/months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NHS = natural history study; NNT = number needed to treat; OL = open label; OR = Oregon; PP = per protocol; SAE = serious adverse effects; SI = suicidal ideation; Sx = symptoms; TCN = tetracycline; TEAE = treatment emergent adverse effects; TG = triglyceride; Tx = treatment; ULN = upper limit of normal; WBCT = whole body commuted tomography; wks = weeks; wt = weight
*=information from FDA Review

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Appendix 1: Prescribing Information Highlights

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

SOHONOS (palovarotene) capsules, for oral use
Initial U.S. Approval: 2023

WARNING: EMBRYO-FETAL TOXICITY and PREMATURE EPIPHYSEAL CLOSURE IN GROWING PEDIATRIC PATIENTS
See full prescribing information for complete boxed warning.

- **SOHONOS is contraindicated in pregnancy (5.1, 8.1) Because of the risk of teratogenicity and to minimize fetal exposure, SOHONOS is to be administered only if conditions for pregnancy prevention are met (5.1, 8.1)**
- **SOHONOS causes premature epiphyseal closure in growing pediatric patients with FOP, close monitoring is recommended (5.2, 8.4)**

----------INDICATIONS AND USAGE----------
SOHONOS is a retinoid indicated for reduction in the volume of new heterotopic ossification in adults and children aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva (FOP) (1).

----------DOSAGE AND ADMINISTRATION----------
- Obtain a negative pregnancy test in females of reproductive potential before initiation of SOHONOS (2.1)
- Recommended dosage includes a chronic daily dose, which can be increased for flare-up symptoms (2.2)
- For adults and pediatric patients 14 years and older: Recommended dosage is 5 mg once daily, with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment) (2.2)
- For pediatric patients under 14 years: Weight-adjusted for daily and flare-up dosing. Recommended daily dosage range from 2.5 to 5 mg. Refer to Table 1 in Full Prescribing Information for complete pediatric dosing (2.2)
- Take SOHONOS with food preferably at same time each day (2.3).
- Reduce the dose in the event of adverse reactions as appropriate (2.4)
- See Full Prescribing Information for complete dosing instructions (2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 1, 1.5, 2.5, 5, 10 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4, 5.1, 8.1)
- Hypersensitivity to retinoids or any component of SOHONOS (4, 11)

----------WARNINGS AND PRECAUTIONS----------
- *Premature Epiphyseal Closure:* Premature epiphyseal closure occurred with SOHONOS. Assess baseline skeletal maturity before SOHONOS therapy and monitor linear growth in growing pediatric patients (5.2)
- *Mucocutaneous Adverse Reactions:* Dry skin, lip dry, pruritus, rash, alopecia, erythema, skin exfoliation, and dry eye occurred with SOHONOS. Prevent or treat with skin emollients, sunscreen, artificial tears. Dosage reduction may be required in some patients (2.4, 5.3)
- *Metabolic Bone Disorders:* Decreased vertebral bone mineral content and bone density may occur. Assess for spinal fracture periodically using radiologic method (5.4)
- *Psychiatric Disorders:* Depression, anxiety, mood alterations and suicidal thoughts and behaviors occurred with SOHONOS. Contact healthcare provider if new or worsening symptoms develop in patients treated with SOHONOS (5.5)
- *Night Blindness:* May occur and make driving at night hazardous (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥10%) are dry skin, lip dry, arthralgia, pruritus, pain in extremity, rash, alopecia, erythema, headache, back pain, skin exfoliation, nausea, musculoskeletal pain, myalgia, dry eye, hypersensitivity, peripheral edema, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact IPSEN Biopharmaceuticals, Inc at 1-855-463-5127 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CYP3A4 Inhibitors: May increase SOHONOS exposure. Avoid concomitant use of strong/moderate CYP3A4 inhibitors. If concomitant use of moderate CYP3A4 inhibitors is unavoidable, reduce the dose of SOHONOS by half (2.5, 7.1)
- CYP3A4 Inducers: May decrease SOHONOS exposure. Avoid concomitant use of strong/moderate CYP3A4 inducers (7.1)
- Vitamin A: May cause additive effects (7.2)
- Tetracyclines: Avoid concomitant use with SOHONOS (7.3)
- Systemic Corticosteroids: No clinically significant drug interaction is expected with concomitant use of SOHONOS (7.4)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm (2.1, 4, 8.1)
- Growing pediatric patients are recommended to undergo baseline assessment of growth and skeletal maturity before starting treatment and continued clinical and radiographic monitoring every 6 to 12 months until patients reach skeletal maturity or final adult height (5.2, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.[2,3]

Parameter	
Mechanism of Action	A RARγ selective agonist. Through binding to RARγ, palovarotene decreases BMP signaling at the ALK2 (ACVR1) receptor and inhibits the phosphorylation of SMAD1/5/8, which reduces ALK2/SMAD-dependent chondrogenesis and osteocyte differentiation resulting in reduced endochondral bone formation.
Oral Bioavailability	Not determined.
Distribution and Protein Binding	Vd=237 L; ~99% protein bound
Elimination	Renal 3.2%; Feces 97.1%; Total Body clearance=19.9 L/hr
Half-Life	8.7 hours
Metabolism	Liver (mostly CYP3A4)

Abbreviations: ACVR1=activin A receptor 1; ALK=activin receptor-like kinase; BMP=bone morphogenetic protein; hr=hour; L=liters; RARγ=retinoic acid receptor gamma; Vd=volume of distribution

Appendix 3: Proposed Prior Authorization Criteria

Palovarotene

Goal(s):

- Promote safe and cost-effective therapy for the treatment of fibrodysplasia ossificans progressiva (FOP).

Length of Authorization:

- Up to 12 months

Requires PA:

- Palovarotene

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

Covered Alternatives:

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

Table 1. FDA-Approved Minimum Age

Sex	Age
Female	8 years or older
Male	10 years or older

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by FFS system?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis heterotopic ossification (HO) due to fibrodysplasia ossificans progressiva (FOP)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the diagnosis confirmed by molecular genetic testing indicating the presence of a mutation in the activin receptor IA (ACVR1) gene?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for an FDA-approved age in Table 1?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the drug prescribed by or in consultation with a specialist in FOP? (e.g., endocrinologist, geneticist, pediatric orthopedist, pediatric rheumatologist)	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there a baseline assessment of skeletal maturity including • hand/wrist and knee x-rays • standard growth curves • pubertal staging -AND- Is there documentation that indicates plans to continue monitoring these factors for the duration of therapy until skeletal maturity or adult final height is reached?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Has the provider documented goals of therapy with objective baseline assessment(s) for one or more of the following: • Cumulative analog joint involvement scale (CAJIS) score? • Reduction or improvement in HO symptoms? • Reduction of HO flare-ups from baseline? • Reduction, stabilization, or slowing of the rate of annualized volume of new heterotopic ossification (HO)? Note: these same assessments should be evaluated for continuation of treatment	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the prescriber performed a recent review of the patient's current medication regimen and attests that there is no concomitant use of strong/moderate 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, etc.), Vitamin A, and tetracyclines per the FDA label?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient female and of reproductive age?	**Yes:** Go to #11	**No:** Approve for 12 months
11. Is there documentation that prescriber has plans to give pregnancy test within 1 week prior to treatment and monitor periodically during therapy?	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation that skeletal maturity or adult final height has been reached?	**Yes**: Go to #3	**No:** Go to #2

Renewal Criteria		
2. Is there documentation that the patient has been assessed in the last year for skeletal maturity including • hand/wrist and knee x-rays • standard growth curves • pubertal staging?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. If the patient is female and of reproductive age?	**Yes**: Go to #4	**No:** Go to #5
4. Is there documentation that the prescriber has plans to monitor pregnancy status periodically during therapy?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been adherent to therapy as verified by claims history or prescriber attestation?	**Yes:** Go to #6 Note: pharmacy profile may be reviewed to verify >80% adherence	**No:** Pass to RPh. Deny; medical appropriateness
6. Has the prescriber performed a recent review of the patient's current medication regimen and attests that the patient is avoiding concomitant use of strong/moderate 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, etc.), Vitamin A, and tetracyclines per the FDA label?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
7. Has there been a documented positive response to treatment compared to baseline as evidenced by one or more of the following: • Decreased or stabilized cumulative analog joint involvement scale (CAJIS) score? • Reduction or improvement in HO symptoms? • Reduction of HO flare-ups from baseline? • Reduction, stabilization, or slowing of the rate of annualized volume of new heterotopic ossification (HO)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/25 (DE)
Implementation: TBD

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Topical Products for Inflammatory Skin Diseases

Date of Review: December 2025

Generic Name: Delgocitinib
Generic Name: Sirolimus

Date of Last Review: December 2022
Dates of Literature Search: 09/01/2022 – 8/19/2025
Brand Name (Manufacturer): ANZUPGO (LEO Pharma Inc.)
Brand Name (Manufacturer): HYFTOR (Nobelpharma America, LLC)

Dossier Received: yes

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

Purpose for Class Update:
The purpose of this update is to review recent evidence for topical agents that are Food and Drug Administration (FDA)-approved for inflammatory skin conditions and evaluate place in therapy for 2 new topical medications. Delgocitinib 2% topical cream was recently FDA-approved for moderate-to-severe chronic hand eczema in adults. Sirolimus 0.2% topical gel is FDA-approved for treatment of facial fibroangiomas associated with tuberous sclerosis complex (TSC).

Plain Language Summary:
- Is there any new evidence for different topical medicines (treatments applied to the skin) for skin conditions including psoriasis (scaly plaques), atopic dermatitis (dry, itchy, red skin), and vitiligo (patchy loss of skin color) that would change the current policy of topical medicines for skin conditions?
- Recent evidence shows the most effective medicines to treat atopic dermatitis are topical corticosteroids (i.e. clobetasol, fluocinonide, betamethasone, fluticasone) and topical calcineurin inhibitors (tacrolimus and pimecrolimus).
- A newer medicine, ruxolitinib, is not recommended by the American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma, and Immunology Joint Task Force or Canada's Drug Agency for atopic dermatitis. These organizations say there is not enough evidence to determine if topical ruxolitinib decreases atopic dermatitis flares because it was only evaluated in short-term studies over 4 to 8 weeks.
- For treatment of plaque psoriasis, Canada's Drug Agency supports the use of roflumilast 0.3% cream in people aged 12 years and older.
- Canada's Drug Agency does not recommend ruxolitinib for vitiligo because studies did not show it improved health related quality of life for people who have this skin condition.
- Another new medicine, delgocitinib, was approved by the FDA to treat chronic hand eczema in adults. Chronic hand eczema causes itching and pain. Two 4-month studies showed that when delgocitinib cream is applied to adults with moderate-to-severe hand eczema, symptoms of hand eczema decreased more than when people used a skin cream without medicine. Side effects to delgocitinib were uncommon. The most frequent side effects were application site pain, itching, redness, numbness, and skin infections. There are no studies that compare delgocitinib to other medicines for eczema.

Author: Deanna Moretz, PharmD, BCPS

- The FDA approved a second medicine, sirolimus, for facial angiofibromas (small red or pink bumps on the skin) in people 6 years of age and older with tuberous sclerosis complex. This is a rare condition with very few treatment options. In one small study, sirolimus gel decreased the size and redness of these facial bumps when compared to a gel without any medicine.
- Providers must explain to the Oregon Health Authority why their patient needs topical roflumilast, ruxolitinib, delgocitinib, and sirolimus before Medicaid will pay for it. This process is called prior authorization. Medicaid will pay for some older and less expensive topical medicines, such as topical corticosteroids, without prior authorization.

Research Questions:

1. Is there new evidence regarding the comparative safety and efficacy of topical agents to manage inflammatory skin conditions including plaque psoriasis (PsO), atopic dermatitis (AD), and vitiligo?
2. For adults with moderate-to-severe chronic hand eczema, what is the safety and effectiveness of delgocitinib 2% cream?
3. For patients with facial angiofibroma associated with TSC, what is the safety and effectiveness of sirolimus 0.2% gel?
4. Are there patients based on demographics characteristics (i.e., age, race, ethnicity, gender), socioeconomic status, concomitant medications, or co-morbidities for which one topical agent is more effective or associated with fewer adverse events in treating inflammatory skin diseases?

Conclusions:

Safety And Efficacy of Topical Agents for Management of Eczema, Atopic Dermatitis, Plaque Psoriasis, and Vitiligo

- Since the last review, 3 systematic reviews have evaluated the safety and efficacy of topical agents for management of eczema and AD.[1-3] Six guidelines were updated to guide treatment of mild-to-moderate AD, PsO, and vitiligo with topical agents.[4-9]
- A 2024 Cochrane systematic review and network meta-analysis (NMA) evaluated topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), Janus kinase (JAK) inhibitors, phosphodiesterase-4 (PDE-4) inhibitors, and tapinarof for eczema.[1] This analysis found that potent and very potent TCS, tacrolimus 0.1% and ruxolitinib 1.5% were among the most effective short-term treatments for improving patient-reported symptoms (40 trials, all low confidence) and clinician-reported signs (32 trials, all moderate confidence) of eczema.[1] Local application site reactions were most common with tacrolimus 0.1% (moderate confidence) and crisaborole 2% (high confidence) and least common with TCS (moderate confidence).[1] Skin thinning was not increased with short-term (3 weeks) use of any TCS potency (low confidence) but skin thinning was reported in 0.3% of participants treated with longer-term TCS (over 6 to 60 months).[1]
- A 2023 systematic review and NMA provided the basis for development of American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) Joint Task Force 2023 guidance on management of AD.[2] The most effective agents for improving AD outcomes are pimecrolimus, tacrolimus, and moderate-potency TCS.[2] Crisaborole was intermediately effective, but with uncertain harm due to low-quality evidence on adverse events.[2] Topical antibiotics are the least effective agents for managing AD.[2] High certainty evidence showed that super-high potency TCS are the best in improving AD severity; tacrolimus (high dose) and high to moderate potency TCS groups 2 to 5 (see **Table 4**) were the best in improving itch severity; pimecrolimus was the best for improving sleep disturbance; and delgocitinib was the best in improving eczema-related quality of life (QoL).[2]
- A 2023 systematic review and meta-analysis evaluated incidence of cancer associated with TCI administration (pimecrolimus and tacrolimus) as part of the 2022 AAAAI/ACAAI guidance update for AD. The absolute risk of any cancer with TCI exposure was not different from controls (absolute risk 4.70 per 1000 with TCI vs 4.56 per 1000 without; odds ratio [OR] 1.03; 95% credible interval [CrI] 0.94 to 1.11; moderate certainty evidence).[3] For all age groups and using data from observational studies and RCTs, the use of pimecrolimus (OR 1.05; 95% CrI 0.94 to 1.15) or tacrolimus (OR 0.99; 95 % CrI 0.89 to 1.09) is likely to have had little to no association with cancer compared with no TCI exposure.[3] For pimecrolimus versus tacrolimus, the finding was similar (OR 0.95; 95% CrI 0.83 to 1.07).[3]

- A 2022 AAAAI/ACAAI Joint Task Force updated 2012 guidance for management of AD in infants, children, and adults.[4] Although moisturization alone may achieve improvement in AD in patient with mild symptoms, and can help improve AD severity and time-to-flare in those with more severe disease, almost all patients will require a prescription anti-inflammatory treatment including TCS, TCIs, or the topical PDE-4 inhibitor, crisaborole. Ruxolitinib, a topical JAK inhibitor, is not recommended by the task force panel because there is insufficient evidence to assess whether topical ruxolitinib reduces AD flares due to imprecision and the short-term (4-8 weeks) nature of the available studies.[4]
- The American Academy of Dermatology (AAD) guidance for management of AD with topical and systemic therapies in adults was updated in 2023.[5,6] For most people with AD, emollients and prescription topical therapies are sufficient to achieve AD control.[5] The use of TCS, TCI, crisaborole, and ruxolitinib for mild to severe AD are all strongly recommended by AAD.[5] Two new strong recommendations supporting the use of tapinarof and roflumilast cream in mild-to-moderate AD are included in the update.
- In May 2025, Canada's Drug Agency (CDA) issued a reimbursement recommendation for the use of the JAK inhibitor, ruxolitinib 1.5% cream, in patients with mild-to-moderate AD.[7] The CDA does not recommend reimbursement for ruxolitinib for treatment of AD in Canadian public drug plans.[7] Evidence from 2 clinical trials showed that ruxolitinib improved the severity of AD compared with placebo in adult and adolescent patients with mild to moderate AD.[7] However, it is unclear if these patients were not adequately controlled with TCS and/or TCI which is the patient population expected to receive ruxolitininb.[7]
- In September 2023, the CDA issued a reimbursement recommendation for roflumilast 0.3% cream, a topical PDE-4 inhibitor, in treatment of PsO for patients aged 12 years and older.[8] Roflumilast may provide an alternative, nonsteroidal topical treatment option for patients living with PsO, including psoriasis in the intertriginous area.[8] CDA Recommendations:
    - Roflumilast should only be covered to treat patients who have a clinical diagnosis of PsO, an Investigator's Global Assessment (IGA) score of at least 2 (mild), an area of PsO appropriate for topical treatment, and an affected body surface area of 2% to 20% (inclusive).[8]
    - Roflumilast should be discontinued if a response has not been demonstrated by 8 weeks. A response to treatment is defined as at least a 2-grade improvement from baseline in IGA score or an IGA score of "clear" or "almost clear" (0 or 1).[8]
- In August 2025, the CDA issued reimbursement recommendations for the use of ruxolitinib for topical treatment of non-segmental vitiligo (NSV) in patients aged 12 years and older.[9] The CDA does not recommend the reimbursement of ruxolitinib in treatment of vitiligo in Canadian public drug plans.[9] Published studies did not show that ruxolitinib led to meaningful improvements in overall health-related quality of life (HRQoL).[9] There is no data on how ruxolitinib compares to other commonly used treatments such as TCS or tacrolimus.[9]
- There is insufficient evidence to evaluate the comparative safety and efficacy of topical agents for treatment of inflammatory skin conditions in specific subpopulations based on demographic characteristics, socioeconomic status, concomitant medications, or co-morbidities.

Efficacy and Safety of Delgocitinib in Management of Chronic Hand Eczema

- Delgocitinib is a JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) inhibitor available as 2% topical cream in the United States (U.S.).[10] The medication received FDA-approval in July 2025 for the treatment of moderate-to-severe chronic hand eczema in adults who have had inadequate response to, or for whom TCS therapies are not advisable.[10]
- Two phase 3 studies, DELTA 1 and DELTA 2, provide data that support the FDA-approval of delgocitinib.[11] These studies were double-blind, placebo-controlled, multi-center RCTs conducted over 16 weeks in adults with moderate-to-severe chronic hand eczema and are described in detail in **Table 4**.[11]
- The primary endpoint of each trial was the Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) at week 16 with a 2-step or greater improvement from baseline.[11] At week 16, a greater proportion of delgocitinib-treated patients versus cream vehicle patients had IGA-CHE treatment success (19.7% vs. 9.9%; difference, 9.8%; 95% confidence interval [CI] 3.6 to 16.1; $p<0.0055$ in DELTA 1 and 29.1% vs. 6.9%; difference, 22.2%; 95% CI 15.8 to 28.5; $p<0.0001$ in DELTA 2; moderate-quality evidence).[11]

- Most adverse events were mild to moderate and not considered related to trial treatment.[11] In both trials, the most frequently reported adverse events reported in <1% of the delgocitinib-treated group included application site pain, paresthesia, pruritis, erythema, and bacterial skin infections.[11]
- Draft recommendations from CDA suggest that delgocitinib be reimbursed for the treatment of moderate-to-severe chronic hand eczema in adults for whom TCS are inadequate or are not advisable, only if specific conditions are met:
    - adults (≥18 years) with moderate-to-severe chronic hand eczema as defined by an IGA-CHE score of 3-4 and who have had an adequate trial (with a documented refractory disease), documented intolerance, or are ineligible for high-potency TCS.[12]
    - Response should be assessed at 12 weeks with renewal for patients who demonstrate either a ≥ 2-step improvement of IGA-CHE or a score of 0 to 1 (clear/almost clear).[12]

Efficacy and Safety of Sirolimus for Facial Angiofibromas

- Low-quality-evidence from one double-blind, randomized trial (n=62) showed that sirolimus improved response rate in people with angiofibroma after 12 weeks of treatment compared to placebo (60% in the sirolimus group vs. 0% with placebo; p<0.001).[13] A 6-category scale was used to evaluate changes in angiofibroma size and color with the following categories: markedly improved, improved, slightly improved, unchanged, slightly aggravated, and aggravated.[13] It is not clear how this scale was developed and validated.[14] There is insufficient evidence to evaluate whether sirolimus improves quality of life; the Dermatology Life Quality Index (DLQI) and Children's DLQI (CDLQI) were evaluated as secondary outcomes and neither outcome achieved statistical significance compared to placebo.[13]
- In a 104-week, open-label safety trial, the most common adverse reactions associated with sirolimus application were application site irritation (31%), dry skin (28%), acne (20%), pruritus (9%), eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), solar dermatitis (1%), and photosensitivity reaction (1%).[15]

Expanded Indications and New Formulations

- In September 2025, ruxolitinib cream was FDA-approved for topical short-term and non-continuous chronic treatment of mild-to-moderate AD in non-immunocompromised patients aged 2 years and older.[16] The prescribing information recommends adults use no more than one 60 gram tube per week and in children no more than one 60 gram tube per 2 weeks.[16] Ruxolitinib cream should not be applied to more than 20% of body surface area (BSA).[16] Prior to this approval, ruxolitinib was FDA-approved for topical treatment of NSV and AD in patients aged 12 years and older.[16]
- A new formulation of roflumilast 0.05% cream received FDA-approval in October 2025. This product is indicated for topical treatment of mild-to-moderate AD in pediatric patients aged 2 to 5 years of age.[17]
- In May 2025, roflumilast 0.3% topical foam received an expanded indication for treatment of PsO in patients at least 12 years of age.[18] Prior to this expanded indication, roflumilast 0.3% foam was FDA-approved for the treatment of seborrheic dermatitis in patients at least 9 years of age.[18]
- Roflumilast 0.15% cream was FDA-approved in July 2024 for the treatment of mild-to-moderate AD in people aged 6 years of age and older.[17] Prior to this approval, roflumilast 0.3% cream was FDA-approved for topical treatment of PsO in patients aged 6 years and older.[17]
- Tapinarof cream received an expanded FDA-approved indication for the topical treatment of AD in adults and children aged 2 years and older in December 2024.[19] Prior to this approval, tapinarof was FDA-approved for the topical treatment of PsO in adults.[19]

Recommendations:

- Revise prior authorization (PA) criteria for the "Topical Agents for Inflammatory Skin Conditions" to include expanded indications for ruxolitinib cream, ruxolitinib foam, roflumilast cream, sirolimus gel, and tapinarof cream.
- Maintain delgocitinib cream and make sirolimus topical gel non-preferred on the preferred drug list (PDL).
- Review drug costs in executive session.

Summary of Prior Reviews and Current Policy

- The Pharmacy and Therapeutics (P & T) committee reviewed the topical agents for inflammatory skin conditions at the December 2022 meeting. The PA criteria for "Topical Agents for Inflammatory Skin Conditions" were revised to include use of ruxolitinib in patients aged 12 years and older for those meeting Health Evidence Review Commission (HERC) guidance for severe nonsegmental vitiligo (NSV) or those having hand, foot, face, or mucous membrane involvement. Topical roflumilast and tapinarof were designated as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP). The PA criteria were revised to include roflumilast and tapinarof and limit their use to:
    - Individuals meeting HERC guidance for severe PsO or those having hand, foot, face, or mucous membrane involvement and,
    - FDA-approved ages (12 years or greater for roflumilast or age of 18 years or greater for tapinarof) and,
    - History of inadequate response to at least 2 moderate-to-high potency TCS for at least 4 weeks.
- After evaluation of costs in the executive session, tazarotene gel was designated as nonpreferred.
- The PDL status for topical medications used for inflammatory skin conditions is provided in **Appendix 1.** Calcipotriene and calcipotriene/betamethasone are designated as preferred topical agents on the PMPDP and do not require PA authorization. Both TCIs used to treat atopic dermatitis (pimecrolimus and tacrolimus) are preferred but require PA to ensure appropriate utilization in FDA-approved populations (**Appendix 8**). Non-preferred topical agents include anthralin, calcitriol, coal tar, crisaborole, tazarotene, and ruxolitinib, which require PA to ensure appropriate utilization in inflammatory skin conditions funded by HERC.

Background:

Atopic Dermatitis

Atopic dermatitis or eczema is a chronic skin disorder characterized by pruritus, recurrent lesions, and inflammation with a relapsing and remitting pattern.[20] The cause is unknown, but may be due to genetics or immunologic dysfunction.[21] Many patients with AD also have allergic asthma, allergic rhinoconjunctivitis, food allergies, or other immediate hypersensitivity (type 1) allergies.[22] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries.[23] Estimated prevalence of AD for adults in the United States (U.S.) is 10%.[23] Both sexes are affected, and the prevalence varies among races and ethnic groups.[24] For example, in the U.S., the prevalence is higher among Black children (19.3%) than among White children (16.1%).[25] Onset of AD is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the condition during the first year of life and 90% by the age of 5 years.[26] Atopic dermatitis can persist into adulthood in about one-third of affected individuals.[27] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life in people with AD.

Therapy for AD is selected according to the clinical stage of disease (mild, moderate, or severe), the extent and location of body surface area (BSA) involved, age, co-existing conditions and medications being taken by the patient, the severity of pruritus, the degree to which quality of life is impaired, and the goals of the patient.[28,29] The National Institute for Health and Care Excellence (NICE) has developed an assessment for the severity of atopic dermatitis as outlined in Table 1.

Table 1. NICE Holistic Assessment of Atopic Eczema[30]

Skin Description	Physical Severity	Impact on Quality of Life and Psychosocial Wellbeing
Clear	Normal skin, no evidence of active AD	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness).	Little impact on everyday activities, sleep, and psychosocial wellbeing

Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening).	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep.
Severe	Widespread areas of dry skin, incessant itching, redness (with or with excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation).	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep.
Abbreviations: AD = atopic dermatitis; NICE = National Institute for Health and Care Excellence		

For all AD stages, general measures include care with frequent application of an emollient to maintain the skin's epidermal barrier, avoidance of triggers, and anti-inflammatory therapy with a TCS or a TCI as needed.[21] The use of TCS and TCI therapies in AD is supported by The American College of Dermatology's 2014 guideline.[31] Topical corticosteroids are recommended for individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of TCS can result in telangiectasia, increased hair, skin tears, easy bruising, poor wound healing, acne, rosacea, and atrophic skin changes, which can be permanent.[32] TCIs are a second-line option in both adults and children with AD who have not responded to TCS therapy or when those treatments are not advisable.[32] Unlike TCS, TCIs do not cause skin atrophy and are, therefore, of particular value in delicate skin areas such as the face, neck, and skin folds. Side effects to TCIs include application site pain, which may be more frequent compared to other topical preparations. FDA labeling for tacrolimus and pimecrolimus also includes boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with long-term TCI administration.[33,34] Additional agents FDA-approved for AD include topical PDE-4 inhibitors, JAK inhibitors, and aryl hydrocarbon receptor agonists (see **Table 2**).

Another topical JAK inhibitor, delgocitinib, recently received FDA approval for management of moderate-to-severe chronic hand eczema in adults.[10] Hand eczema that persists for more than 3 months or recurs 2 or more times within a 12-month time frame is considered chronic.[35] The condition is characterized by extremely itchy, painful, inflamed, dry scaly patches of skin on the hands and wrist that can flake, crack, and bleed.[35] These symptoms can impact quality of life and the ability to complete activities of daily living. Chronic hand eczema is often associated with occupations that involve frequent hand washing, exposure to chemicals, or working in wet environments including health care workers, food handlers, dental technicians, metal workers, cleaners, florists, and hairdressers.[35] Other risk factors include development of AD in childhood, persistent/severe AD, cold/dry weather conditions, and decreased indoor humidity.[35] Chronic hand eczema can be sub-classified as irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, vesicular hand eczema, hyperkeratotic eczema, and protein contact dermatitis/contact urticaria.[35] The 1-year prevalence of hand eczema is at least 9.1% in the general global population (6.4% in men and 10.5% in women).[36]

The European Society of Contact Dermatitis guidance (2021) recommends the use of protective gloves, hand washing in lukewarm (not hot) water, switching from hand washing with soap to alcohol disinfection when hands are not visibly dirty (as alcohol is less irritating than soap), thoroughly rinsing and drying hands after washing, and application of emollients to prevent hand eczema.[35] Initial treatment for moderate-to-severe hand eczema is short-term use of TCS or tacrolimus ointment.[35] Patients with severe or recalcitrant hand eczema that does not respond to TCS may require systemic therapies, including oral corticosteroids, oral immunosuppressants, retinoids or phototherapy.[35]

Symptom scores are designed to specifically assess improvement in chronic hand eczema symptoms (itching, pain, redness, scaling, edema) and are presented in **Table 2**.

Table 2. Assessments for Treatment of Chronic Hand Eczema

Tool	Description
Hand Eczema Severity Index (HECSI)[37,38]	The HECSI is a clinician assessment that evaluates the extent and severity of hand eczema symptoms. Scoring ranges from 0 (clear) to 360 (severe) based upon location involvement and severity of erythema, induration/papulation, vesicles, fissures, scaling and edema. HECSI-75 denotes 75% improvement in the HECSI score from baseline, which is considered clinically significant.
Investigators Global Assessment of Chronic Hand Eczema (IGA-CHE)[39]	IGA-CHE is a clinician assessment for severity of the subject's global disease stage at a given time point and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). Scoring is based upon intensity of erythema, scaling, hyperkeratosis, vesiculation, edema, and fissures.
Hand Eczema Symptom Diary (HESD)[40,41]	The HESD is a 6-item patient-reported instrument designed to assess the severity of chronic hand eczema. Six signs and symptoms (itch, pain, cracking, redness, dryness, and flaking) over the previous 24 hours are rated on an 11-point scale (0 = no symptoms and 10 = severe symptoms). Total score is an average of the 6 signs and symptoms.
Hand Eczema Symptom Diary (HESD) Itch Score[10]	The HESD is a patient-reported instrument to assess itching severity associated with chronic hand eczema over the previous 24 hours. Itch severity is rated on an 11-point scale (0 = no itching and 10 = severe itching).
Hand Eczema Symptom Diary (HESD) Pain Score[10]	The HESD is a patient-reported instrument to assess pain severity associated with chronic hand eczema over the previous 24 hours. Pain severity is rated on an 11-point scale (0 = no pain and 10 = severe pain).

Clinical studies have utilized several scales for defining the severity of AD, including the Scoring Atopic Dermatitis (SCORAD) scale, Eczema Area and Severity Index (EASI), and Investigators Global Assessment (IGA).[22] The SCORAD has been validated for content and construct validity, interobserver reliability, and sensitivity to change in 26 different publications.[42] The SCORAD tool incorporates clinician estimates of disease extent and severity and subjective patient assessment of itching and sleep loss.[43] The extent of AD is graded using a percentage score by the clinician for specific areas of the body (head/neck, upper limbs, lower limbs, trunk and back). Severity includes a clinician assessment of the intensity of redness, swelling, oozing, dryness, scratch marks, and lichenification, which are graded on a 4-point scale rated as 0 (none), 1 (mild), 2 (moderate) or 3 (severe).[43] Subjective symptoms such as itching and sleeplessness are scored by the patient using a visual analog scale (VAS) from 0 (no symptoms) to 10 (worst imaginable) for a total score of 20. Combining extent, severity, and symptoms results in a total SCORAD score ranging between 1 to 100 and categorized as mild (<25), moderate (26-49), and severe (>50).[43]

The EASI was adapted from the Psoriasis Area and Severity Index in 1998.[42] The EASI assesses severity and body surface area affected by AD including erythema, induration, papulation, excoriations, and lichenification.[44] Each symptom is graded in 4 anatomical regions (the head, trunk, arms and legs) and summarized in a composite score. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD.[44] An EASI score of 7 or lower indicates mild disease, 8 to 21 moderate disease, 22 to 50 severe disease, and 51 to 72 very severe disease.[22] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90.

The IGA is a clinician-reported outcome measure used to evaluate severity of AD at a given point in time.[45] In these trials, a 5-point scale ranging from 0 (clear) to 4 (severe) was used to assess changes in the severity of skin lesions. In most trials, scores less than or equal to 1 were generally classified as "treatment success," whereas scores greater than 1 were considered "treatment failure."[46] The IGA does not assess disease extent as body regions are not included in the IGA scoring. One systematic review concluded that although the IGA is easy to perform, the lack of standardization precludes any meaningful comparisons between studies which impedes data synthesis to inform clinical decision making.[45] The Investigator's Static Global Assessment (ISGA) does not assess changes in severity of skin lesions with treatment and may use a 6-point scale ranging from 0 (clear) to 5 (very severe).

Plaque Psoriasis

Plaque psoriasis (PsO) is a chronic, immune-mediated inflammatory disorder of the skin which affects about 3% of the U.S. adult population.[47] Plaque psoriasis is characterized by erythematous scaly patches or plaques that occur commonly on extensor surfaces, but it can also affect the intertriginous areas, palms, soles of the feet, and nails.[48] The onset generally occurs between 20 and 30 years of age.[47] Approximately 1% of children are affected by psoriasis, typically with onset during adolescence.[49] A 2020 population-based cross-sectional study sampled the U.S. civilian population and estimated psoriasis prevalence as highest in White individuals at 3.6%, followed by other racial/ethnic groups (non-Hispanic, including multiracial) at 3.1%, Asian individuals at 2.5%, Hispanic individuals (including Mexican American and other Hispanic individuals) at 1.9%, and Black individuals at 1.5%.[47]

The development of psoriasis is complex and appears to be influenced by many factors, including genetic changes, local trauma, infections, certain drugs (such as beta-blockers, lithium, chloroquine, and non-steroidal anti-inflammatory drugs), endocrine factors, sunlight, alcohol, smoking, and stress.[50] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of BSA and has little to no impact on quality of life or function.[48] Mild PsO is not a funded condition per HERC Guideline Note 21.[51] An estimated 20% of patients with PsO have moderate-to-severe disease, defined as greater than 10% of BSA.[47]

According to the 2021 American Academy of Dermatology/National Psoriasis Foundation (AAD/NPF) guidance, first-line topical agents to treat mild-to-moderate PsO include: TCS, anthralin, vitamin D analogues (e.g., calcipotriene, calcitriol), retinoids (e.g., tazarotene), TCIs, or salicylic acid.[52] Recently approved topical agents for treatment of PsO include roflumilast and tapinarof.[17,19] The relative efficacy of roflumilast and tapinarof compared with TCS regimens is unclear. High potency TCS are usually prescribed for the initial treatment of plaques in sites at low risk for corticosteroid-induced skin atrophy (e.g., nonfacial, no intertriginous plaques) because of their rapid efficacy and wide availability. Moderate-to-severe PsO may need to be treated with systemic TIMs including PDE-4 inhibitors, tumor necrosis factor (TNF) inhibitors, interleukin (IL)-12/23 antagonists, IL-23 antagonists, or IL-17 antagonists.[53] The TIMs may be added for patients with moderate-to-severe PsO not controlled by other therapies.[53]

In clinical trials assessing treatments for PsO, symptom improvement is often evaluated using the Psoriasis Area and Severity Index (PASI). The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head, arms and legs, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[54,55] It does not consider symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[54] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, an improvement of 100%, indicating complete disease clearance, is considered more clinically significant.[55] This tool is rarely used in clinical practice to assess psoriasis severity due to the substantial amount of time required to complete the scoring.[52] The Physician Global Assessment (PGA) is a scoring system that assesses degree of erythema, induration, and scaling.[52] There are several different versions of the PGA, with most severity scores ranging from 0 to 4 or 0 to 5.[52] Higher scores indicate more severe disease. The PGA is also used in research, but not frequently used in clinical practice.[52] The Investigator Global Assessment (IGA) has also been used to measure the severity of PsO based on skin thickening and hyperpigmentation in clinical trials.[56] Similar to the PGA, the IGA is a 5 point scale ranging from 0 (clear), 1 (almost clear), 2 (mild symptoms), 3 (moderate symptoms) to 4 (severe symptoms).[56] Response to therapy is indicated by an IGA score of 0 or 1 plus at least a 2-grade improvement from baseline.[56]

Vitiligo

Vitiligo is a chronic autoimmune disorder and is the most frequent cause of skin depigmentation worldwide with an estimated global prevalence of 1%.[57] It usually begins after birth and has an average age of onset of about 20 years.[58] This condition can be psychologically devastating and stigmatizing, especially in dark skinned individuals.[57] Vitiligo is clinically characterized by the development of white macules due to the loss of functioning melanocytes in the skin or hair,

or both.[57] Two forms of the disease are recognized: segmental vitiligo (SV) and NSV.[59] Non-segmental vitiligo is characterized by symmetrical and bilateral white patches.[57] The most commonly affected sites are the fingers, wrists, axillae, groin, mouth, eyes and genitalia.[60] Different NSV clinical subtypes have been described, including generalized, mucosal, acrofacial, and universal, all with a bilateral distribution.[57] In contrast, SV is less common than NSV and usually has asymmetrical, one-sided or band-shaped distribution.[57] Segmental vitiligo accounts for 5–16% of overall vitiligo cases and tends to occur at a younger age, before age 30 years in 87% of cases and before age 10 years in 41% of cases.[57]

Many studies support the association of vitiligo with thyroid disorders and other associated autoimmune diseases, such as rheumatoid arthritis, psoriasis, adult-onset diabetes mellitus, Addison's disease, pernicious anemia, alopecia areata, and systemic lupus erythematosus.[57] Almost one-third of people with vitiligo have a positive family history of the disease.[57] Several corresponding relevant genes associated with both vitiligo and other pigmentary, autoimmune and autoinflammatory disorders have now been identified.[61] They are involved in immune regulation, melanogenesis and apoptosis.[61]

The diagnosis of vitiligo is based upon the finding of acquired, amelanotic, non-scaly, chalky-white macules with distinct margins in a typical distribution: periorificial, lips and tips of distal extremities, penis, segmental and areas of friction.[61] The diagnosis of vitiligo does not usually require confirmatory laboratory tests.[61] A skin biopsy or other tests are not necessary except to exclude other disorders.[61] The diagnosis of vitiligo may be facilitated by the use of a Wood's lamp, a hand-held ultraviolet irradiation device that emits ultraviolet A rays.[61] It helps identify focal melanocyte loss and detect areas of depigmentation that may not be visible to the naked eye, particularly in pale skin.[61] Under the Wood's light, the vitiligo lesions emit a bright blue-white fluorescence and appear sharply demarcated.[61]

Treatment of vitiligo aims to halt disease spread and facilitate repigmentation.[62] Choice of treatment depends on several factors including: the subtype of the disease, the extent, distribution and activity of disease as well as the patient's age, phototype, effect on quality of life and motivation for treatment.[61] The face, neck, trunk and mid-extremities respond best to therapy, while the lips and distal extremities are more resistant to treatment.[61] The 2021 British Association of Dermatologists (BAD) guidance recommends high potency or very high potency TCS or topical tacrolimus as first-line treatment.[63] Commonly prescribed TCS include betamethasone dipropionate, betamethasone valerate, clobetasol dipropionate and fluticasone propionate.[63] Use of TCS or tacrolimus ointment to treat vitiligo is off-label.[64] Topical tacrolimus, as monotherapy or in combination with phototherapy, is just as effective as TCS therapy but has a safer side-effect profile.[63] Second-line treatments consist of narrowband ultraviolet B or psoralen ultraviolet A phototherapy and systemic steroid treatment.[63] Third-line treatment consists of surgical grafting techniques.[63] Despite the autoimmune nature of vitiligo, there is insufficient evidence to support the use of immunosuppressive therapies in managing vitiligo.[63] Phototherapy has been a mainstay of treatment for vitiligo for several years.[58] Phototherapy is typically administered 3 times per week and is more effective if initiated early on in the disease.[65] It is used as first-line therapy in extensive disease. It can be used in combination with TCS or topical tacrolimus.[63] The JAK inhibitor, ruxolitinib 1.5% cream, is FDA-approved for the treatment of nonsegmental vitiligo in patients aged 12 years and older.[16]

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder of cellular proliferation with produces benign tumors that affect the skin.[66] Brain involvement in people with TSC may be associated with seizures, cognitive deficits, and neurodevelopmental disorders including autism.[14] This condition arises due to mutations in either the TSC1 or TSC2 genes, which are responsible for overactivation of the mammalian target of rapamycin (mTOR) protein, which gives rise to noncancerous growths in multiple organs.[67,68] It is estimated the TSC affects approximately 1 per 6,000 to 10,000 individuals.[66] Males and females are affected in equal numbers, and the disorder occurs in all races and ethnic groups.[14] Expression of the disease varies substantially among individuals and within

families.[14] Some individuals with TSC may demonstrate only dermatologic features, while others may develop more serious neurologic or systemic manifestations.[68]

The dermatologic features of TSC include hypopigmented macules, angiofibromas, Shagreen patches, and fibrous forehead plaques.[14] Angiofibromas begin to appear as early as within the first 2 years of life, and by adolescence angiofibromas are present in approximately 80% of patients with TSC.[14] The lesions may begin as erythematous macules and then mature into pink to red, or red to brown, papules or papulonodules, which may coalesce into plaques.[14] Angiofibromas typically develop over the central face and cheeks and may cause hemorrhage, obstruction of facial orifices, and disfigurement, which can lead to emotional distress.[14] When not prominent, the skin lesions do not require treatment. However, closer surveillance and intervention is recommended for skin lesions that rapidly change in size or number and for those that cause pain, bleeding, functional impairment, or social problems.[14]

Rapidly changing, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context, using approaches such as surgical excision, cryotherapy, dermabrasion, laser treatments, or application of a topical mTOR inhibitor (sirolimus).[66] The surgical and laser procedures may be performed several times to reduce recurrence of the lesions, may be painful, and may have poor treatment outcomes due to lesion recurrence and scarring.[67] Larger angiofibromas may be recalcitrant to topical treatment and may benefit from laser therapy.[69] Some clinicians have suggested that topical sirolimus may be effective as pretreatment for larger fibrous angiofibromas to reduce the aggressiveness of ablative therapy.[69] Due to the rarity of TCS, the evidence for the standard of care for treating facial angiofibromas is limited, and no guidelines have been published.

Sirolimus, also known as rapamycin, is a naturally occurring macrolide antifungal and mTOR inhibitor.[67] The oral formulation of sirolimus (RAPAMUNE) was approved by the FDA for prophylaxis of organ rejection in 1999.[70] Topical sirolimus has been studied in a range of concentrations for the treatment of angiofibromas in tuberous sclerosis and has been prescribed or compounded “off-label” since 2006.[67] More details about the FDA approval of the 0.2% gel formulation of sirolimus are presented below. The Oregon Health Evidence Review Commission recommends that treatment of hemangiomas of the skin and subcutaneous tissue are funded when they are ulcerated, infected, currently hemorrhaging, or function-threatening (e.g., eyelid hemangioma) as outlined in Guideline Note 13.[71] Otherwise, hemangiomas are not funded.[71] HERC will be assessing the inclusion of angiofibromas in Guideline Note 13 at their December meeting.

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), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:

Cochrane: Topical Anti-Inflammatory Treatments for Eczema

A 2024 Cochrane systematic review and NMA evaluated the efficacy and safety of topical anti-inflammatory eczema treatments.[1] Literature was searched through June 2023 and 291 RCTs (n=45,846) met inclusion critiera.[1] Participants had eczema that was not clinically infected and was not diagnosed as contact dermatitis, seborrheic eczema, or hand eczema.[1] Interventions included topical anti-inflammatory treatments (i.e., TCS, TCI, JAK inhibitors, PDE-4 inhibitors, and tapinarof).[1] The non-TCS, FDA-approved topical anti-inflammatory agents for management of eczema and AD are presented in **Table 3.** The TCS are classified as mild, moderate, potent or very potent. A summary of TCS classified by potency is presented in **Table 4**.

RCTs included in the systematic review compared therapies to no treatment/vehicle or another topical anti-inflammatory agent.[1] Primary outcomes included the clinician assessments: EASI, SCORAD, and IGA and patient-reported symptoms of eczema.[1] Secondary outcomes included health-related quality of life (QoL) based upon the Dermatology Life Quality Index (DLQI), long-term control of eczema, local adverse effects (application site reactions, pigmentation changes, skin thinning/atrophy), and withdrawal due to adverse effects.[1]

Table 3. FDA-Approved Topical Agents for Inflammatory Skin Conditions[64]

Generic Drug Name	Brand Name	Mechanism of Action	Minimum Age	Indication (Severity)
Crisaborole 2% ointment	EUCRISA	PDE-4 Inhibitor	3 months	Atopic Dermatitis (Mild-to-Moderate)
Roflumilast 0.05% cream Roflumilast 0.15% cream Roflumilast 0.3% cream Roflumilast 0.3% foam Roflumilast 0.3% foam	ZORYVE	PDE-4 Inhibitor	2 to 5 years 6 years 6 years 9 years 12 years	Atopic Dermatitis (Mild-to-Moderate) Atopic Dermatitis (Mild-to-Moderate) Plaque Psoriasis Seborrheic Dermatitis Plaque Psoriasis
Delgocitinib 2% cream	ANZUPGO	JAK Inhibitor	18 years	Chronic Hand Eczema (Moderate-to-Severe)
Ruxolitinib 1.5% cream	OPZELURA	JAK Inhibitor	12 years	Atopic Dermatitis (Mild-to-Moderate)
Pimecrolimus 1% cream	ELIDEL	TCI	2 years	Atopic Dermatitis (Mild-to-Moderate)
Tacrolimus 0.03% ointment	PROTOPIC	TCI	2 years	Atopic Dermatitis (Moderate-to-Severe)
Tacrolimus 0.1% ointment	PROTOPIC	TCI	18 years	Atopic Dermatitis (Moderate-to-Severe)
Tapinarof 1% cream	VTAMA	Aryl Hydrocarbon Receptor Agonist	2 years 18 years	Atopic Dermatitis Plaque Psoriasis
Abbreviations: FDA = Food and Drug Administration; JAK = Janus kinase; PDE-4 = phosphodiesterase; TCI = topical calcineurin inhibitor				

Trials were mainly conducted in high-income countries (n=243) especially Europe and North America.[1] Adults were included in most of the RCTs with only 31 RCTs limited to children aged less than 12 years.[1] Male and female participants and multiple ethnic groups were present in most RCTs, but trials populations were mainly White participants.[1] Trials were primarily industry-funded (97%) and evaluated short-term (3 weeks) outcomes.[1] Most RCTs (89%) had a high risk of bias due to selective reporting, due to absence of prospective trial registration/protocol availability.[1] Other issues included insufficient information for allocation concealment, risk for contamination in within-participant trials, poor reporting of participants included in outcome analyses, exclusions from analysis for potentially inappropriate reasons such as adverse events, and trials with high proportions of randomized participants missing from analyses.[1] Certainty of evidence was assessed using the Confidence In Network Meta-Analysis (CINeMA) approach.[1] The CINeMA approach considers 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.[72]

Patient-reported eczema symptoms were assessed in 40 RCTs (n=6,482) and most commonly reported a 4-point improvement in the Peak Pruritus Numerical Rating Scale (PPNRS).[1] High potency TCS (OR 5.99; 95% CI 2.83 to 12.69), tacrolimus 0.1% (OR 6.27; 95% CI 1.19 to 32.98), and ruxolitinib 1.5% (OR 5.64; 95% CI 1.26 to 25.25) were ranked as the most effective agents.[1] Mild potency TCS (OR 1.35; 95% CI 0.51 to 3.53), roflumilast 0.15% (OR 1.03; 95% CI 0.12 to 9.23), and crisaborole 2% (OR 1.15; 95% CI 0.17 to 7.71) were ranked as the least effective agents to relieve itching.[1] Confidence intervals were wide and overlapping for most comparisons, and CINeMA ratings were low except for roflumilast 0.15%, which was rated as moderate certainty of evidence.[1] Evidence certainty was downgraded for within-trial bias in all CINeMA ratings, and some were also downgraded for imprecision and heterogeneity.[1]

Clinician-reported eczema symptoms were reported in 32 RCTs (n=4,121) and commonly included EASI-75.[1] High potency TCS (OR 8.15; 95% CI 4.90 to 13.57), tacrolimus 0.1% (OR 8.06; 95% CI 3.30 to 19.67), ruxolitinib 1.5% (OR 7.72; 95% CI 4.92 to 12.10) and delgocitinib 0.5% (OR 7.61; 95% CI 3.72 to 15.58) were ranked as most effective agents to achieve EASI-75.[1] Mild TCS (OR 2.22; 95% CI 0.74 to 6.64), roflumilast 0.15% (OR 2.43; 95% CI 0.88 to 6.70), crisaborole 2% (OR 2.98; 95% CI 1.42 to 6.26) and tapinarof 1% (OR 2.45; 95% CI 1.00 to 6.02) were ranked as least effective agents.[1] Confidence intervals were wide and overlapping for most comparisons, but CINeMA ratings were moderate or high for most interventions.[1] CINeMA downgrades were most commonly made for within-trial bias, but also imprecision and heterogeneity.[1]

The NMA included 140 RCTs (n=23,383) which reported clear or almost clear eczema on a 6-point IGA (0 or 1, respectively).[1] High potency TCS (OR 5.00; 95% CI 3.80 to 6.58), medium potency TCS (OR 8.34; 95% CI 4.73 to 14.67), ruxolitinib 1.5%, (OR 9.34; 95% CI 4.80 to 18.18), delgocitinib 0.5% (OR 10.08, 95% CI 2.65 to 38.37), delgocitinib 0.25% (OR 6.87; 95% CI 1.79 to 26.33), and tacrolimus 0.1% (OR 5.06; 95% CI 3.59 to 7.13) were ranked as most effective agents to achieve clear or almost clear skin.[1] Mild potency TCS (OR 1.38; 95% CI 0.94 to 2.02), roflumilast 0.15% (OR 2.43; 95% CI 0.65 to 9.01), crisaborole 2% (OR 2.14; 95% CI 1.22 to 3.76), tacrolimus 0.03% (OR 3.53; 95% CI 2.60 to 4.80), and pimecrolimus 1% (OR 2.39; 95% CI 1.78 to 3.21) were ranked as least effective agents.[1] Confidence intervals were wide and overlapping for most comparisons, and CINeMA ratings were low or moderate for most interventions.[1] The CINeMA downgrades were most commonly made for within-trial bias.[1] In a sensitivity analysis of low risk of bias data (12 trials, n=1,639), potent TCS and the JAK inhibitors delgocitinib 0.5% and delgocitinib 0.25% ranked as most effective, while pimecrolimus 1%, and roflumilast 0.15%, were the least effective agents.[1]

The NMA included 83 trials (n=18,992) reporting tolerability events, burning, stinging and/or irritation reactions.[1] Tacrolimus 0.1% and 0.03%, pimecrolimus 1%, and crisaborole 2% were ranked as most likely to cause application site reactions.[1] The mild to medium potency TCS were least likely to cause application site reactions.[1] Confidence intervals were wide for most comparisons, and CINeMA ratings were low or moderate for most interventions, but high for crisaborole 2%.[1] CINeMA downgrades were most commonly made for within-trial bias and imprecision.[1]

The NMA included 25 trials (n=3,691; 36 events) reporting skin thinning, atrophy, striae and/or telangiectasia.[1] On these short-term trials there was no significant increase in odds of skin thinning/atrophy with mild to medium potency TCS, tacrolimus 0.1%, or pimecrolimus 1% compared with vehicle.[1] CINeMA ratings were low for all comparisons, due to within-trial bias and imprecision.[1] Longer-term data over 6 to 60 months for this outcome were insufficient for NMA but were reported for TCS versus TCI in 3 trials, showing an increase in long-term skin thinning with TCS (6 events in 2044 participants with TCS versus 0 events in 2025 participants with TCI; p = 0.031).[1] The 3 included trials evaluated high potency TCS versus tacrolimus 0.1% over 6 months follow-up, moderate potency TCS versus pimecrolimus 1% over 1-year follow-up and mild/medium potency TCS versus pimecrolimus 1% over 5 years follow-up.[1] The 3 trials were all funded by TCI manufacturers and included treatment of both facial and non-facial areas affected by eczema.[1] The trial authors did not comment on reversibility of the skin thinning changes nor did they provide details about location and nature of the identified changes.[1]

Due to insufficient data, an NMA was not possible for HRQoL, long-term symptom control or longer-term outcome assessment for any of the above outcomes.[1] The NMA of pigmentary changes (8 trials of TCS and a PDE-4 inhibitor, n=1,786; 3 events) did not show any significant increase in odds of pigmentation changes compared to vehicle, with low confidence for mild, medium or high potency TCS and moderate confidence for crisaborole 2%.[1] The NMA of withdrawal due to short-term adverse events (11 trials of TCS, TCI, JAK inhibitors and other interventions, n=2,404) did not show any significant increase in odds of withdrawal compared to vehicle with any intervention, with low confidence.[1] Long-term safety data is lacking.[1]

In summary, the NMA ranked potent and/or very potent TCS, tacrolimus 0.1% and ruxolitinib 1.5% among the most effective short-term treatments for improving patient-reported symptoms (40 trials, all low confidence) and clinician-reported signs (32 trials, all moderate confidence) of eczema.[1] For IGA assessment, ruxolitinib 1.5%, delgocitinib 0.5% or 0.25%, high/medium potency TCS and tacrolimus 0.1% were ranked as most effective (140 trials, all moderate confidence).[1] Local application site reactions were most common with tacrolimus 0.1% (moderate confidence) and crisaborole 2% (high confidence) and least common with TCS (moderate confidence).[1] Skin thinning was not increased with short-term use of any TCS potency (low confidence), but skin thinning was reported in 6/2044 (0.3%) participants treated with longer-term TCS (over 6–60 months).[1] Data from almost 300 trials suggest that high potency TCS, JAK inhibitors and tacrolimus 0.1% are among the most effective topical treatments for eczema.[1] Local reactions were most common with tacrolimus 0.1% and crisaborole and least common with TCS.[1]

Topical Treatments for Atopic Dermatitis

A 2023 systematic review and NMA provided the basis for development of AAAAI/ACAAI Joint Task Force 2022 guidance on management of AD.[2] Literature was searched through September 5, 2022 for RCTs addressing topical therapies to manage AD.[2] Of the 219 included RCTs (n=43,123), 156 included children, 59 included only adults, 67 included both children and adults, and 4 did not report age data.[2] The mean age was 18.5 years (range of means 0.35-49 years), and a median 53% were female (range of proportions 0-78%); most studies addressed patients with mild-to-moderate AD.[2] Individual outcomes of most studies had low risk of bias.[2] Limitations from missing outcome data were the most frequent issue.[2] Interventions of interest included TCS, TCIs, JAK inhibitors, PDE-4 inhibitors), antibiotics, prescription moisturizers, and tapinarof.[2] The TCS were stratified by U.S. classification of potency with TCS groups 1 and 2 classified as super-high and high potency, TCS groups 3, 4, and 5 classified as medium potency, and TCS groups 6 and 7 classified as low potency (see **Table 4** for specific TCS products).[2]

Table 4. Potency Of Topical Corticosteroid Preparations Using United States Classification[3]

Potency Group	Corticosteroid	Strength	Formulation
Lowest Potency (Group 7)	Hydrocortisone Base and Hydrocortisone Acetate	0.5%, 1.0%, 2.0%	cream, ointment, gel, lotion, solution
Low Potency (Group 6)	Alcometasone dipropionate	0.05%	cream, ointment
	Betamethasone valerate	0.05%	lotion
	Desonide	0.05%	cream
	Fluocinolone acetonide	0.01%	cream, oil, shampoo, solution
	Triamcinolone acetonide	0.1%	cream
Medium-Low Potency (Group 5)	Betamethasone dipropionate	0.05%	lotion
	Betamethasone valerate	0.1%	cream
	Betamethasone valerate	0.01%	cream, lotion
	Desonide	0.05%	lotion, ointment
	Fluocinolone acetonide	0.025%	cream

	Flurandrenolide	0.05%	cream
	Fluticasone propionate	0.05%	cream
	Hydrocortisone butyrate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Prednicarbate	0.1%	cream
	Triamcinolone acetonide	0.1%	lotion
Medium Potency (Group 4)	Betamethasone valerate	0.12%	foam
	Desoximetasone	0.05%	cream
	Fluocinolone acetonide	0.025%	ointment
	Fluocinolone acetonide	0.2%	cream
	Flurandrenolide	0.05%	ointment
	Halcinonide	0.025%	cream
	Hydrocortisone probutate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Mometasone furoate	0.1%	cream, lotion, solution
	Prednicarbate	0.1%	ointment
Medium-High Potency (Group 3)	Amcinonide	0.1%	cream, lotion
	Betamethasone valerate	0.1%	ointment
	Diflorasone diacetate	0.05%	cream
	Fluocinonide	0.05%	cream
	Fluticasone propionate	0.005%	ointment
	Halcinonide	0.1%	ointment, solution
	Triamcinolone acetonide	0.5%	cream
	Triamcinolone acetonide	0.1%	ointment
High Potency (Group 2)	Amcinonide	0.1%	ointment
	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	cream, lotion
	Betamethasone dipropionate, unaugmented (Diprosone®)	0.05%	cream, ointment
	Desoximetasone	0.25%	cream, ointment, spray
	Desoximetasone	0.05%	gel
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.05%	cream, gel, ointment, solution
	Halcinonide	0.1%	cream
	Mometasone furoate	0.1%	ointment
	Triamcinolone acetonide	0.5%	ointment
Super-High Potency (Group 1)	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	gel, ointment
	Clobetasol propionate	0.05%	cream, foam, gel, lotion, ointment, shampoo, spray
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.1%	cream
	Flurandrenolide	4 mcg/cm^2	tape
	Halobetasol propionate	0.05%	cream, ointment

A total of 187 RCTs (n=34,926) assessed the effects of topical interventions on AD severity compared with placebo or standard care.[2] The NMA results are presented using SCORAD results (0-103, higher score indicates greater severity):

- Most effective: Group 1 TCS (mean difference [MD] -17.81; CrI -21.32 to -14.30; high certainty evidence).[2]
- Intermediate superior efficacy: high-dose tacrolimus (MD −13.05; 95% CrI −15.15 to −10.95; high-certainty evidence), TCS group 2 (MD −13.82; 95% CrI −18.74 to −8.89; high-certainty evidence), TCS group 3 (MD −11.57; 95% CrI −14.80 to −8.37; high-certainty evidence), and TCS group 4 (MD −12.26; 95% CrI −15.02 to −9.50; high-certainty evidence).[2]
- Intermediate inferior efficacy: pimecrolimus (MD −7.23; 95% CrI −8.76 to −5.72; high-certainty evidence), low-dose tacrolimus (MD −9.38; 95% CrI −11.22 to −7.55; moderate-certainty evidence), TCS group 5 (MD −8.46; 95% CrI −10.90 to −6.03; high-certainty evidence), TCS group 6/7 (MD −4.68; 95% CrI −7.10 to −2.29; moderate-certainty evidence), combination TCS group 5 and pimecrolimus (MD −10.45; 95% CrI −18.64 to −2.20; moderate-certainty evidence), combination TCS group 5 and tacrolimus (MD −10.22; 95% CrI −19.01 to −1.33; low-certainty evidence), delgocitinib (MD −9.98; 95% CrI −13.81 to −6.15; high-certainty evidence), ruxolitinib (MD −4.82; 95% CrI −5.65 to −4.00; high-certainty evidence), and crisaborole (MD −4.89; 95% CrI −8.69 to −1.08; high-certainty evidence).[2]
- Not effective: topical antibiotics (MD −1.48; 95% CrI −6.77 to 3.81; moderate certainty evidence) and prescription moisturizers (MD −1.94; 95% CrI −4.83 to 0.95; low certainty evidence).[2]

A total of 100 RCTs (n=19,685) evaluated itch severity.[2] The NMA results are presented as measured using a numeric rating scale (0-10, higher score indicates greater severity).[2] High-certainty evidence showed that high-dose tacrolimus (MD −2.27; 95% CrI −2.84 to −1.70), TCS group 2 (MD −3.39; 95% CrI −5.02 to −1.76), TCS group 3 (MD −2.37; 95% CrI −3.18 to −1.57), TCS group 4 (MD −2.62; 95% CrI −3.26 to −1.98), and TCS group 5 (MD −2.09; 95% CrI −2.54 to −1.64) were among the most effective interventions.[2] Other interventions were of lower effectiveness or certainty.[2]

A total of 15 RCTs (n=3,801) evaluated sleep disturbance.[2] Results are presented based on a 10-point numeric rating scale with higher score indicating greater sleep disturbance.[2] High-certainty evidence showed that pimecrolimus (MD −2.13; 95% CrI −3.15 to −1.01) was the most effective intervention.[2] No trials investigating tacrolimus, crisaborole, delgocitinib, or prescription moisturizers evaluated sleep disturbance.[2] Other interventions were of lower effectiveness.[2]

A total of 33 RCTs (n=8,170) evaluated eczema QoL using the DLQI (0-30, higher score indicates greater impairment to eczema QoL).[2] High-certainty evidence showed that delgocitinib (MD −7.41; 95% CrI −10.16 to −4.66) was the most effective intervention.[2] High-dose tacrolimus (MD −3.65; 95% CrI −5.59 to −1.83; high-certainty evidence), TCS group 4 (MD −5.96; 95% CrI −8.53 to −3.56; moderate-certainty evidence), and ruxolitinib (MD −4.82; 95% CrI −6.35 to −3.44; high-certainty evidence) were among those with intermediate superior effectiveness.[2] Other interventions were of lower effectiveness.[2]

A total of 44 RCTs (n=13,557) evaluated reduction of flares.[2] Moderate- or high-certainty evidence showed that tacrolimus (odds ratio [OR] 0.25; 95% CrI 0.10 to 0.54; risk difference: 70 fewer per 1000 patients; 95% CrI 85 to 41 fewer), pimecrolimus (OR 0.42; 95% CrI 0.29 to 0.57 risk difference: 53 fewer per 1000; 95% CrI 66 to 39 fewer), TCS group 5 (OR 0.12; 95% CrI 0.03 to 0.38; risk difference: 83 fewer per 1000; 95% CrI 92 to 57 fewer), and prescription moisturizers (OR 0.35; 95% CrI 0.13 to 0.94; risk difference: 60 fewer per 1000; 95% CrI 82 to 5 fewer) were among the most effective agents to decrease the number of patients experiencing flares.[2] Other interventions were of lower effectiveness or lower certainty.[2]

A total of 130 RCTs (n=32,200) evaluated adverse events.[2] There was high-certainty evidence that people prescribed TCS group 4 (OR 0.67; 95% CrI 0.44 to 0.99; risk difference: 76 fewer per 1000; 95% CrI 142 to 1 fewer) and TCS group 5 (OR 0.58; 95% CrI 0.46 to 0.73; risk difference: 102 fewer per 1000; 95% CrI 138 to 63 fewer) experienced the fewest adverse events.[2] JAK inhibitors (OR 0.83; 95% CrI 0.62 to 1.12; risk difference: 37 fewer per 1000; 95% CrI 93 fewer to 25 more),

pimecrolimus (OR 1.10; 95% CrI 0.93 to 1.31; risk difference: 21 more per 1000; 95% CrI 15 fewer to 59 more), and tacrolimus (OR 1.14; 95% CrI 0.92 to 1.42; risk difference: 29 more per 1000; 95% CrI 18 fewer to 79 more) were not different from control (moderate-certainty evidence).[2] All other interventions were of lower-certainty evidence.[2] Skin infections (bacterial, viral, or overall) as an adverse event were seldom reported and based on low- to very low–certainty evidence.[2]

A total of 115 RCTs (n=30,483) evaluated adverse events leading to discontinuation.[2] There was moderate-certainty evidence that TCS group 1 (OR 0.09; 95% CrI 0.02 to 0.33; risk difference: 25 fewer per 1000; 95% CrI 27 to 18 fewer) and the JAK inhibitors (OR 0.22; 95% CrI 0.10 to 0.47; risk difference: 21 fewer per 1000; 95% CrI 25 to 15 fewer) had the fewest number of patients experiencing adverse events leading to discontinuation.[2] Pimecrolimus (OR 0.61; 95% CrI 0.41 to 0.91; risk difference: 11 fewer per 1000 patients; 95% CrI 16 to 3 fewer), tacrolimus (OR 0.43; 95% CrI 0.30 to 0.62]; risk difference: 15 fewer per 1000; 95% CrI 19 to 10 fewer), and TCS group 5 (OR 0.32; 95% CrI 0.16 to 0.57; risk difference: 18 fewer per 1000; 95% CrI 23 to 12 fewer) were among those with intermediate effect in reducing the number of patients experiencing adverse events leading to discontinuation based on moderate or high-certainty evidence.[2] Other interventions were of lesser effect or lower-certainty evidence.[2]

In summary, for individuals with AD, pimecrolimus, tacrolimus, and moderate-potency TCS are among the most effective in improving and maintaining multiple AD outcomes.[2] Crisaborole was intermediately effective, but with uncertain harm due to low-quality evidence.[2] Topical antibiotics may be among the least effective agents for managing AD.[2] The TCS group 1 was among the best in improving AD severity; tacrolimus (high dose) and TCS groups 2 to 5 were among the best in improving itch severity; pimecrolimus was among the best in improving sleep disturbance; and delgocitinib was among the best in improving eczema-related QoL.[2]

Cancer Risk with Topical Calcineurin Inhibitors for Atopic Dermatitis

A 2023 systematic review and meta-analysis evaluated cancer associated with TCI administration (pimecrolimus and tacrolimus) as part of the 2022 AAAAI/ACAAI guidance update for AD.[3] Literature was searched through June 6, 2022 for RCTS and observational studies that addressed cancer risk in patients with AD using TCIs.[3] The authors identified 110 studies, including 52 RCTs and 60 observational trials, including 3.4 million patients followed for a mean of 11 months (range 0.7 to 120).[73] The absolute risk of any cancer with TCI exposure was not different from controls (absolute risk 4.70 per 1000 with TCI vs. 4.56 per 1000 without; OR 1.03; 95% CrI 0.94 to 1.11; moderate certainty).[3] For all age groups and using data from observational studies and RCTs, the use of pimecrolimus (OR 1.05; 95% CrI 0.94 to 1.15) or tacrolimus (OR 0.99; 95 % CrI 0.89 to 1.09) is likely to have had little to no association with cancer compared with no TCI exposure.[3] For pimecrolimus versus tacrolimus, the finding was similar (OR 0.95; 95% CrI 0.83 to 1.07).[3] Findings were similar in infants, children, and adults, and robust to trial sequential, subgroup, and sensitivity analyses.[3] The authors concluded that among individuals with AD, moderate-certainty evidence shows that TCIs do not increase the risk of cancer.[3]

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses),[74-76] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force: Atopic Dermatitis Guidance
In 2022, a Joint Task Force comprised of AAAAI and ACAAI members updated 2012 guidance for management of AD in infants, children, and adults.[4] Although moisturization alone may achieve this goal in the mildest of patients, and can help improve AD severity and time-to-flare in those with more severe disease, almost all patients will require a prescription anti-inflammatory treatment including TCS, TCIs, or the topical PDE-4 inhibitor, crisaborole. Ruxolitinib, a topical JAK inhibitor, is not recommended by the task force panel.[4] The task force concluded that there insufficient evidence to assess whether topical ruxolitinib reduces AD flares due to imprecision and the short-term (4-8 weeks) nature of the available studies.[4] Overall, adverse events were similar between topical ruxolitinib and control groups in the short-term studies.[4] However, the direct data were too short and did not contain enough adults (at risk) to credibly estimate the effect on death, cancer, thrombosis, or serious infections observed with oral JAK inhibitors.[4]

The AAAAI/ACAAI recommendations focused on topical therapies are summarized below.

- In patients with uncontrolled AD refractory to moisturization alone, addition of a TCS is recommended over no TCS (strong recommendation, high-certainty evidence).[4]
- In patients aged 3 months or older with uncontrolled AD refractory to moisturization alone, addition of a TCI (pimecrolimus, tacrolimus) is recommended over no added TCI (strong recommendation, high certainty evidence).[4]
- In patients with uncontrolled AD using mid-to high-potency topical treatments (tacrolimus, TCS US classes 1-5), applying the medication once per day over twice per day is suggested (conditional recommendation, moderate certainty evidence).[4]
- In patients with mild-moderate AD refractory to moisturization alone, adding topical crisaborole 2% ointment over usual care alone is suggested (conditional recommendation, high-certainty evidence).[4]
- In adolescent and adult patients with mild-moderate AD refractory to moisturization alone, the panel suggests against adding topical ruxolitinib over continued usual care alone (conditional recommendation, low-certainty evidence).[4]
- In patients with uncontrolled AD and no serious bacterial skin infection (i.e., without severe weeping, crusting, pustules, or painful skin or other signs of extensive infection or systemic illness), the panel suggests against adding topical antimicrobials to standard topical treatments (conditional recommendation, very low-certainty evidence).[4]
- In patients with AD and a relapsing course, proactive therapy with a TCI or mid-potency TCS (US classes 3-5) in areas that frequently flare is recommended over applying topical treatments only in reaction to flares (strong recommendation, moderate-certainty evidence).[4]

American Academy of Dermatology: Management of Atopic Dermatitis in Adults
The AAD guidance for AD management in adults was updated in 2023.[5,6] For most people with AD, emollients and prescription topical therapies are sufficient to achieve AD control.[5] Phototherapy or systemic therapies may be needed to improve disease control and QoL in people with severe or widespread AD, people with substantially impaired QoL and individuals whose AD is refractory to optimized topical therapy.[5] The use of TCS, TCI, crisaborole, and ruxolitinib for mild to severe AD are strongly recommended by AAD.[5] Two new recommendations for the use of tapinarof and roflumilast cream were also included in the update.

There are over 100 RCTs examining the efficacy of TCS in AD, and studies have shown TCS are effective in acute AD, chronic AD, pruritus due to AD, active disease, and prevention of relapses.[6] When choosing a steroid potency, it is important to consider the anatomical site (i.e., using lower potency agents on the

face, neck, genitals, and body folds).[6] While some dermatologists prefer high and very high potency steroids (at least initially) to control active disease, others use the lowest potency agent needed for the situation and increase potency if needed.[6] Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient.[6] Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled.[6] Maintenance in between AD flares with once to twice weekly use of TCS is another approach (available data indicate fewer and increased time between relapses with this strategy).[6] The incidence of adverse events with TCS is low.[6] Though TCS are associated with a variety of cutaneous side effects (i.e., purpura, telangiectasia, hypopigmentation, focal hypertrichosis, acneiform eruptions, and striae), skin atrophy is generally the most concerning for physicians and patients.[6] Risk factors for atrophy include higher potency TCS use, occlusion, use on thinner and intertriginous skin, older patient age, and long-term continuous use.[6]

Based on a review of studies of TCIs compared to vehicle, there is high certainty evidence to strongly recommend the use of tacrolimus 0.1% and 0.03% ointments to treat AD patients.[6] In AD patients with mild-to-moderate disease, there is high certainty evidence to strongly recommend pimecrolimus 1% cream.[6] Of note, recommendations were based heavily on consideration of change in clinical signs, as there are limited data on pruritus and quality of life outcomes for adults with AD.[6] The FDA labeling contains a box warning for elevated risk of cancer with TCIs, and several long-term safety studies suggest TCI may increase relative risk of lymphoma but no other cancers.[6] However, given the low absolute risk of lymphoma, cancer risk from TCIs is likely not clinically meaningful.[6]

Crisaborole 2% ointment is indicated in mild-to-moderate AD and used as an alternative to TCS and TCIs.[6] Crisaborole ointment had a small but significant improvement in dermatitis symptoms in 4 RCTs compared to vehicle.[6] Crisaborole has also improved pruritus in 3 studies.[6] Crisaborole appears to have a favorable safety profile (i.e., small percentage of patients with application burning, stinging, and/or pain) and discontinuation rate comparable to placebo.[6] The work group strongly recommends its use for mild-to-moderate AD, based on high certainty evidence.[6]

Topical ruxolitinib 1.5% cream is FDA-approved for short-term and noncontinuous chronic treatment of mild-to-moderate AD in patients 12 years of age and older.[6] The treatment area should not exceed 20% body surface area, and a maximum of 60 g should be applied per week; these stipulations are aimed at reducing systemic absorption, as black box warnings include serious infections, mortality, malignancies (e.g., lymphoma), major adverse cardiovascular events, and thrombosis.[6] Based on moderate certainty evidence, there are enough data to strongly recommend topical JAK inhibitors in AD.[6] However, this recommendation is based on short-term efficacy and safety data, and may require updating in the future as long-term safety data become available.[6]

Two phase 2 and two phase 3 randomized, double-blind, vehicle-controlled trials evaluated tapinarof 1% cream over 8 weeks.[5] The workgroup determined that the overall balance of benefits and potential harms favors using tapinarof cream for the management of AD.[5] Similar recommendations were made for roflumilast based on two phase 3 randomized, double-blind, vehicle-controlled trials that evaluated roflumilast 0.15% cream over 4 weeks.[5]

For management of AD in adults, the following therapies are recommended by AAD:

- TCS or tacrolimus 0.03% or 0.1% ointment (strong recommendation, high-certainty evidence).[6]
- Intermittent use of medium potency TCS as maintenance therapy (2 times/wk) to reduce disease flares and relapses (strong recommendation, high-certainty evidence).[6]
- For mild-to-moderate AD, pimecrolimus 1% cream, crisaborole ointment, or roflumilast 0.15% cream (strong recommendation, high-certainty evidence).[5,6]
- For mild-to-moderate AD, ruxolitinib cream (strong recommendation, moderate-certainty evidence).[6]
- For moderate-to-severe AD, tapinarof cream (strong recommendation, high-certainty evidence).[5]

Canada's Drug Agency: Delgocitinib for Chronic Hand Eczema

A draft of CDA's reimbursement recommendation for the use of delgocitinib in treating chronic hand eczema was published October 2025.[12] In Canadian clinical practice, treatment escalation for chronic hand eczema typically progresses from low- or mid-potency TCS to high-potency TCS, sometimes with the addition of TCIs, followed by phototherapy or systemic therapies such oral immunosuppressants (e.g., methotrexate, cyclosporine).[12] While delgocitinib has been directly compared with vehicle, there is no direct evidence available for its effectiveness and safety relative to other key comparators, creating uncertainty about its place in therapy.[12] The Canadian Drug Expert Committee (CDEC) emphasized that the definition of "inadequate response" to TCS remains unclear and may rely on clinical judgment.[12] Although TCIs may precede delgocitinib use, they should not be mandatory due to their lower efficacy compared to high-potency TCS.[12] Delgocitinib's topical formulation and favorable safety profile make it an option for patients seeking disease control before systemic treatments.[12] However, uncertainties persist regarding its long-term safety and efficacy beyond 36 weeks, and its role versus systemic agents (e.g., immunosuppressants, JAK inhibitors, dupilumab).[12]

The CDA recommends that delgocitinib be reimbursed for the treatment of moderate to severe chronic hand eczema in adults for whom TCS are inadequate or are not advisable, only if specific conditions are met:

- Treatment with delgocitinib should be initiated in adults (≥18 years) with moderate-to-severe chronic hand eczema as defined by an IGA-CHE score of 3-4 and who have had an adequate trial (with a documented refractory disease), were intolerant (with documented intolerance), or are ineligible for high-potency TCS.[12]
- Response should be assessed at 12 weeks for renewal of coverage.[12]
- Requests should be renewed if patients demonstrate either a ≥ 2-step improvement of IGA-CHE or a score of 0 to 1 (clear/almost clear).
- Delgocitinib should be prescribed by a practitioner experienced in the management of chronic hand eczema.[12]

Canada's Drug Agency: Ruxolitinib for Atopic Dermatitis

In May 2025, CDA recommended against reimbursement for ruxolitinib 1.5% cream in patients with mild-to-moderate AD.[7] Evidence from 2 clinical trials showed that ruxolitinib treatment improved the severity of AD compared with placebo in adult and adolescent patients with mild to moderate AD.[7] However, it is unclear if these patients were representative of the population expected to receive ruxolitinib including patients whose disease is not adequately controlled with TCS and/or TCI, or for whom such treatment(s) is not advisable.[7] Furthermore, there is insufficient evidence that directly compares ruxolitinib to currently available treatments for mild-to-moderate AD.[7]

Canada's Drug Agency: Roflumilast for Plaque Psoriasis

In September 2023, the CDA issued a reimbursement recommendation for the use of roflumilast 0.3% cream in treatment of PsO for patients aged 12 years and older.[8] Evidence from 2 phase 3 RCTs demonstrated that roflumilast improved severity of psoriasis over 8 weeks, including in intertriginous areas, and reduced the severity of itch compared to treatment with vehicle.[8] Roflumilast may provide an alternative, nonsteroidal topical treatment option for patients living with PsO, including psoriasis in the intertriginous area.[8]

CDA Recommendations:

- Roflumilast should only be covered to treat patients who have a clinical diagnosis of PsO with an IGA score of at least 2 (mild) and an area of PsO appropriate for topical treatment covering a body surface area of 2% to 20% (inclusive).[8]
- Roflumilast should be discontinued if a response has not been demonstrated by 8 weeks. A response to treatment is defined as at least a 2-grade improvement from baseline in IGA score or an IGA score of "clear" or "almost clear" (0 or 1).[8]

Canada's Drug Agency: Ruxolitinib for Vitiligo

In August 2025, the CDA recommended against reimbursement of topical ruxolitinib for NSV.[9] Evidence from 2 phase 3 RCTs demonstrated that about 30% of patients using ruxolitinib saw significant improvement in facial repigmentation, compared to around 8% to 11% using a placebo.[9] More patients also reported that their vitiligo became less noticeable or no longer noticeable compared to those who received placebo.[9] However, the impact of vitiligo on daily life varies, and the treatment did not lead to meaningful improvements in overall HRQoL.[9] The studies only compared ruxolitinib to a placebo; therefore, there is no data on how it performs against other commonly used treatments.[9] The Canadian Drug Expert Committee (CDEC) recognized that vitiligo can seriously affect people's lives, especially those with darker skin tones, who may face stigma, loss of identity, and low self-esteem.[9] Most trial participants had lighter skin tones, and the treatment did not improve their HRQoL. These limitations make it difficult to know how effective ruxolitinib would be for those most affected by vitiligo.[9]

After review, 2 guidelines were excluded due to poor quality.[77,78]

New Indications and New Formulations:

- A new formulation of roflumilast 0.05% cream received FDA-approval in October 2025. This product is indicated for topical treatment of mild-to-moderate AD in pediatric patients aged 2 to 5 years of age.[17]

- In September 2025, ruxolitinib cream received expanded FDA-approved for topical short-term and noncontinuous chronic treatment of mild-to-moderate AD in non-immunocompromised patients at least 2 years of age.[16] The prescribing information recommends adults not use more one 60 gram tube per week in adults and in children no more than one 60 gram tube per 2 weeks.[16] Ruxolitinib cream should not be applied to more than 20% of body surface area (BSA).[16] Prior to this approval, topical ruxolitinib was FDA-approved for NSV in patients at least 12 years of age.[16] Ruxolitinib cream has a box warning for risk of serious infections, all-cause mortality, and major cardiovascular events based on studies of oral JAK inhibitors.[16] Malignancies and thromboembolic events have been reported with topical ruxolitinib and are also included in the box warning.[16]

  Two double-blind, vehicle controlled RCTs (n=1249) evaluated ruxolitinib in patients at least 12 years of age with AD (TRuE-AD1 and TRuE-AD2) over 8 weeks.[16] Patients enrolled in these studies had an affected BSA of 3 to 20%, and an IGA score of 2 (mild) to 3 (moderate) on a severity scale of 0 to 4.[16] The primary efficacy endpoint was the proportion of subjects at week 8 achieving IGA treatment success defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2 grade improvement from baseline.[16] In TRuE-AD1, 53.8% of ruxolitinib-treated patients achieved IGA treatment success compared with 15.1% of placebo-treated patients (difference 38.9%; 95% CI 30.3 to 47.4).[16] In TruE-AD2, similar results were observed with ruxolitinib versus placebo (51.3% vs. 7.6%; difference 44.1%; 95% CI 36.2 to 52).[16] A third RCT, TruE-AD3, conducted in pediatric patients 2 to 11 years of age (n=330) showed more IGA treatment success with ruxolitinib than placebo at week 8 (56.5% vs. 10.8%; 95% CI 34.7 to 56.8%).[16]

  Adverse reactions occurred in TRuE-AD1 and TRuE-AD2 infrequently (less than 1%) in the ruxolitinib group and none were reported in the vehicle group. [16] In TRuE-AD3, the most frequently adverse effects associated with ruxolitinib included upper respiratory tract infections, application site reactions, pyrexia, and decrease in white blood cell counts.[16]

- In May 2025, roflumilast 0.3% topical foam received an expanded indication for treatment of PsO in patients at least 12 years of age.[18] Prior to this expanded indication, roflumilast 0.3% foam was FDA-approved for the treatment of seborrheic dermatitis in patients at least 9 years of age.[18] Two randomized, double-blind, vehicle-controlled trials (ARRECTOR [NCT05028582] and Trial 204 [NCT04128007]) enrolled a total of 736 adult and pediatric subjects 12 years of age and older with mild to severe PsO of the scalp and body.[18] In each trial, subjects were randomized 2:1 to receive roflumilast foam, 0.3%, or vehicle foam

applied once daily for 8 weeks.[18] The combined trial population was 55% female, 85% White, 5% Black, 6% Asian, and 4% other races.[18] The median age was 47 years (range 12 to 87 years).[18]
In both trials, Scalp Investigator Global Assessment (S-IGA) treatment success, a primary endpoint in ARRECTOR and Trial 204, and Body Investigator Global Assessment (B-IGA) treatment success, a primary endpoint in ARRECTOR, were defined as a score of "Clear" (0) or "Almost Clear" (1), plus a 2-grade improvement from baseline.[18] In both trials, roflumilast foam was superior to vehicle foam at Week 8 at achieving S-IGA and B-IGA success as presented in **Table 5**. The most frequently reported adverse events with roflumilast foam were headache, diarrhea, nausea, and nasopharyngitis.[18]

Table 5. Treatment Success at Week 8 with Roflumilast Foam versus Vehicle Foam in Patients with Plaque Psoriasis Trials[18]

	ARRECTOR Trial		**Trial 204**	
	Roflumilast 0.3% Foam (n=281)	Vehicle Foam (n=151)	Roflumilast 0.3% Foam (n=200)	Vehicle Foam (n=104)
Percent of Patients with S-IGA Success (Clear or Almost Clear)	66.4%	27.8%	56.7%	11.0%
Difference (95% CI)	37.1% (27.1 to 47.1)		47.7% (37.9 to 57.5)	
Percent of Patients with B-IGA Success (Clear or Almost Clear)	45.5%	20.1%	39.0%	7.4%
Difference (95% CI)	24.8% (15.0 to 34.6)		32.4 (23.3 to 41.6)	
Abbreviations: B-IGA = Body Investigator Global Assessment; CI = Confidence Interval; S-IGA = Scalp Investigator Global Assessment				

- Roflumilast 0.15% cream was FDA-approved in July 2024 for the treatment of mild-to-moderate AD in people at least 6 years of age.[17] Prior to this approval, roflumilast 0.3% cream was FDA-approved for PsO in patients at least 6 years of age.[17] Two double-blind, vehicle-controlled RCTs (n=1337) evaluated the efficacy of once daily roflumilast 0.15% cream in patients with mild-to-moderate AD over 4 weeks (INTEGUMENT-1 and INTEGUMENT-2).[17] The primary endpoint was the proportion of subjects who achieved IGA-AD treatment success, defined as a score of 0 (clear) or 1 (almost clear) at Week 4.[17] More patients in both trials achieved IGA-AD treatment success with roflumilast compared to vehicle cream (INTEGUMENT-1: 32% vs. 15.2%; difference 17.4%; 95% CI 11.09 to 23.75 and INTEGUMENT-2: 28.9% vs. 12.0%; difference 16.5%; 95% CI 10.61 to 22.42).[17] The most frequently reported adverse effects with roflumilast in these 4-week RCTs included headache, nausea, application site pain, diarrhea, and vomiting.[17]

- Tapinarof cream received an expanded FDA-approved indication for AD in people at least 2 years of age in December 2024.[19] Prior to this approval, tapinarof was FDA-approved for PsO in adults.[19] Two multicenter, double-blind, vehicle-controlled trials (n=813) evaluated the safety and efficacy of tapinarof cream over 8 weeks in patients with AD (ADORING 1 and ADORING 2).[19] Eighty percent of enrolled patients were 2 to 17 years of age. Baseline disease severity was graded using the 5-point IGA-AD. The majority of subjects had "Moderate" disease (87%), while 13% had "Severe" disease at baseline.[19] The primary efficacy endpoint in both studies was the proportion of subjects who achieved treatment success, defined as a IGA-AD score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline.[19] At 8 weeks, more tapinarof-treated patients achieved IGA-AD treatment success compared with vehicle-treated patients (ADORING 1: 45% vs. 14%; difference 32%; 95% CI 23 to 40 and ADORING 2: 46% vs. 18%; difference 29%; 95% CI 19 to 38).[19] Adverse

effects reported with tapinarof over 8 weeks included respiratory tract infection, folliculitis, headache, asthma, vomiting, ear infection, pain in extremity and abdominal pain.[19]

New FDA Safety Alerts: No new FDA safety alerts were identified for this class of drugs.

Randomized Controlled Trials:
A total of 36 citations were manually reviewed from the initial literature search. After further review, 36 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Delgocitinib (ANZUPGO)
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 4**.

Clinical Efficacy:
Delgocitinib is a JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) inhibitor available as 2% topical cream in the United States.[10] The medication received FDA-approval in July 2025 for moderate-to-severe chronic hand eczema in adults who have had inadequate response to, or for whom TCS therapies are not advisable.[10] FDA-approval was supported by 2 double-blind, placebo-controlled, multi-center phase 3 RCTs, DELTA 1 and DELTA 2, in adults with moderate-to-severe chronic hand eczema (**Table 6)**.[11] Adults enrolled in the trial were randomly assigned 2:1 to twice-daily delgocitinib cream or placebo.[11] The trials were conducted in Europe and Canada. The primary endpoint of each trial was IGA-CHE treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) at week 16 with a 2-step or greater improvement from baseline.[11]

DELTA 1 enrolled 487 patients (181 male and 306 female) while DELTA 2 enrolled 473 patients (161 male and 321 female) with an IGA-CHE score of 3 or 4 and inadequate response or contraindication to the use of TCS or for whom TCS were documented to be medically inadvisable as assessed by the investigator.[11] The mean age of enrolled patients was 44 years, 64% were female, 90% were White, 4% were Asian, and 1% were Black.[10] The primary classifications of chronic hand eczema by subtype were atopic hand eczema (35.9%), hyperkeratotic eczema (21.5%), irritant contact dermatitis (19.6%), allergic contact dermatitis (13.9%), vesicular hand eczema (9.1%), and contact urticaria/protein contact dermatitis (0.1%).[10] The use of hand emollients was permitted in both trials; however, patients were instructed to avoid using emollients on the affected area 2 hours before and after application of the study drug.[11] If medically necessary, rescue treatment for chronic hand eczema (i.e., treatment initiated to control intolerable chronic hand eczema symptoms during the treatment and follow-up periods) was prescribed to patients at the investigator's discretion. Once rescue treatment was initiated, patients had to stop trial treatment immediately and were not allowed to restart it.[11] At week 16, a greater proportion of patients using delgocitinib had IGA-CHE treatment success compared to vehicle cream (19.7% vs. 9.9%; difference, 9.8%; 95% CI 3.6 to 16.1; $p<0.0055$ in DELTA 1 and 29.1% vs. 6.9%; difference, 22.2%; 95% CI 15.8 to 28.5; $p<0.0001$ in DELTA 2).[11]

Key secondary endpoints included reduction of Hand Eczema Symptoms Diary (HESD) overall score, reduction of HESD itch score, and reduction of HESD pain score as measured by a change in weekly averaged patient-reported diary scores of at least 4 points from baseline at week 16 and at least 75% improvement in Hand Eczema Severity Index (HECSI) score from baseline (HECSI-75) at week 16.[11] At baseline, mean HESD itch and pain scores were 7.1 and 6.7, respectively.[10] Delgocitinib was superior to placebo for all key secondary endpoints (**Table 4)**. Both trials were conducted over a relatively short time frame (16 weeks) and included a mostly White patient population.

Eligible patients (n=801) were followed over 36 weeks in an open-label, long-term extension trial.[79] Overall, 82.9% (664/801) completed DELTA 3, and 17.1% (137/801) of the patients discontinued trial treatment.[79] The most common reasons for trial discontinuation were lack of efficacy (6.9% [55/137]) and patient withdrawal from the trial (6.5% [52/137]).[79] Rescue treatment was used by 29 (3.6%) patients.[79] Among patients previously treated with delgocitinib cream 20 mg/g who had achieved IGA-CHE 0/1 at DELTA 3 baseline (i.e., parent trial responders in DELTA 1 or DELTA 2 at week 16), the proportion who maintained IGA-CHE 0/1 response without treatment was 40.6% at week 4 and 28.3% at week 8.[79]

Clinical Safety:
Most adverse events were mild to moderate and not considered related to trial treatment.[11] In both trials, the most frequently reported adverse events occurred in less than 1% of people treated with delgocitinib and included application site pain, paresthesia, pruritis, erythema, and bacterial skin infections.[11] The proportion of patients reporting adverse events leading to discontinuation of trial treatment was lower in delgocitinib treatment groups (2 [1%] in DELTA 1 and 1 [<1%] in DELTA 2) compared with their corresponding cream vehicle groups (6 [4%] in DELTA 1 and 5 [3%] in DELTA 2).[11] In both trials, few serious adverse events were reported (≤2% of patients), and all were determined to be unrelated to trial drug by both trial investigator and sponsor; none led to any safety concerns.[11] In the open-label extension trial, eczema herpeticum was observed in one patient and herpes zoster was observed in 2 patients treated with delgocitinib.[10] In this trial delgocitinib was well-tolerated with most frequent adverse events being COVID-19 (17%), nasopharyngitis (16%), and upper respiratory tract infection (4%).[79]

The manufacturer recommends completing any necessary immunizations, including herpes zoster vaccinations, prior to initiating delgocitinib therapy.[11] Use with other JAK inhibitors or potent immunosuppressants is not recommended.[11] It is not known if topical delgocitinib is associated with adverse reactions (i.e., cardiovascular events, deep venous thrombosis, malignancies) that have been observed with oral JAK inhibitors.[11] At this time, delgocitinib does not carry the boxed warning of oral JAK inhibitors for the risk of serious infections, mortality, malignancy, cardiovascular events, and thrombosis.
Look-alike / Sound-alike Error Risk Potential: No issues identified in Micromedex

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Hand eczema symptoms (reduced redness, itching, pain, cracking, flaking, dryness)
2) Quality of life or functional improvement
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement on the 5-point scale at week 16.

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints (assessed at 16 weeks)	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Bissonnette, R., et al[11] DELTA 1 and DELTA 2 DB, PC, Phase 3 RCT	1. Delgocitinib 2% cream applied twice daily over 16 weeks 2. Cream vehicle applied twice daily over 16 weeks	Demographics: **DELTA 1** -Mean Age: 44 yo -Female: 63% -Race: White: 88% Black: < 1% Asian: 4% Geographic Region: Europe: 80% North America: 20% -Baseline IGA-CHE score: Moderate (3 points): 67% Severe (4 points): 33% **DELTA 2** Mean Age: 44 yo -Female: 66% -Race: White: 93% Black: < 1% Asian: 3% -Geographic Region: Europe: 80% North America: 20% -Baseline IGA-CHE score: Moderate (3 points): 76% Severe (4 points): 24% Key Inclusion Criteria: -Adults ≥ 18 yo -Diagnosis of CHE that had persisted for > 3 mos or returned 2 or more times in the previous 12 mos -IGA-CHE score of 3 (moderate) to 4 points (severe) at baseline -HESD itch score ≥ 4 points at baseline -Documentation of inadequate response to	**DELTA 1** ITT: 1. 325 2. 162 PP: 1. 305 2. 141 Attrition: 1. 20 (6%) 2. 21 (13%) **DELTA 2** ITT: 1. 314 2. 159 PP: 1. 291 2. 122 Attrition: 1. 23 (7%) 2. 37 (23%)	**DELTA 1** Primary Endpoint: People with IGA-CHE score of 0/1 1. 64 (19.7%) 2. 16 (9.9%) Difference: 9.8% 95% CI 3.6 to 16.1; P<0.0055 Secondary Endpoints: People with ≥ 4 points reduction in HESD score* 1. 146 (47.2%) 2. 38 (24.4%) Difference: 22.8% 95% CI 14.0 to 31.7; P<0.0001 People with ≥ 4 points reduction in HESD itch score* 1. 152 (47.1%) 2. 37 (23%) Difference: 24.1% 95% CI 15.5 to 32.6; P<0.0001 People with ≥ 4 points reduction in HESD pain score* 1. 143 (49.1%) 2. 41 (27.5%) Difference: 21.7% 95% CI 12.4 to 30.9; P<0.0001 People with 75% improvement in HECSI score 1. 160 (49.2%) 2. 38 (23.5%) Difference: 25.7% 95% CI 17.2 to 34.3; P<0.0001 **DELTA 2** Primary Endpoint: People with IGA-CHE score of 0/1 1. 91 (29.1%) 2. 11 (6.9%)	9.8/ 11 22.8 /5 24.1 /5 21.7 /5 25.7 /4	**DELTA 1** Adverse Events 1. 147 (45%) 2. 82 (51%) RD = -5.4 95% CI -14.7 to 4.0 Adverse Events Leading to Discontinuation 1. 2 (1%) 2. 6 (4%) RD = -3.1 95% CI -7.3 to -0.5 Serious Adverse Events 1. 6 (2%) 2. 3 (2%) RD = 0 95% CI -3.6 to 2.4 **DELTA 2** Adverse Events 1. 143 (46%) 2. 71 (45%) RD = 1.0 95% CI -8.4 to 10.4 Adverse Events Leading to Discontinuation 1. 1 (<1%) 2. 5 (3%) RD = -2.8 95% CI -5.5 to 4.6 Serious Adverse Events 1. 5 (2%)	NS 3.1/3 3 NS NS NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to delgocitinib or cream vehicle via interactive response technology system and stratified by baseline CHE severity (moderate vs. severe) and region (Europe vs. North America). Baseline characteristics were comparable between active treatment and cream vehicle arms. Performance Bias: Low. Active drug and placebo vehicle were identical in appearance and scent. Patient and investigators blinded to treatment arms. Protocol standardized across all trial sites. Detection Bias: Unclear. Primary outcome (IGA-CHE) was conducted by investigators. Secondary outcomes were primarily patient reported in a daily diary, which may be affected by recall bias and subjective assessment of improvement. Attrition Bias: High. Higher percentage of vehicle-treated patients withdrew from both studies due to lack of efficacy and adverse events. Missing data imputed as non-response. Reporting Bias: Low. Protocol available online. All pre-specified outcomes reported as outlined in the protocol. Other Bias: High. Manufacturer had a role in trial design, data collection, data analysis, data interpretation, writing of the report and trial funding. **Applicability**: Patient: More females enrolled in the study, which is typical for CHE. Most participants were White, which limits applicability to a more diverse population. All patients had inadequate response to TCS prior to enrollment (potency not reported). Intervention: Strength and dosing of delgocitinib cream determined in Phase 2 RCTs. Comparator: Placebo cream is appropriate, although comparison to TCS or TCI would provide more meaningful outcomes. Outcomes: Primary outcome was the IGA-CHE, which was approved by the FDA as an effective

		TCS within 1 yr prior to study enrollment <u>Key Exclusion Criteria</u>: -Concurrent skin disease on the hands including significant infection -Active psoriasis on any part of the body -Active atopic dermatitis requiring medical treatment in regions other than the hands and feet -Previous treatment with systemic therapy or topical JAK-I		Difference: 22.2% 95% CI 15.8 to 28.5; P<0.0001 <u>Secondary Endpoints</u>: People with ≥ 4 points reduction in HESD score* 1. 137 (44.5%) 2. 32 (20.9%) Difference: 23.7% 95% CI 15.1 to 32.3; P<0.0001 People with ≥ 4 points reduction in HESD itch score* 1. 146 (47.2%) 2. 31 (19.9%) Difference: 27.4% 95% CI 19.0 to 35.8; P<0.0001 People with ≥ 4 points reduction in HESD pain score* 1. 143 (48.6%) 2. 32 (22.7%) Difference: 26.0% 95% CI 17.0 to 35.1; P<0.0001 People with 75% improvement in HECSI score 1. 155 (49.5%) 2. 29 (18.2%) Difference: 31.3% 95% CI 23.1 to 39.5; P<0.0001 *11-point scale	22.2 /5 23.7 /5 27.4 /4 26/4 31.3 /4	2. 3 (2%) RD = -0.3 95% CI -3.9 to 2.1		assessment tool. Trial was conducted over a relatively short period, 16 weeks. <u>Setting</u>: **DELTA 1**: 53 sites in 6 countries -Canada: 20% France: 17% -Germany: 28% Italy: 9% -Poland: 22% United Kingdom: 5% **DELTA 2**: 50 sites in 7 countries: -Belgium: 5% Canada: 20% -Denmark: 5% Germany: 28% -Netherlands: 5% Poland: 22% -Spain: 14%
<u>Abbreviations</u>: ARR = absolute risk reduction; CHE = chronic hand eczema; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; HESD = Hand Eczema Symptom Diary; HECSI = Hand Eczema Severity Index; IGA-CHE = Investigator's Global Assessment of Chronic Hand Eczema; ITT = intention to treat; JAK-I = Janus kinase inhibitor; mos= months; N = number of subjects; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; TCS = topical corticosteroids; yo = years old								

NEW DRUG EVALUATION: Sirolimus (HYFTOR)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 6**.

Sirolimus 0.2% gel is indicated as topical treatment for facial angiofibromas associated with TSC in adults and pediatric patients aged 6 years and older.[15] The mechanism of action of sirolimus in the treatment of angiofibroma associated with TSC is unknown.[15] The gel is applied twice daily to the areas of the face with angiofibromas.[15] The maximum daily dosage for patients 6 to 11 years of age is 600 mg (2 cm), while patients at least 12 years of age have a maximum daily dosage of 800 mg (2.5 cm).[15]

Clinical Efficacy:

A phase 3, double-blind, placebo-controlled, randomized trial was conducted in 62 patients at least 3 years of age with angiofibromas due to TSC.[13] This trial is described in detail below in **Table 8**. The trial was conducted at 9 centers in Japan.[13] Patients were eligible for this study if they had a diagnosis of TSC with 3 or more facial angiofibromas that were 2 or more mm in diameter.[13] Patients were excluded if they had received treatment with a local or systemic mTOR inhibitor within the preceding 12 months or had undergone laser or surgical treatment within the preceding 6 months.[13] Enrolled participants were randomized 1:1 to receive sirolimus 0.2% gel or placebo gel , each applied topically twice daily for 12 weeks.[13] Dosing was modified based upon age (400 mg, 600 mg, and 800 mg for patients younger than 6 years, 6 to 11 years, and older than 11 years, respectively).[13] Concurrent use of the following medications was not permitted: any mTOR inhibitors, topical tacrolimus, topical steroids, topical antibiotics, topical vitamin D3, adapalene, benzoyl peroxide, ibuprofen piconol, resorcinol, and zinc-salicylic acid.[13] Laser therapy and surgery of the site of topical application were also not permitted.[13]

Patients underwent a 12-week treatment plan with lesion assessment every 4 weeks and the final evaluation at a 4-week follow-up after completing treatment.[13] At each visit, patients were medically examined and their facial lesions were photographed with the same digital camera at all sites.[13] A color chart with a scale was used to calibrate the color tones and clarity of all photographs taken and to measure the size of skin lesions.[13] The primary end point was composite improvement in the combined size and color of angiofibromas as documented in photographs obtained at week 12 of treatment.[13] Three blinded dermatologists assessed the changes using a 6-category scale with the following categories: markedly improved, improved, slightly improved, unchanged, slightly aggravated, and aggravated.[13] It is not clear how this scale was developed and validated.[14] The proportion of patients with angiofibroma improvement after 12 weeks was 60% in the sirolimus group compared to 0% in the placebo group ($p<0.001$).[13] Secondary endpoints included changes from baseline in the Dermatology Life Quality Index (DLQI) and Children's DLQI (CDLQI) based upon the patient's age; neither outcome achieved statistical significance compared to placebo.[13] An additional secondary outcomes was the in person investigator assessment of improvement in size and color of the fibroangioma lesions. The proportion of patients assessed in person by the investigator (instead of by photograph) as "improved" or "markedly improved" at Week 12 was 23% for sirolimus-treated patients compared to 6% of vehicle-treated patients, which did not reach statistical significance.[14] Because the study was not powered to detect differences in secondary outcomes it is unclear if these secondary endpoint results are related to a type 2 error (finding no difference when one actually exists).

Trial Limitations

The FDA identified several issues with primary outcome used in this trial. The photographic technique was not standardized in terms of lighting, background, distance from the camera to the subject, or subject position.[14] Investigators, as well as personnel who performed the editing of photographs, were blinded only to the treatment arm, and not to whether photographs were taken before or after treatment.[14] In addition, the reliability of the scale used to document

angiofibroma improvement was not confirmed prior to its use in the study.[14] The final assessment score could be modified based upon consensus discussions of the blinded assessors. The rationale for conducting the consensus discussions was not provided by the investigators. The need to discuss and change the scores of several assessments during the trial raises concerns related to accuracy and inter-rater reliability of the rating instrument.[14] The FDA reviewers concluded that composite improvement scale was not appropriate to support regulatory decision making based on its design and lack of sufficient supportive evidence of content validity (e.g., evidence of clinician's understanding of the categories, descriptors, threshold, etc.).[14] A key limitation of the scale was that it assesses changes in angiofibromas relative to baseline, instead of assessing absolute angiofibroma severity.[14] Because of these issues, the FDA based its approval on the secondary endpoint, the investigator's in person assessment of composite changes in angiofibromas.[14]

Clinical Safety:

A summary of adverse events reported during the 12-week trial of sirolimus compared to placebo vehicle is presented in **Table 7**. In a 104-week, open-label safety trial, the most common adverse reactions associated with sirolimus application were application site irritation (31%), dry skin (28%), acne (20%), pruritus (9%), eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), solar dermatitis (1%), and photosensitivity reaction (1%).[15] Adverse reactions occurred with similar frequency in adult and pediatric subjects 6 years of age and older.[15] Systemic exposure of drugs that are both substrates and inhibitors of CYP3A could be increased with coadministration with sirolimus.[15] Concomitant use of sirolimus with inhibitors of CYP3A4 has the potential to increase the systemic exposure of sirolimus and increases the risk of sirolimus adverse reactions.[15] Live vaccines should not be administered while using topical sirolimus, as the vaccines may be less effective.[15] Sirolimus is systemically absorbed after topical administration and may result in fetal exposure.[15] Effective contraceptive methods are recommended for females of reproductive potential during treatment and for 12 weeks after completing sirolimus therapy.[15]

Table 7. Adverse Reactions Reported in Sirolimus Trial Compared to Placebo Vehicle Through Week 12[15]

Adverse Event	Sirolimus (n = 30)	Vehicle (n = 32)
Dry Skin and Asteatosis	12 (40%)	4 (13%)
Application Site Irritation	11 (37%)	9 (28%)
Pruritis	5 (17%)	4 (13%)
Acne	2 (7%)	0
Acneiform Dermatitis	1 (3%)	0
Ocular Hyperemia	1 (3%)	0
Skin Hemorrhage	1 (3%)	0
Skin Irritation	1 (3%)	0

Look-alike / Sound-alike Error Risk Potential: Rapamune or Rapaflo

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Decreased size of facial angiofibromas
2) Decreased redness of facial angiofibromas

Primary Study Endpoint:
1) Composite assessment of improvement in size and redness of fibroangiomas

3) Improved quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Table 8. 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. Wataya-Kaneda, et al[13] Phase 3 MC, DB, PC, RCT	1. Sirolimus 0.2% gel applied topically twice daily for 12 weeks. Dosing determined by age. 2. Placebo applied twice daily for 12 weeks	Demographics: -Adults: n=35 -Pediatrics: n=27 -Male: 57% (n=17) in group 1 and 34% (n=11) in group 2 -Mean age: 22.5 yrs (range 6 -53 yrs) -Mean baseline total DLQI/CDLQI score: 1.8 (total score = 30) Key Inclusion Criteria: -Male and females aged 3 years or older -Diagnosis of TSC -Three or more facial angiofibromas ≥ 2 mm in diameter with redness in each -Inability to photograph lesions -Local or systemic treatment with mTOR inhibitor within previous 12 months -Not eligible for surgery or laser therapy or did not want these therapies	ITT: 1. 30 2. 32 Attrition: 1. 0 2. 0	Primary Endpoint Percent of patients with "marked improvement" and "improvement" in composite assessment (size and redness) of angiofibroma observed *in photographs* after 12 weeks of treatment using 6-point scale. 1. n=18 (60%) 2. n=0 95% CI, 41 to 77 P<0.001 Secondary Endpoints Percent of patients with composite angiofibroma improvement based on *in-person assessment* at week 12 ("marked improvement" and "improvement"). 1. n=7 (23%) 2. n=2 (6%) NS* Mean change in DLQI at week 12 1. -0.2 2. -0.5 Difference = -0.3 NS* Mean change in CDLQI at week 12 1. 2.9 2. 2.3 Difference = 0.6	60%/2 NA NA NA	Any Adverse Event 1. n=27 (90%) 2. n=22 (69%) Dry Skin 1. n=11 (37%) 2. n=4 (13%) Application Site Irritation 1. n=11 (37%) 2. n=9 (28%) Pruritus 1. n=7 (23%) 2. n=4 (13%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 using 4 block permutation by an independent statistician. Stratified by age (3-18 yrs and > 18 yrs). More males enrolled in the active comparator group, otherwise baseline demographics were similar. Performance Bias: Low. Sirolimus gel and placebo were identical in appearance. Patients and investigators blinded to treatment allocation. Detection Bias: High. Independent review committee of 3 dermatologists assessed the photographs using a 6-point scale (markedly improved, improved, slightly improved, unchanged, slightly aggravated, aggravated). Scale was not validated prior to use in the RCT. Committee could confer if assessments differed and modify their assessment based on consensus of the 3 reviewers. Attrition Bias: Low. No patients withdrew from the study. Photographic results of one placebo-treated patients were deemed unassessable as the pictures were unfocused. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Study was sponsored by manufacturer. Conflict of interest declarations for investigators was not provided. **Applicability**: Patient: Conducted in Japan, applicability to Oregon Medicaid patients is unclear. Intervention: Phase 2 RCTs evaluated doses of 0.05%, 0.1% and 0.2% gel with largest benefit compared to placebo in patients randomized to the 0.2% dose.

		Key Exclusion Criteria: -Skin lesions that were ulcerated or had erosions -Poorly controlled dyslipidemia -Local or systemic treatment with an mTOR inhibitor (sirolimus, everolimus) within previous 12 months -Laser therapy or surgery within previous 6 months		NS* *p-value and CIs not reported				Comparator: No currently approved drugs for this condition. Placebo is an appropriate comparator. Outcomes: Instrument used to assess angiofibroma improvement was not validated prior to its use in this RCT. Setting: Conducted at 9 sites in Japan
Abbreviations: CI = confidence interval; CDLQI = Children's Dermatology Life Quality Index; DB = double-blind; DLQI = Dermatology Life Quality Index; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; mm = millimeters; mTOR = mammalian target of rapamycin; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; TSC = tuberous sclerosis complex; yrs = years								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
calcipotriene	CALCIPOTRIENE	TOPICAL	CREAM (G)	Y
pimecrolimus	ELIDEL	TOPICAL	CREAM (G)	Y
pimecrolimus	PIMECROLIMUS	TOPICAL	CREAM (G)	Y
tazarotene	TAZAROTENE	TOPICAL	CREAM (G)	Y
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE	TOPICAL	OINT. (G)	Y
tacrolimus	TACROLIMUS	TOPICAL	OINT. (G)	Y
anthralin	ANTHRALIN	TOPICAL	CREAM (G)	N
ruxolitinib phosphate	OPZELURA	TOPICAL	CREAM (G)	N
tapinarof	VTAMA	TOPICAL	CREAM (G)	N
roflumilast	ZORYVE	TOPICAL	CREAM (G)	N
calcipotriene	CALCIPOTRIENE	TOPICAL	FOAM	N
calcipotriene/betamethasone	ENSTILAR	TOPICAL	FOAM	N
calcipotriene	SORILUX	TOPICAL	FOAM	N
roflumilast	ZORYVE	TOPICAL	FOAM	N
tazarotene	TAZAROTENE	TOPICAL	GEL (GRAM)	N
halobetasol propion/tazarotene	DUOBRII	TOPICAL	LOTION	N
calcipotriene	CALCIPOTRIENE	TOPICAL	OINT. (G)	N
calcitriol	CALCITRIOL	TOPICAL	OINT. (G)	N
crisaborole	EUCRISA	TOPICAL	OINT. (G)	N
calcitriol	VECTICAL	TOPICAL	OINT. (G)	N
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE	TOPICAL	SUSPENSION	N
calcipotriene/betamethasone	TACLONEX	TOPICAL	SUSPENSION	N
tazarotene	FABIOR	TOPICAL	FOAM	N
tazarotene	TAZAROTENE	TOPICAL	FOAM	N
tazarotene	ARAZLO	TOPICAL	LOTION	N
coal tar	DHS TAR	TOPICAL	SHAMPOO	N
coal tar	DHS TAR GEL	TOPICAL	SHAMPOO	N
coal tar	THERA-GEL	TOPICAL	SHAMPOO	N
coal tar	T-PLUS	TOPICAL	SHAMPOO	N
delgocitinib	ANZUPGO	TOPICAL	CREAM (G)	
sirolimus	HYFTOR	TOPICAL.	GEL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to August 19, 2025>

1	tapinarof.mp.	182
2	exp Tacrolimus/	18681
3	pimecrolimus.mp.	1080
4	Administration, Topical/	41802
5	Anti-Inflammatory Agents, Non-Steroidal/	74426
6	crisaborole.mp.	268
7	ruxolitinib.mp.	3589
8	roflumilast.mp.	996
9	Calcitriol/	15100
10	tazarotene.mp.	735
11	Betamethasone/ or Calcitriol/	21249
12	Anthralin/	948
13	Coal Tar/	2370
14	delgocitinib.mp.	115
15	calcipotriene.mp.	1294
16	crisaborole.mp.	268
17	Sirolimus/	21760
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	180988
19	exp Psoriasis/th [Therapy]	5154
20	exp Dermatitis, Atopic/th [Therapy]	2809
21	exp Eczema/th [Therapy]	1148
22	exp Vitiligo/th [Therapy]	1127
23	19 or 20 or 21 or 22	9869
24	18 and 23	802
25	limit 24 to (english language and humans and yr="2022 -Current")	36

Appendix 3: Prescribing Information Highlights

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

ANZUPGO® (delgocitinib) cream, for topical use
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
ANZUPGO is a Janus kinase (JAK) inhibitor indicated for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. (1)

Limitations of Use: Use of ANZUPGO in combination with other JAK inhibitors or potent immunosuppressants is not recommended. (1)

----------DOSAGE AND ADMINISTRATION----------
- See the full prescribing information for recommended immunizations prior to treatment. (2.1)
- Do not use more than 30 grams per 2 weeks or 60 grams per month.
- Apply twice daily to skin of the affected areas only on the hands and wrists. (2.2)
- For topical use only. Not for oral, ophthalmic, or intravaginal use. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Cream: Each gram of ANZUPGO cream contains 20 mg of delgocitinib. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Serious Infections: ANZUPGO may increase the risk of infection. Eczema herpeticum was observed in a subject treated topically with ANZUPGO. Avoid use of ANZUPGO in patients with an active or serious infection. If a serious infection develops, discontinue ANZUPGO until the infection resolves. (5.1)
- Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell carcinoma have been reported in subjects treated with ANZUPGO. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer. (5.2)
- Immunizations: Avoid vaccination with live vaccines immediately prior to, during, and immediately after ANZUPGO treatment. (5.3)
- Potential Risks Related to JAK Inhibition: It is not known whether ANZUPGO may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in rheumatoid arthritis (RA) patients. ANZUPGO is not approved for use in RA. Treatment with oral and topical JAK inhibitors has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. (5.4)

----------ADVERSE REACTIONS----------
Adverse reactions that were reported in ≤ 1% of subjects were application site pain, paresthesia, pruritus, erythema, and bacterial skin infections including finger cellulitis, paronychia, other skin infections, leukopenia, and neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LEO Pharma Inc. at 1-877-494-4536 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 7/2025

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

HYFTOR® (sirolimus topical gel)
Initial U.S. Approval: 1999

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

HYFTOR is an mTOR inhibitor immunosuppressant indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older. (1)

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

- Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to HYFTOR initiation. (2)
- Apply to the skin of the face affected with angiofibroma twice daily. (2)
- The maximum daily dosage is:
  - 600 mg (2 cm) for patients 6 to 11 years of age. (2)
  - 800 mg (2.5 cm) for patients 12 years of age and older. (2)
- Do not use with occlusive dressings. (2)
- For topical use only. Not for oral, ophthalmic, or intravaginal use. (2)

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

Topical gel, 0.2%: 2 mg of sirolimus per gram. (3)

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

History of hypersensitivity to sirolimus or any other component of HYFTOR. (4)

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

- *Hypersensitivity Reactions*: Oral sirolimus has been associated with hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis. Discontinue HYFTOR immediately if symptoms of hypersensitivity occur. (5.1)
- *Serious Infection*: Serious infections, including opportunistic infections and latent viral infections, such as progressive multifocal leukoencephalopathy, have been reported with oral sirolimus. Discontinue HYFTOR immediately if symptoms of infection occur. (5.2)
- *Malignancy*: Oral sirolimus has been associated with malignancy, including lymphoma and skin cancer. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using HYFTOR. (5.3)
- *Hyperlipidemia*: Oral sirolimus has been associated with increased serum cholesterol and triglycerides requiring treatment. Monitor for hyperlipidemia during treatment. (5.4)
- *Interstitial Lung Disease (ILD)/Non-infectious Pneumonitis*: Oral sirolimus has been associated with ILD, sometimes fatal. Discontinue HYFTOR if ILD symptoms occur. (5.5)
- *Immunizations:* During treatment with HYFTOR, vaccinations may be less effective. Avoid use of live vaccines during treatment with HYFTOR. (5.6)
- *Embryo-Fetal Toxicity*: Based on animal studies, HYFTOR can cause fetal harm. Use of effective contraception is recommended for females of reproductive potential prior to and throughout treatment, and for 12 weeks after final dose of HYFTOR. (5.7, 8.1, 8.3)
- *Male Infertility*: Oral sirolimus has been associated with azoospermia and oligospermia. Advise males that HYFTOR may impair fertility. (5.8, 8.3, 13.1)

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

Most common adverse reactions (≥1%) are dry skin, application site irritation, pruritus, acne, acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Nobelpharma America, LLC at 1 (877) 375-0825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- *CYP3A4 Inhibitors:* During concomitant use of HYFTOR with CYP3A4 inhibitors, monitor for adverse reactions of HYFTOR. (7.1)
- *Substrates and Inhibitors of CYP3A*: During concomitant use of HYFTOR with drugs that are both substrates and inhibitors of CYP3A, monitor for adverse reactions of the CYP3A substrate and inhibitor. (7.2)

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

Lactation: Breastfeeding not recommended. (8.2)

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

101-101-02
Revised: 5/2025

Appendix 4. Delgocitinib Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Janus kinase inhibitor
Bioavailability	Maximum plasma concentration was 1.53 nanograms/milliliter
Distribution and Protein Binding	Protein binding: 22-29%; Volume of distribution not reported
Elimination	75% of total dose after oral administration was found unchanged in the urine
Half-Life	21 hours
Metabolism	Metabolized primarily through CYP3A enzyme pathway. Drug interaction studies with delgocitinib have not been conducted.

Appendix 5: Key Inclusion Criteria for Delgocitinib Trial

Population	Adults with moderate to severe chronic hand eczema
Intervention	Delgocitinib topical cream
Comparator	Placebo
Outcomes	Improvement in eczema symptoms to clear or almost clear
Timing	16 weeks
Setting	Outpatient

Appendix 6. Sirolimus Pharmacology and Pharmacokinetic Properties.[15]

Parameter	
Mechanism of Action	Inhibits activation of the mammalian target of rapamycin (mTOR). Exact mechanism of action in the treatment of angiofibromas is unknown.
Bioavailability	Not applicable
Distribution and Protein Binding	No evidence of sirolimus systemic accumulation after topical application
Elimination	Studies have not been conducted on metabolism of topical sirolimus
Half-Life	Studies have not been conducted on metabolism of topical sirolimus
Metabolism	Studies have not been conducted on metabolism of topical sirolimus

Appendix 7: Key Inclusion Criteria for Sirolimus Trial

Population	Adults and children aged 3 years and older
Intervention	Sirolimus 0.2% gel applied twice daily in doses based upon age
Comparator	Placebo
Outcomes	Improvements in size and redness of facial angiofibromas
Timing	12 weeks
Setting	Outpatient

Appendix 8: Prior Authorization Criteria

Topical Agents for Inflammatory Skin Disease

Goal(s):

- Restrict dermatological drugs only for funded OHP diagnoses. Treatments are funded on the OHP for severe forms of certain inflammatory skin diseases including: psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis rubra pilaris, discoid lupus and vitiligo. Treatments for mild or moderate psoriasis, mild or moderate atopic dermatitis, seborrheic dermatitis, keratoderma and other hypertrophic and atrophic conditions of skin are not funded.
- Allow case-by-case review for members covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program.

Length of Authorization:

- From 6 to 12 months

Requires PA:

- Non-preferred topical medications for inflammatory skin conditions.
- All topical medications approved for treatment of inflammatory skin conditions for adults 21 years and older.
- This PA does not apply to oral or injectable targeted immune modulators for psoriasis or atopic dermatitis which are subject to separate clinical PA criteria.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Ages and Evidence-Supported Indications for Topical Drugs Approved for Inflammatory Skin Conditions

Generic Drug Name	Brand Name	Minimum Age	Indication (severity)

Anthralin Shampoo Anthralin Cream	ZITHRANOL	12 years 18 years	Plaque Psoriasis
Calcipotriene cream, solution, and ointment Calcipotriene foam	DOVONEX SORILUX	18 years 4 years	Plaque Psoriasis
Calcipotriene/Betamethasone ointment, suspension, foam Calcipotriene/Betamethasone cream	TACLONEX ENSTILAR WYNZORA	12 years 18 years	Plaque Psoriasis
Calcitriol ointment	VECTICAL	2 years	Plaque Psoriasis
Crisaborole 2% ointment	EUCRISA	3 months	Atopic Dermatitis (Mild-to-Moderate)
Delgocitinib 2% cream	ANZUPGO	18 years	Chronic Hand Eczema (Moderate-to-Severe)
Halobetasol propionate/Tazarotene Lotion	DUOBRII	18 years	Plaque Psoriasis
Pimecrolimus 1% cream	ELIDEL	2 years	Atopic Dermatitis (Mild-to-Moderate)
Roflumilast 0.05% cream Roflumilast 0.15% cream Roflumilast 0.3% cream Roflumilast 0.3% foam Roflumilast 0.3% foam	ZORYVE	2-5 years 6 years 6 years 9 years 12 years	Atopic Dermatitis (Mild-to-Moderate) Atopic Dermatitis (Mild-to-Moderate) Plaque Psoriasis Seborrheic Dermatitis Plaque Psoriasis
Ruxolitinib 1.5% cream	OPZELURA	2 years 12 years	Atopic Dermatitis (Mild-to-Moderate) Nonsegmental Vitiligo
Sirolimus 0.2% gel	HYFTOR	6 years	Facial Angiofibromas Associated with Tuberous Sclerosis Complex (TSC)
Tacrolimus 0.03% ointment	PROTOPIC	2 years	Atopic Dermatitis (Moderate-to-Severe)
Tacrolimus 0.1% ointment	PROTOPIC	18 years	Atopic Dermatitis (Moderate-to-Severe)
Tapinarof 1% cream	VTAMA	2 years 18 years	Atopic Dermatitis Plaque Psoriasis
Tazarotene cream and gel	TAZORAC	12 years	Plaque Psoriasis

Table 2. Topical First-Line Treatment Options Based on Disease Severity

Atopic Dermatitis (AD)	• Mild to Moderate AD: Low-, Medium-, or High-Potency Corticosteroids* for 2-4 weeks or Calcineurin Inhibitors (pimecrolimus, tacrolimus) • Severe AD: High to Super-High Potency Corticosteroids for 2 weeks or Tacrolimus
Plaque Psoriasis (PsO)	• Mild to Moderate PsO: Moderate- to High-Potency Corticosteroids* for 4 weeks, Calcineurin Inhibitors (pimecrolimus, tacrolimus) for 8 weeks, Vitamin D Analogues (calcitriol, calcipotriene) for 4 weeks, or Tazarotene for 8 weeks[1] • Severe PsO: High to Super-High Potency Corticosteroids for 4 weeks[1]
Nonsegmental Vitiligo	• Mild to Severe Vitiligo: Moderate- to High-Potency Corticosteroids* for 2 months or Calcineurin Inhibitors (pimecrolimus, tacrolimus) for 3 months[2]
Note: *Strength of corticosteroid determined by patient age, site of inflammation, and severity of the condition	

Table 3. Potency Of Topical Corticosteroid Preparations Using U.S. Classification[3]

Potency Group	Corticosteroid	Strength	Formulation
Lowest Potency (Group 7)	Hydrocortisone Base and Hydrocortisone Acetate	0.5%, 1.0%, 2.0%	cream, ointment, gel, lotion, solution

Low Potency (Group 6)	Alcometasone dipropionate	0.05%	cream, ointment
	Betamethasone valerate	0.05%	lotion
	Desonide	0.05%	cream
	Fluocinolone acetonide	0.01%	cream, oil, shampoo, solution
	Triamcinolone acetonide	0.1%	cream
Medium-Low Potency (Group 5)	Betamethasone dipropionate	0.05%	lotion
	Betamethasone valerate	0.1%	cream
	Betamethasone valerate	0.01%	cream, lotion
	Desonide	0.05%	lotion, ointment
	Fluocinolone acetonide	0.025%	cream
	Flurandrenolide	0.05%	cream
	Fluticasone propionate	0.05%	cream
	Hydrocortisone butyrate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Prednicarbate	0.1%	cream
	Triamcinolone acetonide	0.1%	lotion
Medium Potency (Group 4)	Betamethasone valerate	0.12%	foam
	Desoximetasone	0.05%	cream
	Fluocinolone acetonide	0.025%	ointment
	Fluocinolone acetonide	0.2%	cream
	Flurandrenolide	0.05%	ointment
	Halcinonide	0.025%	cream
	Hydrocortisone probutate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Mometasone furoate	0.1%	cream, lotion, solution
	Prednicarbate	0.1%	ointment
Medium-High Potency (Group 3)	Amcinonide	0.1%	cream, lotion
	Betamethasone valerate	0.1%	ointment
	Diflorasone diacetate	0.05%	cream
	Fluocinonide	0.05%	cream
	Fluticasone propionate	0.005%	ointment
	Halcinonide	0.1%	ointment, solution
	Triamcinolone acetonide	0.5%	cream
	Triamcinolone acetonide	0.1%	ointment
High Potency (Group 2)	Amcinonide	0.1%	ointment
	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	cream, lotion
	Betamethasone dipropionate, unaugmented (Diprosone®)	0.05%	cream, ointment
	Desoximetasone	0.25%	cream, ointment, spray
	Desoximetasone	0.05%	gel
	Diflorasone diacetate	0.05%	ointment

	Fluocinonide	0.05%	cream, gel, ointment, solution
	Halcinonide	0.1%	cream
	Mometasone furoate	0.1%	ointment
	Triamcinolone acetonide	0.5%	ointment
Super-High Potency (Group 1)	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	gel, ointment
	Clobetasol propionate	0.05%	cream, foam, gel, lotion, ointment, shampoo, spray
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.1%	cream
	Flurandrenolide	4 mcg/cm^2	tape
	Halobetasol propionate	0.05%	cream, ointment

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for treatment of severe ~~inflammatory~~ skin disease? Severe disease is defined as:[4] • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: 1. At least 10% body surface area involved OR 2. Hand, foot, face, or mucous membrane involvement	**Yes:** Go to #6	**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. Is there documentation of disease severity based on DLQI (or other validated scale) AND body surface area (BSA) involvement?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~4.~~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.)? Examples include quality of life scores indicating moderate disease (DLQI ≥ 6)	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity
6. Does the patient meet the age requirements per the FDA label? Note: minimum ages for commonly prescribed drugs are listed in **Table 1**	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~7. Is the diagnosis plaque psoriasis, atopic dermatitis, chronic hand eczema, or nonsegmental vitiligo?	**Yes:** Go to #8	**No:** Go to #10
~~6.~~8. Is the requested product preferred?	**Yes**: Approve for 6 months	**No**: Go to #9
~~7.~~9. Does the patient have a documented contraindication, intolerance or failed trials of at least 1 topical corticosteroid and 1 additional non-steroidal preferred agent (Table 2)?	**Yes:** Document drug and dates trialed, and intolerances or contraindications (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
~~8.~~10. Is the diagnosis facial angiofibroma associated with tuberous sclerosis complex?	**Yes:** Go to #11	**No:** Go to #16

Approval Criteria		
~~9.~~11. Is there documentation of functional impairment, ulceration, recurrent bleeding, infection, or pain related to the facial angiofibromas?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical necessity
~~10.~~12. Is the medication prescribed by a dermatologist, neurologist, or in consultation with another provider with expertise in managing tuberous sclerosis complex (TSC) and its complications?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient of childbearing potential?	**Yes:** Go to #14	**No:** Approve for 12 weeks
14. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant and has the patient been advised to use effective contraception during therapy and for 12 weeks after stopping treatment?	**Yes:** Approve for 12 weeks	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~16. Is the request for an FDA approved indication and age OR is supporting literature provided?	**Yes**: Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for plaque psoriasis, atopic dermatitis, chronic hand eczema, or nonsegmental vitiligo ?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved after treatment with topical therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI from when treatment started OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score or attainment of clear or almost clear skin?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request to renew therapy for treatment of facial angiofibroma due to TSC?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there provider documentation of response to therapy (improvement in size and redness of skin lesions)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

**The Health Evidence Review Commission has stipulated via Guideline Note 21 that mild and moderate uncomplicated inflammatory skin conditions including psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis rubra pilaris, and discoid lupus are not funded. Uncomplicated is defined as no functional impairment; and/or involving less than 10% of body surface area and no involvement of the hand, foot, or mucous membranes.*

References:

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2. *Eleftheriadou, V., Atkar, R., Batchelor, J., McDonald, B., etal., British Association of Dermatologists guidelines for the management of people with vitiligo 2021*. Br J Dermatol, 186: 18-29. https://doi.org/10.1111/bjd.20596*
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P&T/DUR Review: 12/25 (DM); 12/22; 6/22; 12/20; 10/20; 7/19; 5/19; 3/18; 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06
Implementation: TBD, 2/1/23; 7/1/22; 1/1/2021, 11/1/20; 8/19/19; 4/16/18; 10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06