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 1st, 2022 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	R. Citron (OSU)
	D. Approval of Minutes	R. Citron (OSU)
	E. Department Update	A. Gibler (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Quarterly Utilization Reports	
	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. Asthma Guidance Update with a Focus on Changes for Managing Patients with Mild Asthma	
	2. Population Trends in the Use of Migraine Preventative Treatments	

IV. DUR NEW BUSINESS

1:40 PM	A. Polypharmacy Drug Utilization Evaluation	
	1. Drug Utilization Evaluation	D. Engen (OSU)
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

1:55 PM	B. Early Periodic Screening Diagnosis and Treatment (EPSDT) 1. Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	J. Ickes (OHA/HSD) S. Fletcher (OSU)
	V. DUR OLD BUSINESS	
2:20 PM	A. Sedatives Prior Authorization Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
	VI. PREFERRED DRUG LIST NEW BUSINESS	
2:35 PM	A. Growth Hormone Prior Authorization Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
2:50 PM	BREAK	
3:05 PM	B. Drugs for Asthma/COPD Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
3:20 PM	C. Influenza Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
3:40 PM	D. Topical Products for Inflammatory Skin Conditions Class Update and New Drug Evaluations 1. Class Update/Prior Authorization Criteria 2. Zoryve™ (roflumilast cream) New Drug Evaluation 3. Vtama® (tapinarof cream) New Drug Evaluation 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:55 PM	VII. EXECUTIVE SESSION	
4:50 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS	
	IX. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Patrick DeMartino, MD	Physician	Pediatrician	Portland	December 2022
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, Dental3	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2024
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2024
Vacant	Physician			December 2024

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, October 6th, 2022 1:00 - 5:00 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: Bill Origer, MD; Patrick DeMartino, MD; Tim Langford, PharmD; Cat Livingston, MD; Caryn Mickelson, PharmD; Robin Moody, MPH; Eddie Saito, PharmD

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

Audience: Becky Martin, SK Life Science; Bill McDougall, Biogen; Brandie Feger, Advanced Health CCO; **Brandon Yip, Sanofi**; Car Livingston, Health Share; Chris Tanaka, ViiVhealthcare; Evie Knisely; Fabiola Garcia, Biocodex; Garth Wright, Genentech; Jennifer Shear, Jazz Pharmaceuticals; Jenny Todenhagen, Genentech; **Jessica Chardoulias, Novo Nordisk**; Jim Slater; John Stancil, Artia Solutions; Kailey Skelton, PacificSource Health Plan; **Kaitlin Nguyen, ViiV Healthcare**; Kaitlyn Molina, Samaritan Health Plan; **John Flatt, Marinus**; Kara, Genzyme; Luara Jeffcoat, Abbvie; Lori McDermott, Viking HCS**; Lynda Finch, Biogen**; Mark Kantor, AllCare CCO; Matt Worthy, OHSU; Melissa Bailey-Hall; Michael Foster, BMS; Michele Sabados, Alkermes; Mike Donabedian, Sarepta Therapeutics; Minha Choi, Biogen; Nana Ama Kuffour, IHN; Nguyen Trinh; Paul Thompson, Alkermes; Rick Frees, Vertex Pharmaceuticals; Saghi Maleki, Takeda Pharmaceuticals; **Shirley Quach, Norvartis**; **Sophia Yun, Janssen Scientific Affairs**; **Stuart O'Brochta**, **Gilead**; Sydney Thomas; Teion Turner, UCB Pharma; Terry Lee, Gilead; Tiffany Jones; Tiina Andrews, UHA; Tom Telly; Trish Olson, SK Life Science Inc.; **Troy Whitworth, Neurelis**; Uche Mordi, BMS; YJ Shukla, EOCCO Moda Health; Erin Nowak, Abbvie

(*) Provided verbal testimony
Written testimony: Posted to OSU Website

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I. CALL TO ORDER

A. Roll Call & Introductions
- Called to order at approx. 1:02 p.m., introductions by Committee and staff

B. Approval of Agenda - Antiepileptic Drug Class Update with New Drug Evaluation (NDE) pulled off consent agenda to allow for discussion and public comment

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

D. Approval of August 2022 Minutes presented by Roger Citron
ACTION: Motion to approve, 2nd, all in favor

E. Department Update provided by Trevor Douglass, DC

II. CONSENT AGENDA TOPICS

A. TIMS DERP Summary
Recommendations:
- No PDL changes recommended based on clinical review
- Modify prior authorization (PA) criteria to reflect updated indications for risankizumab, baricitinib, and ustekinumab
- Evaluate costs in executive session

B. Colony Stimulating Factors Literature Scan
Recommendations:
- No PDL changes recommended based on clinical review
- Evaluate costs in executive session

C. P&T Annual Report
No Public Comment was offered
ACTION: Motion to approve, 2nd, all in favor

III. PREFERRED DRUG LIST NEW BUSINESS

A. Antiepileptic Class Update and NDE: Sara Fletcher, PharmD
Recommendations:
- Designate ganaxolone as voluntary non-preferred and implement safety edit to restrict to FDA approved indication and dose
- Change class name to “Outpatient Antiepileptics” and include new autoinjector formulation of midazolam as non-preferred
- No other PDL changes recommended based on clinical information
- Evaluate costs in executive session

Public Comment: John Flatt, Marinus; Troy Whitworth, Neurelis
ACTION: Motion to approve, 2nd, all in favor

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B. Multiple Sclerosis Class Update with NDE: Deanna Moretz, PharmD
Recommendations:
- No PDL changes recommended based on clinical review
- Consolidate injectable MS criteria as presented
- Evaluate costs in executive session
Public Comment: Shirley Quach, Novartis; Lynda Finch, Biogen; Sophia Yun, Janssen
ACTION: The Committee recommended amending the oral MS PA criteria to remove required step therapy
Motion to approve, 2nd, all in favor

C. Human Immunodeficiency Virus (HIV) Lit Scan: Sara Fletcher, PharmD
Recommendations:
-Designate stavudine, didanosine, saquinavir, and nelfinavir as non-preferred on the PDL
Public Comment: Kaitlin Nguyen, ViiV Healthcare; Stuart O'Brochta, Gilead
ACTION: Motion to approve, 2nd, all in favor

D. GLP-1 Receptor Agonists & SGLT-2 Inhibitors Drug Class Updates with NDE:
Kathy Sentena, PharmD
Recommendations:
- Include the glucose-dependent insulinotropic polypeptide (GIP) therapies in the PA criteria with GLP-1 RAs
- Update the GLP-1 RA PA criteria to remove concomitant prandial insulin restriction
- Maintain SGLT2 inhibitors PA criteria and require renal function evaluation annually
- Maintain tirzepatide as non-preferred on the preferred drug list (PDL) and subject to the GLP-1 RA and GLP + GIP agonist PA criteria
- Evaluate costs in executive session
Public Comment: Jessica Chardoulias, Novo Nordisk
ACTION: Motion to approve, 2nd, all in favor

E. Dupixent® (dupilumab) PA Criteria Update: Deanna Moretz, PharmD
Recommendations:
- Update clinical prior authorization (PA) criteria to: Approve treatment of eosinophilic esophagitis in patients aged 12 years of age and older who weigh at least 40 kg
- Allow appropriate step therapy for PPIs in patients with eosinophilic esophagitis
- Approve treatment of moderate-to-severe atopic dermatitis in patients not adequately controlled with topical therapies, or in patients 6 months or older when topical therapies are not advisable
Public Comment: Brandon Yip, Sanofi
ACTION: Motion to approve, 2nd, all in favor

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IV. DUR NEW BUSINESS

A. Attention-Deficit/Hyperactivity Disorder (ADHD) Literature Scan and DUE: Dave Engen, PharmD**;** Sarah Servid, PharmD

Recommendations:

- No PDL changes recommended based on clinical review
- Revise PA criteria to reflect maximum age and dose limits as specified in product labeling or supported compendia
- Exclude patients initiated on an ADHD medication as a child from PA if they exceed maximum age limit
-Evaluate costs in executive session

Motion to approve, 2nd, all in favor

B. Lumateperone Drug Use Evaluation: Ted Williams, PharmD

Recommendations:

- Consider outreach to providers and regions with higher use of lumateperone to identify reasons for practice differences
- Consider provider education programs to raise awareness of the similar outcomes and higher costs associated with lumateperone
- No changes to utilization controls for lumateperone are warranted at this time

Motion to approve, 2nd, all in favor

C. Annovera® (ethinyl estradiol/segesterone) PA Update: Sara Fletcher, PharmD

Recommendations:

- Implement 300-day minimum supply for POS prescriptions
- Require POS override for 1st refill if less than 300 days from previous prescription fill
- Implement quantity limit for 2nd refill within 12-months

Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

Members Present: Bill Origer, MD; Patrick DeMartino, MD; Tim Langford, PharmD; Cat Livingston, MD; Caryn Mickelson, PharmD; Eddie Saito, PharmD

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

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VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. **TIMS DERP Summary**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

B. **Colony Stimulating Factors Literature Scan**
Recommendation: Make Granix (tbo-filgrastim) non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

C. **Antiepileptic Class Update and NDE:**
Recommendation: Make Nayzilam (midazolam spray) and Valtoco (diazepam spray) preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

D. **Multiple Sclerosis Class Update with NDE:**
Recommendation: Make peginterferon (Plegridy) preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

E. **GLP-1 Receptor Agonists & SGLT-2 Inhibitors Drug Class Updates with NDE**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

F. **ADHD Literature Scan & DUE**
Recommendation: Make Qelbree® (viloxazine) preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: April 2021 - March 2022

Eligibility	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
Total Members (FFS & Encounter)	1,186,439	1,195,359	1,203,243	1,212,729	1,222,901	1,230,474	1,238,036	1,249,056	1,258,864	1,270,424	1,276,063	1,284,291	1,235,657
FFS Members	108,646	109,364	105,833	109,457	112,375	108,825	111,347	109,132	112,664	117,322	110,548	109,789	110,442
OHP Basic with Medicare	7,998	8,048	7,967	8,110	8,273	8,141	8,429	8,051	8,195	8,488	8,161	8,271	8,178
OHP Basic without Medicare	11,063	11,039	10,911	10,947	11,003	10,811	10,888	10,718	10,697	10,889	10,579	10,500	10,837
ACA	89,585	90,277	86,955	90,400	93,099	89,873	92,030	90,363	93,772	97,945	91,808	91,018	91,427
Encounter Members	1,077,793	1,085,995	1,097,410	1,103,272	1,110,526	1,121,649	1,126,689	1,139,924	1,146,200	1,153,102	1,165,515	1,174,502	1,125,215
OHP Basic with Medicare	79,521	80,356	81,391	82,240	83,030	83,993	84,715	86,139	86,570	87,412	88,084	89,468	84,410
OHP Basic without Medicare	67,232	67,380	67,600	67,639	67,674	68,041	67,983	68,260	68,173	68,310	68,509	68,469	67,939
ACA	931,040	938,259	948,419	953,393	959,822	969,615	973,991	985,525	991,457	997,380	1,008,922	1,016,565	972,866

Gross Cost Figures for Drugs	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	YTD Sum
Total Amount Paid (FFS & Encounter)	$100,665,669	$97,869,708	$104,579,212	$100,692,045	$103,954,317	$105,556,200	$97,452,164	$100,565,206	$102,922,270	$102,189,758	$98,364,609	$115,473,676	$1,230,284,834
Mental Health Carve-Out Drugs	$11,749,655	$11,387,567	$12,047,001	$11,631,916	$11,834,111	$11,281,482	$10,845,527	$11,007,015	$11,203,325	$11,265,200	$10,866,485	$12,312,835	$137,432,120
OHP Basic with Medicare	$7,638	$5,904	$5,729	$2,855	$5,699	$4,725	$8,509	$5,705	$2,848	$279	$11,277	$7,858	$69,027
OHP Basic without Medicare	$4,597,447	$4,351,340	$4,647,664	$4,468,750	$4,505,475	$4,324,722	$4,007,144	$4,054,056	$4,178,170	$4,088,431	$3,906,575	$4,431,427	$51,561,203
ACA	$7,064,107	$6,950,377	$7,307,973	$7,071,936	$7,234,386	$6,874,575	$6,748,202	$6,864,482	$6,934,726	$7,084,088	$6,858,558	$7,775,199	$84,768,609
FFS Physical Health Drugs	$4,754,690	$4,392,860	$4,835,200	$4,615,975	$4,679,918	$4,547,061	$4,527,691	$4,495,222	$4,574,471	$4,998,704	$4,520,044	$5,050,728	$55,992,564
OHP Basic with Medicare	$162,078	$168,217	$178,739	$167,274	$169,504	$164,733	$165,578	$171,138	$158,437	$187,415	$177,448	$202,733	$2,073,293
OHP Basic without Medicare	$1,225,033	$1,016,511	$1,183,292	$1,156,152	$1,203,299	$1,138,809	$1,201,476	$1,027,605	$1,116,748	$1,132,413	$989,597	$1,094,633	$13,485,569
ACA	$3,214,016	$3,090,980	$3,333,421	$3,159,504	$3,144,462	$3,051,649	$3,004,511	$3,132,397	$3,199,235	$3,530,344	$3,242,247	$3,637,889	$38,740,655
FFS Physician Administered Drugs	$1,356,219	$1,176,350	$1,706,851	$1,380,778	$1,273,138	$1,107,466	$1,451,820	$1,230,113	$1,095,710	$1,084,467	$1,504,831	$1,614,726	$15,982,471
OHP Basic with Medicare	$103,084	$157,882	$115,366	$109,816	$126,364	$105,013	$79,267	$165,213	$183,068	$162,355	$150,889	$128,245	$1,586,560
OHP Basic without Medicare	$289,205	$266,609	$740,489	$357,635	$209,919	$222,045	$584,257	$413,339	$236,106	$188,666	$393,524	$448,541	$4,350,335
ACA	$522,307	$375,412	$409,544	$534,484	$475,370	$448,279	$427,900	$362,142	$419,699	$405,833	$641,884	$595,706	$5,618,559
Encounter Physical Health Drugs	$64,933,438	$63,403,956	$66,964,920	$64,706,301	$65,518,538	$64,362,743	$63,588,314	$66,091,474	$68,071,457	$67,363,193	$64,533,852	$73,979,405	$793,517,591
OHP Basic with Medicare	$411,634	$391,933	$456,747	$424,867	$398,755	$416,221	$399,423	$446,477	$473,165	$424,902	$394,612	$440,739	$5,079,477
OHP Basic without Medicare	$15,983,078	$15,499,845	$16,277,253	$15,562,646	$16,284,287	$15,447,764	$15,476,512	$16,311,264	$16,377,550	$16,514,732	$16,150,492	$17,631,528	$193,516,952
ACA	$47,693,043	$46,708,425	$49,192,831	$47,565,187	$47,804,940	$47,641,242	$46,957,165	$48,575,148	$50,328,085	$49,558,110	$47,138,766	$54,874,062	$584,037,005
Encounter Physician Administered Drugs	$17,871,667	$17,508,974	$19,025,240	$18,357,074	$20,648,611	$24,257,448	$17,038,812	$17,741,382	$17,977,306	$17,478,194	$16,939,396	$22,515,982	$227,360,087
OHP Basic with Medicare	$916,775	$900,098	$973,938	$833,185	$934,912	$899,654	$986,593	$939,383	$908,205	$1,058,132	$857,009	$1,047,964	$11,255,850
OHP Basic without Medicare	$3,790,054	$4,177,233	$4,095,403	$4,016,128	$3,955,134	$10,676,495	$3,765,959	$4,182,092	$4,261,807	$3,763,358	$3,973,760	$5,479,006	$56,136,429
ACA	$12,832,034	$12,139,993	$13,760,079	$12,927,961	$15,392,398	$12,348,586	$12,114,318	$12,345,390	$12,602,581	$12,402,340	$11,855,839	$15,764,174	$156,485,692

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 28, 2022

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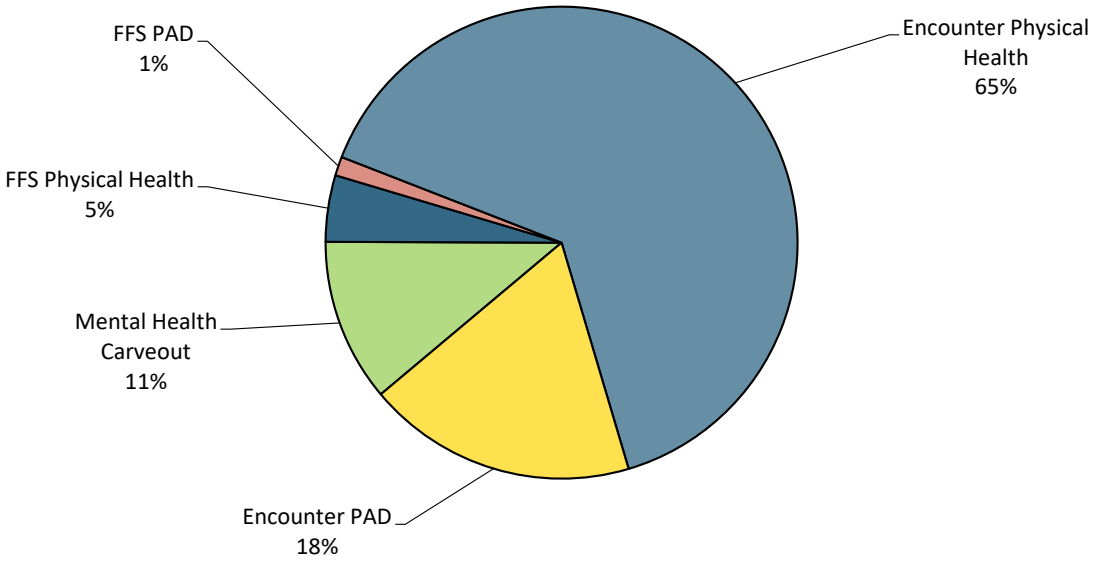
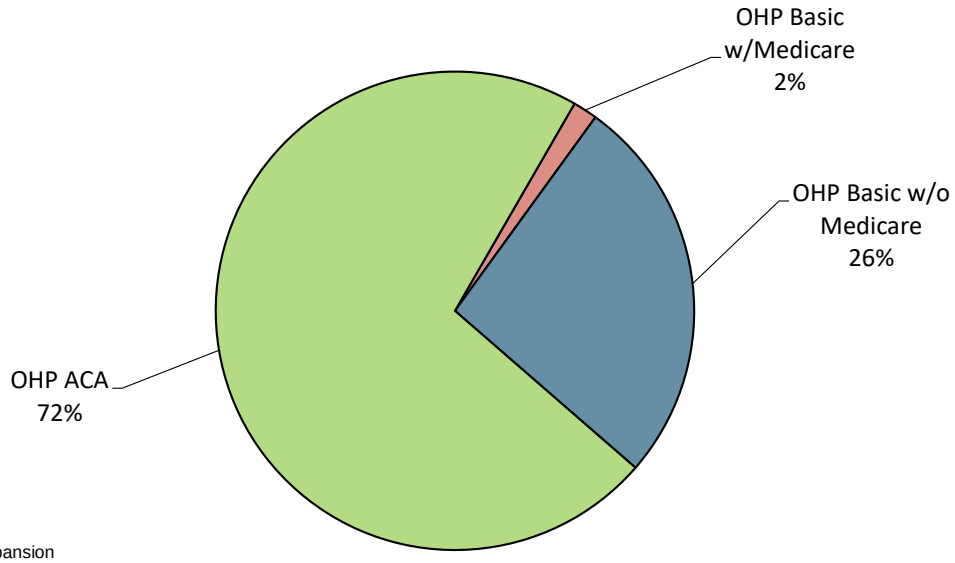
YTD Percent Paid Amounts





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

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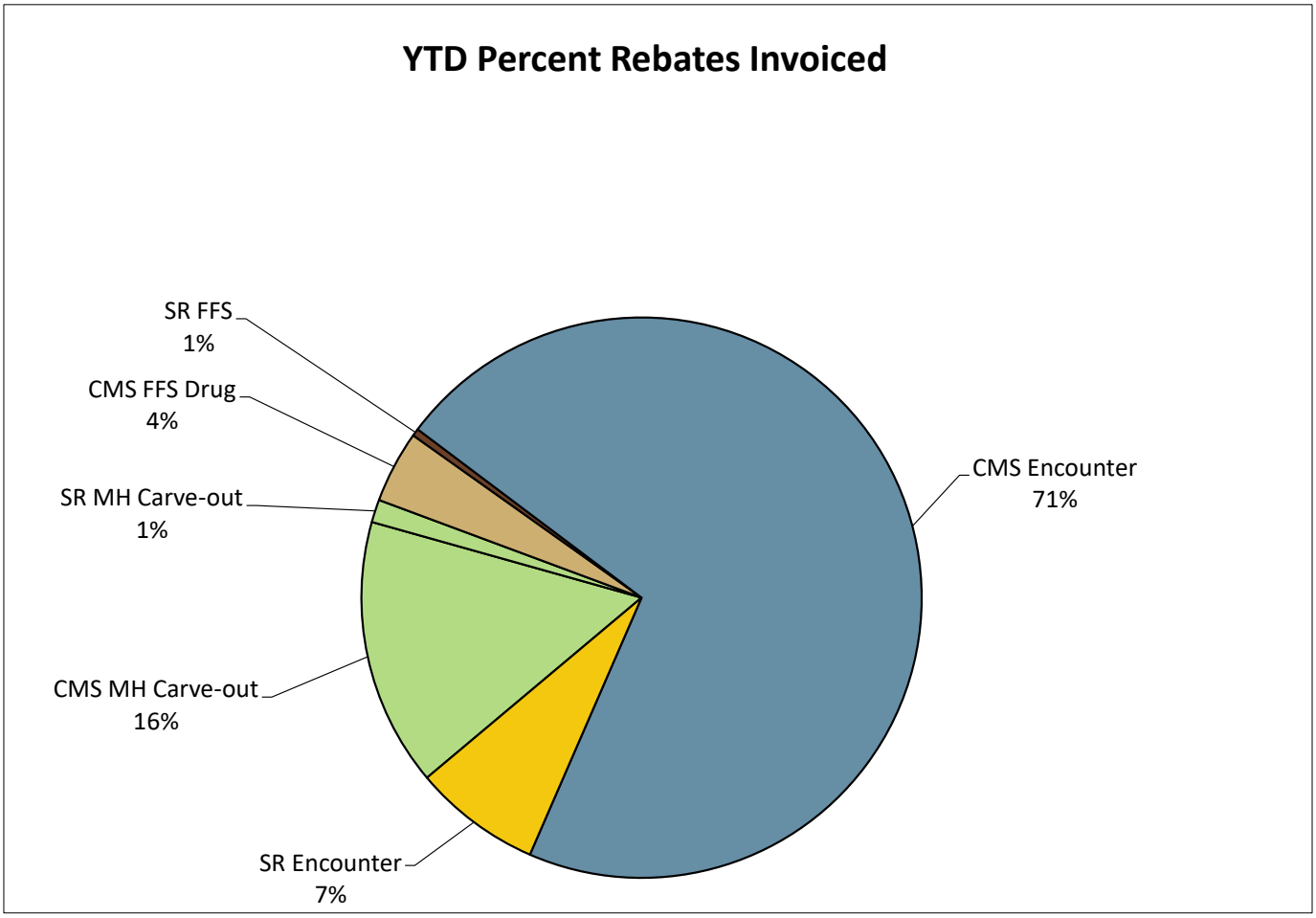
Pharmacy Utilization Summary Report: April 2021 - March 2022

Quarterly Rebates Invoiced	2021-Q2	2021-Q3	2021-Q4	2022-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$119,964,250	$115,533,134	$112,913,069	$120,722,592	$469,133,045
CMS MH Carve-out	$19,331,841	$18,516,840	$17,609,601	$17,091,410	$72,549,692
SR MH Carve-out	$1,416,074	$1,615,300	$1,793,886	$1,338,990	$6,164,250
CMS FFS Drug	$5,337,467	$4,613,930	$4,766,432	$4,819,949	$19,537,779
SR FFS	$512,938	$452,218	$548,725	$497,416	$2,011,298
CMS Encounter	$84,671,311	$81,368,669	$79,504,305	$88,782,079	$334,326,364
SR Encounter	$8,694,619	$8,966,176	$8,690,120	$8,192,747	$34,543,662

Quaterly Net Drug Costs	2021-Q2	2021-Q3	2021-Q4	2022-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$183,150,339	$194,669,428	$188,026,571	$195,305,451	$761,151,789
Mental Health Carve-Out Drugs	$14,436,307	$14,615,371	$13,652,380	$16,014,120	$58,718,178
FFS Phys Health + PAD	$12,371,766	$12,538,188	$12,059,870	$13,456,134	$50,425,959
Encounter Phys Health + PAD	$156,342,266	$167,515,870	$162,314,321	$165,835,196	$652,007,652



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

Last Updated: October 28, 2022

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

Pharmacy Utilization Summary Report: April 2021 - March 2022

Gross PMPM Drug Costs (Rebates not Subtracted)	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$84.85	$81.87	$86.91	$83.03	$85.01	$85.78	$78.72	$80.51	$81.76	$80.44	$77.08	$89.91	$82.99
Mental Health Carve-Out Drugs	$9.90	$9.53	$10.01	$9.59	$9.68	$9.17	$8.76	$8.81	$8.90	$8.87	$8.52	$9.59	$9.28
FFS Physical Health Drugs	$43.76	$40.17	$45.69	$42.17	$41.65	$41.78	$40.66	$41.19	$40.60	$42.61	$40.89	$46.00	$42.26
FFS Physician Administered Drugs	$12.48	$10.76	$16.13	$12.61	$11.33	$10.18	$13.04	$11.27	$9.73	$9.24	$13.61	$14.71	$12.09
Encounter Physical Health Drugs	$60.25	$58.38	$61.02	$58.65	$59.00	$57.38	$56.44	$57.98	$59.39	$58.42	$55.37	$62.99	$58.77
Encounter Physician Administered Drugs	$16.58	$16.12	$17.34	$16.64	$18.59	$21.63	$15.12	$15.56	$15.68	$15.16	$14.53	$19.17	$16.84

Claim Counts	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
Total Claim Count (FFS & Encounter)	1,134,580	1,124,659	1,163,195	1,130,263	1,128,395	1,095,450	1,096,328	1,096,804	1,110,163	1,122,238	1,047,406	1,197,850	1,120,611
Mental Health Carve-Out Drugs	186,942	183,884	191,468	188,042	190,945	185,222	183,253	185,522	188,495	190,997	179,938	204,527	188,270
FFS Physical Health Drugs	41,551	41,038	41,605	38,323	38,661	36,754	35,423	35,165	35,896	38,022	34,914	38,379	37,978
FFS Physician Administered Drugs	10,486	10,007	9,918	9,984	9,340	9,096	9,470	8,804	9,114	10,358	9,305	11,052	9,745
Encounter Physical Health Drugs	773,379	768,149	796,244	770,759	772,713	754,708	751,429	751,122	765,431	773,035	717,771	819,791	767,878
Encounter Physician Administered Drugs	122,222	121,581	123,960	123,155	116,736	109,670	116,753	116,191	111,227	109,826	105,478	124,101	116,742

Gross Amount Paid per Claim (Rebates not Subtracted)	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$88.73	$87.02	$89.91	$89.09	$92.13	$96.36	$88.89	$91.69	$92.71	$91.06	$93.91	$96.40	$91.49
Mental Health Carve-Out Drugs	$62.85	$61.93	$62.92	$61.86	$61.98	$60.91	$59.18	$59.33	$59.44	$58.98	$60.39	$60.20	$60.83
FFS Physical Health Drugs	$114.43	$107.04	$116.22	$120.45	$121.05	$123.72	$127.82	$127.83	$127.44	$131.47	$129.46	$131.60	$123.21
FFS Physician Administered Drugs	$129.34	$117.55	$172.10	$138.30	$136.31	$121.75	$153.31	$139.72	$120.22	$104.70	$161.72	$146.10	$136.76
Encounter Physical Health Drugs	$83.96	$82.54	$84.10	$83.95	$84.79	$85.28	$84.62	$87.99	$88.93	$87.14	$89.91	$90.24	$86.12
Encounter Physician Administered Drugs	$146.22	$144.01	$153.48	$149.06	$176.88	$221.19	$145.94	$152.69	$161.63	$159.14	$160.60	$181.43	$162.69

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.27	$21.84	$22.89	$22.20	$22.40	$21.83	$22.02	$22.59	$22.85	$23.10	$23.25	$23.56	$22.57
Mental Health Carve-Out Drugs	$17.26	$17.01	$17.05	$17.01	$16.68	$16.14	$16.23	$16.45	$16.36	$16.49	$16.42	$16.30	$16.62
FFS Physical Health Drugs	$73.18	$72.77	$78.47	$78.01	$78.26	$77.72	$78.06	$81.31	$81.06	$84.24	$84.27	$86.86	$79.52
Encounter Physical Health Drugs	$21.23	$20.83	$21.92	$21.11	$21.48	$20.96	$21.15	$21.80	$22.22	$22.25	$22.40	$22.75	$21.67

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$479.23	$431.54	$468.26	$527.60	$512.72	$505.20	$517.77	$547.53	$535.67	$538.92	$607.36	$648.32	$526.68
Mental Health Carve-Out Drugs	$1,030.75	$1,018.33	$1,013.53	$1,012.88	$1,019.09	$1,005.24	$964.65	$932.31	$950.89	$946.44	$965.63	$963.34	$985.26
FFS Physical Health Drugs	$236.21	$193.78	$228.97	$270.46	$261.83	$273.16	$319.52	$291.24	$273.49	$283.28	$317.10	$347.85	$274.74
Encounter Physical Health Drugs	$460.37	$414.30	$448.37	$508.13	$492.42	$484.34	$495.29	$533.68	$522.54	$526.36	$595.31	$637.10	$509.85

Generic Drug Use Percentage	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
Generic Drug Use Percentage	87.1%	85.9%	86.8%	88.3%	87.9%	87.5%	88.0%	88.3%	87.9%	88.3%	89.3%	90.0%	88.0%
Mental Health Carve-Out Drugs	95.5%	95.5%	95.4%	95.5%	95.5%	95.5%	95.5%	95.3%	95.4%	95.4%	95.4%	95.4%	95.4%
FFS Physical Health Drugs	74.7%	71.7%	74.9%	77.9%	76.7%	76.5%	79.4%	77.8%	75.9%	76.3%	80.6%	82.9%	77.1%
Encounter Physical Health Drugs	85.7%	84.3%	85.4%	87.1%	86.6%	86.1%	86.6%	87.1%	86.7%	87.1%	88.2%	89.0%	86.7%

Preferred Drug Use Percentage	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Avg Monthly
Preferred Drug Use Percentage	89.71%	89.80%	89.70%	89.98%	89.92%	89.83%	89.81%	89.76%	89.69%	89.78%	89.74%	89.82%	89.8%
Mental Health Carve-Out Drugs	93.02%	93.05%	93.04%	93.11%	93.07%	93.01%	93.12%	92.99%	93.00%	92.97%	92.95%	92.97%	93.0%
FFS Physical Health Drugs	94.35%	94.38%	94.36%	94.68%	94.90%	94.70%	94.80%	94.96%	94.98%	94.52%	94.43%	94.54%	94.6%
Encounter Physical Health Drugs	88.68%	88.79%	88.67%	89.00%	88.91%	88.82%	88.78%	88.73%	88.65%	88.78%	88.73%	88.84%	88.8%

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 28, 2022

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2022

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA*	Antipsychotics, 2nd Gen	$6,926,459	16.4%	5,501	$1,259	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,937,419	9.3%	1,744	$2,258	Y
3	VRAYLAR*	Antipsychotics, 2nd Gen	$3,333,692	7.9%	2,879	$1,158	Y
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,108,700	5.0%	968	$2,178	Y
5	REXULTI*	Antipsychotics, 2nd Gen	$2,008,654	4.8%	1,672	$1,201	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	$1,012,560	2.4%	147	$6,888	Y
7	ARISTADA	Antipsychotics, Parenteral	$827,963	2.0%	344	$2,407	Y
8	TRINTELLIX	Antidepressants	$802,573	1.9%	1,904	$422	V
9	INVEGA*	Antipsychotics, 2nd Gen	$696,088	1.6%	1,775	$392	V
10	SERTRALINE HCL	Antidepressants	$573,868	1.4%	58,985	$10	Y
11	BUPROPION XL	Antidepressants	$548,441	1.3%	41,892	$13	Y
12	DULOXETINE HCL	Antidepressants	$527,049	1.2%	37,271	$14	Y
13	FLUOXETINE HCL	Antidepressants	$479,055	1.1%	43,355	$11	Y
14	STRATTERA*	ADHD Drugs	$475,619	1.1%	1,773	$268	Y
15	TRAZODONE HCL	Antidepressants	$473,946	1.1%	46,654	$10	
16	CAPLYTA*	Antipsychotics, 2nd Gen	$454,567	1.1%	328	$1,386	V
17	ESCITALOPRAM OXALATE	Antidepressants	$402,305	1.0%	41,324	$10	Y
18	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$314,812	0.7%	26,565	$12	
19	LAMOTRIGINE	Outpatient Antiepileptics	$312,361	0.7%	29,075	$11	Y
20	CHOLBAM*	Bile Therapy	$298,829	0.7%	3	$99,610	N
21	Epoetin Beta Esrd Use	Physican Administered Drug	$288,998	0.7%	39	$7,410	
22	LYBALVI*	Antipsychotics, 2nd Gen	$283,289	0.7%	227	$1,248	V
23	ATOMOXETINE HCL*	ADHD Drugs	$276,427	0.7%	5,692	$49	Y
24	BIKTARVY	HIV	$253,526	0.6%	105	$2,415	Y
25	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$244,380	0.6%	252	$970	Y
26	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$243,957	0.6%	19,456	$13	Y
27	SPRAVATO*	Antidepressants	$237,002	0.6%	145	$1,634	V
28	VENLAFAXINE HCL ER	Antidepressants	$235,449	0.6%	18,840	$12	Y
29	BUPROPION XL	Antidepressants	$229,073	0.5%	1,231	$186	V
30	LAMOTRIGINE ER	Outpatient Antiepileptics	$224,787	0.5%	3,198	$70	V
31	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$219,895	0.5%	19,715	$11	Y
32	VILAZODONE HCL	Antidepressants	$209,037	0.5%	1,447	$144	V
33	TRIKAFTA*	Cystic Fibrosis	$205,077	0.5%	21	$9,766	N
34	VENLAFAXINE HCL ER	Antidepressants	$185,288	0.4%	2,372	$78	V
35	CONCERTA*	ADHD Drugs	$185,050	0.4%	513	$361	Y
36	Elosulfase Alfa, Injection	Physican Administered Drug	$184,540	0.4%	12	$15,378	
37	CITALOPRAM HBR	Antidepressants	$176,970	0.4%	20,573	$9	Y
38	AMITRIPTYLINE HCL*	Antidepressants	$172,548	0.4%	13,914	$12	Y
39	MIRTAZAPINE	Antidepressants	$156,510	0.4%	11,424	$14	Y
40	OLANZAPINE*	Antipsychotics, 2nd Gen	$153,585	0.4%	12,315	$12	Y
		Top 40 Aggregate:	**$30,880,347**		**475,650**	**$3,983**	
		All FFS Drugs Totals:	**$42,207,701**		**705,697**	**$585**	

*** 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 28, 2022

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2022

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	CHOLBAM*	Bile Therapy	$298,829	3.3%	3	$99,610	N
2	Epoetin Beta Esrd Use	Physican Administered Drug	$288,998	3.2%	39	$7,410	
3	BIKTARVY	HIV	$253,526	2.8%	105	$2,415	Y
4	TRIKAFTA*	Cystic Fibrosis	$205,077	2.3%	21	$9,766	N
5	CONCERTA*	ADHD Drugs	$185,050	2.0%	513	$361	Y
6	Elosulfase Alfa, Injection	Physican Administered Drug	$184,540	2.0%	12	$15,378	
7	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$147,687	1.6%	610	$242	
8	MAVENCLAD*	Multiple Sclerosis	$137,148	1.5%	2	$68,574	N
9	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$127,279	1.4%	227	$561	Y
10	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$127,082	1.4%	7	$18,155	
11	IBRANCE*	Antineoplastics, Newer	$125,866	1.4%	9	$13,985	
12	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$121,870	1.3%	12	$10,156	Y
13	EPIDIOLEX*	Outpatient Antiepileptics	$120,136	1.3%	75	$1,602	N
14	LANTUS SOLOSTAR*	Diabetes, Insulins	$119,919	1.3%	373	$321	Y
15	Etonogestrel Implant System	Physican Administered Drug	$105,572	1.2%	152	$695	
16	Aflibercept Injection	Physican Administered Drug	$104,072	1.2%	228	$456	
17	ELIQUIS	Anticoagulants, Oral and SQ	$99,696	1.1%	259	$385	Y
18	ADVATE	Antihemophilia Factors	$98,568	1.1%	7	$14,081	
19	HUMIRA(CF) PEN*	Targeted Immune Modulators	$98,144	1.1%	35	$2,804	Y
20	Iron Sucrose Injection	Physican Administered Drug	$96,065	1.1%	258	$372	
21	COSENTYX PEN (2 PENS)*	Targeted Immune Modulators	$94,821	1.0%	23	$4,123	Y
22	SABRIL	Outpatient Antiepileptics	$93,000	1.0%	3	$31,000	N
23	VYVANSE*	ADHD Drugs	$91,324	1.0%	604	$151	Y
24	Inj Pembrolizumab	Physican Administered Drug	$90,687	1.0%	42	$2,159	
25	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$80,597	0.9%	1,317	$61	Y
26	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$78,569	0.9%	2,437	$32	Y
27	METYROSINE	STC 71 - Other Hypotensives	$74,815	0.8%	3	$24,938	
28	SKYRIZI PEN*	Targeted Immune Modulators	$73,130	0.8%	4	$18,283	N
29	Mirena, 52 Mg	Physican Administered Drug	$68,114	0.8%	104	$655	
30	PROMACTA	Thrombocytopenia Drugs	$61,999	0.7%	8	$7,750	Y
31	STELARA*	Targeted Immune Modulators	$59,975	0.7%	17	$3,528	N
32	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$55,027	0.6%	2	$27,513	
33	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$54,587	0.6%	30	$1,820	Y
34	REVLIMID	STC 30 - Antineoplastic	$52,723	0.6%	7	$7,532	
35	Hyqvia 100mg Immuneglobulin	Physican Administered Drug	$51,643	0.6%	11	$4,695	
36	VERZENIO*	Antineoplastics, Newer	$49,959	0.6%	4	$12,490	
37	XYWAV	STC 47 - Sedative Non-barbiturate	$49,889	0.6%	6	$8,315	N
38	Mifepristone, Oral, 200 Mg	Physican Administered Drug	$48,046	0.5%	605	$79	
39	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$44,788	0.5%	5	$8,958	N
40	BUDESONIDE-FORMOTEROL FUMAR	Corticosteroids/LABA Combination, Inhaled	$43,026	0.5%	203	$212	Y
		Top 40 Aggregate:	**$4,361,843**		**8,382**	**$10,791**	
		All FFS Drugs Totals:	**$9,033,355**		**112,374**	**$589**	

*** 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 28, 2022

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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
futibatinib	Lytgobi
teclistamab-cqyv	Tecvayli
tremelimumab	Imjudo

Recommendation:

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

Oncology Agents

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

Length of Authorization:
- Up to 1 year

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

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

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

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

Approval Criteria

9. 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 11/1/2022)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

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

Generic Name	Brand Name
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
futibatinib	LYTGOBI
gilteritinib	XOSPATA

Generic Name	Brand Name
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
mobecertinib	EXKIVITY
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
nivolumab; relatlimab-rmbw	OPDUALAG
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA

Generic Name	Brand Name
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
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

Generic Name	Brand Name
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF

Generic Name	Brand Name
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK

Generic Name	Brand Name
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

P&T/DUR Review: 6/2020 (JP)
Implementation: 10/1/22

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. New orphan drugs

Generic Name	Brand Name
sodium thiosulfate	PEDMARK

Recommendation:

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

Orphan Drugs

Goal(s):

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

Length of Authorization:

- Up to 6 months

Requires PA:

- See Table 1 (pharmacy and physician administered claims)

Covered Alternatives:

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

Table 1. Indications for orphan drugs based on FDA labeling

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

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

Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 wks) Initial: 0.4mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 wks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥1 yr: 0.9 mg/kg	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 yrs	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests • Blood homocysteine levels-If homocysteine elevated, assess folate, vitamin B12, and vitamin B6
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 mo AND ≥0.39 m^2 BSA	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels	N/A	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months **≥ 20 kg**	N/A

			Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 yr	Initial: 1 mg/kg SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 1 yr	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 390 mcg/kg once daily after 1 week on initial dose, as tolerated	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Mitapivat (PYRUKYND)	Hemolytic anemia in adults with pyruvate kinase (PK) deficiency.	≥ 18 yr	Initial: 5 mg twice daily Titration: If Hb less than normal range or patient required transfusion in previous 8 weeks, then after 4 weeks increase to 20 mg twice daily, and after another 4 weeks increase to 50 mg twice daily. Max dose: 50 mg twice daily Discontinuation should include down-titration.	Baseline/Ongoing Monitoring • Hgb, transfusion requirement

Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)	≥ 3 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments Max dose: 120 mcg/kg once daily; not to exceed 6 mg	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Plasminogen, human-tvmh (RYPLAZIM)	Treatment of patients with plasminogen deficiency type 1 (hypoplasmino-genemia)	N/A	6.6 mg/kg body weight given IV every 2 to 4 days	Baseline Monitoring • Plasminogen activity level (allow 7 day washout if receiving with fresh frozen plasma) • CBC (bleeding) Ongoing Monitoring • Trough Plasminogen activity level 72 hours after initial dose and every 12 wks with ongoing therapy • CBC (bleeding)
Sodium thiosulfate (PEDMARK)	Decrease ototoxicity associated with cisplatin infusions lasting ≤ 6 hours. Not approved for use with longer infusions.	≥ 1 mo to <18 yr	< 5 kg: 10 g/m^2 5-10 kg: 15 g/m^2 >10 kg: 20 g/m^2	Baseline Monitoring • Serum potassium and sodium
Sutimlimab-jome (ENJAYMO)	Decrease need for RBC transfusion due to hemolysis in cold agglutinin disease (CAD)	≥ 18 yr	Dosed IV infusion weekly for two weeks, then every two weeks thereafter. **39 to <75 kg** 6500 mg **≥75 kg** 7500 mg	Baseline Monitoring • Vaccination against encapsulated bacteria (*Neisseria meningititides* (any serogroup), *Streptococcus pneumonia,* and *Haemophilus influenza*) at least prior to treatment or as soon as possible if urgent therapy needed

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

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

Approval Criteria		
3. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5

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

P&T/DUR Review: 6/22(SF); 4/22; 12/21; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: 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 2022
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	5	3	0	2	0.0%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	1,895	470	0	1,424	1.3%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	7,595	2,109	1	5,485	5.3%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	92,073	17,506	77	74,478	64.8%	**19.0%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	29,420	7,766	13	21,621	20.7%	**N/A**
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	802	186	0	619	0.6%	**N/A**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	7	7	0	0	0.0%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	798	212	0	585	0.5%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	468	178	0	289	0.3%	**N/A**
PA (Drug/Age Precaution)	Products containing Codeine or Tramadol being billed and patient is less than 18 years of age	Set alert/Pay claim	5	3	0	2	0.0%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	32	25	0	7	0.0%	**78.1%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	9,057	2,640	0	6,410	6.3%	**N/A**
		Totals	**142,157**					

ProDUR Report for July through September 2022
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	7,458	1,288	6,170	77,641	9.6%	17.3%
ER	Prozac (Fluoxetine)	5,667	993	4,493	56,877	10.0%	17.5%
ER	Lexapro (Escitalopram)	5,276	885	4,391	56,537	9.3%	16.8%
ER	Celexa (Citalopram)	2,103	321	1,781	25,730	8.2%	15.3%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Trazodone	6,525	1,169	5,356	60,718	10.7%	17.9%
ER	Wellbutrin (Bupropion)	6,181	1,194	5,986	75,802	8.2%	19.3%
ER	Cymbalta (Duloxetine)	4,939	898	4,168	50,300	9.8%	18.2%
ER	Effexor (Venlafaxine)	2,831	449	2,382	30,267	9.4%	15.9%
ER	Remeron (Mirtazapine)	1,726	260	1,466	15,088	11.4%	15.1%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	4,405	999	3,405	31,593	13.9%	22.7%
ER	Abilify (Aripiprazole)	3,585	550	3,035	28,471	12.6%	15.3%
ER	Zyprexa (Olanzapine)	2,479	556	1,923	19,626	12.6%	22.4%
ER	Risperdal (Risperidone)	1,917	411	1,506	13,710	14.0%	21.4%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	3,465	597	2,867	35,521	9.8%	17.2%
ER	Lorazepam	324	90	234	12,236	2.6%	27.8%
ER	Alprazolam	216	45	171	7,598	2.8%	20.8%
ER	Diazepam	132	34	98	4,247	3.1%	25.8%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	6,106	1,202	4,902	46,591	13.1%	19.7%
ER	Intuniv (Guanfacine ER)	1,708	266	1,441	12,534	13.6%	15.6%
ER	Suboxone (Buprenorphine/Naloxone)	101	33	68	1,941	5.2%	32.7%

ProDUR Report for July through September 2022

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	3,892	204	238	551	7	2,611	83	0	198
ER	August	4,578	216	354	720	5	2,986	115	0	182
ER	September	653	17	31	112	1	452	17	0	23
	Total =	**9,123**	**437**	**623**	**1,383**	**13**	**6,049**	**215**	**0**	**403**
	Percentage of Total Overrides =		**4.8%**	**6.8%**	**15.2%**	**0.1%**	**66.3%**	**2.4%**	**0.0%**	**4.4%**

ProDUR Report for July through September 2022			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
July	DA	2	83.91
	DC	2	$4,501.99
	DD	34	$7,157.32
	ER	319	$74,027.61
	HD	1	$21.56
	ID	37	$6,427.24
	LR	4	$188.17
	MC	2	$303.00
	MX	3	$86.37
	PG	1	$2,103.91
	TD	13	$3,745.89
		July Savings =	**$98,646.97**
August	DC	1	$146.99
	DD	16	$2,890.40
	ER	33	$6,227.93
	ID	13	$3,641.06
	LR	2	$6.57
	TD	3	$135.83
		August Savings =	**$13,048.78**
September	DD	22	$5,239.20
	ER	91	$18,331.45
	HD	6	$44.70
	ID	19	$2,767.52
	MC	1	$219.99
	NF	2	$89.88
	TD	1	$104.20
		September Savings =	**$26,796.94**
		Total 3Q2022 Savings =	**$138,492.69**

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Retro-DUR Intervention History by Quarter FFY 2021 - 2022

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		13	6	9
		Unique Patients Identified		13	6	9
		Total Faxes Successfully Sent		8	4	6
		Prescriptions Changed to Recommended Within 6 Months of Intervention		7	3	2
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$39,736	$14,321	$3,507
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	61	103	74	56
		Unique Patients Identified	62	105	75	58
		Total Faxes Successfully Sent	45	73	41	38
		Prescriptions Changed to Recommended Within 6 Months of Intervention	36	69	37	16
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$57,612	$75,118	$30,611	$6,287
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	191	262	131	121
		Unique Patients Identified	193	271	131	122
		Total Faxes Successfully Sent	133	186	77	82
		Prescriptions Changed to Recommended Within 6 Months of Intervention	100	119	53	32
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$53,545	$48,986	$8,190	$2,196

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Retro-DUR Intervention History by Quarter FFY 2021 - 2022

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	30	33	13	11
		Total Faxes Successfully Sent	9	17	7	6
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	4	5	6	5
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	3	1	
		Prescriptions Unchanged after 3 Months of Fax Sent	19	14	5	
		Safety Monitoring Profiles Identified	1	2		1
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$4,028	$7,882	$5,795	$4,592

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	801	796	783	791
		High risk patients identified	9	4	7	6
		Prescribers successfully notified	9	4	7	3
		Patients with change in antipsychotic drug in following 90 days	1			
		Patients with continued antipsychotic therapy in the following 90 days	7	3	7	3
		Patients with discontinuation of antipsychotic therapy in the following 90 days	1			

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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	81	45	55	59
		Total prescribers identified	80	45	54	59
		Prescribers successfully notified	80	44	50	59
		Patients with claims for the same antipsychotic within the next 90 days	35	27	26	27
		Patients with claims for a different antipsychotic within the next 90 days	5	1	4	

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Retro-DUR Intervention History by Quarter FFY 2021 - 2022

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	5	213	80	72
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	2	55	23	22
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	19	604	172	177
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed		109	26	9
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	13	18	14	26
		Letters Sent To Providers	9	9	10	13
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	50	40	1	
		Letters Sent To Providers	64	45		
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	16	13	15	22
		Letters Sent To Providers	11	11	8	13
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed			18	48
		Letters Sent To Providers			5	9
	Lock-In	RetroDUR Profiles Reviewed	20	4	11	19
		Letters Sent To Providers	4		2	1
		Locked In	3	0	2	1
	Polypharmacy	RetroDUR Profiles Reviewed	1			12
		Letters Sent To Providers				1

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	90	85	102	97
		Total prescribers identified	90	85	102	97
		Prescribers successfully notified	90	85	102	89
		Patients with discontinuation of therapy within next 90 days	25	19	30	47
		Patients with new prescription for naloxone within next 90 days	3	7	6	3
		Average number of sedative drugs dispensed within next 90 days	22	27	27	12
		Average number of sedative prescribers writing prescriptions in next 90 days	22	27	27	12
	Denied Claims due to Antipsychotic Dose Consolidation	Total patients identified	79	56	75	9
		Patients with a paid claim for the drug (based on HSN) within 14 days	53	30	34	5
		Patients without a paid claim within 14 days	26	26	41	4
	Oncology Denials	Total patients identified	1	2	1	3
		Total prescribers identified	1	2	1	3
		Prescribers successfully notified	1	2	1	2
		Patients with claims for the same drug within the next 90 days	1	1		2
		Patients with claims for any oncology agent within the next 90 days	1	2		2

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
	TCAs in Children	TCA Denials in Children	27	29	57	48
		Total patients identified	6	13	22	8
		Total prescribers identified	6	13	22	8
		Prescribers successfully notified	3	11	13	4
		Patients with claims for a TCA within the next 90 days		2	3	1
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days	2		1	

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April 2022 Volume 12 Issue 3

Asthma Guidance Update with a Focus on Changes for Managing Patients with Mild Asthma

Kathy Sentena, Pharm.D., Oregon State University Drug Use Research and Management Group

Asthma is a common illness affecting over 11% of Oregonians with a higher prevalence among those on the Oregon Health Plan (OHP).[1,2] The incidence of asthma emergency department visits is approximately 50 per 10,000 individuals per year in the United States (U.S.), representing substantial morbidity and cost to the health care system.[3] In 2013 the total cost of asthma in the U.S. was $81.9 billion.[4] Annual prescription medications for asthma accounted for the highest per-person expense, estimated at $1,830 based on 2015 dollars.[4]

Controlling asthma symptoms through reductions in exacerbations is a primary target of asthma management. Recommendations for managing asthma have recently been revised by the Global Initiative for Asthma (GINA).[5] Inhaled corticosteroids (ICS)/rapid onset long-acting beta-agonists (LABA) are referred to as single maintenance and reliever therapy (SMART) or maintenance reliever therapy (MART). This combination is being used to manage patients with persistent asthma and more recently also recommended as reliever therapy for patients with mild asthma.[5,6] Budesonide/formoterol is used for this purpose due to the pharmacokinetics of formoterol, which provides a quick onset suitable for reliever therapy and budesonide as the anti-inflammatory component. The purpose of this newsletter is to review the evidence and recommendations for mild asthma.

Evidence for ICS/formoterol as Reliever Therapy

Evidence has demonstrated that combination ICS and rapid acting LABA (e.g., budesonide/formoterol), used as reliever therapy reduces asthma exacerbations requiring medical visits or systemic corticosteroids, compared to short-acting beta-agonist (SABA) reliever therapy.[5] Additional data suggests that this combination improves asthma control and quality of life, with less reliance on adherence to daily maintenance therapy. A steroid-sparing effect with budesonide/formoterol may prevent adverse events related to systemic corticosteroid exposure. Studies have found no increase in adverse events with budesonide/formoterol therapy compared to daily ICS or ICS/LABA used with SABA for symptom relief.[5] Specifics on evidence used to support the use of budesonide/formoterol as reliever therapy are displayed in **Table 1**.

Table 1. Evidence for the Use of Budesonide/formoterol as Reliever Therapy

Study Design	Results	Strength of Evidence
Beasely, et al[7] (n=668), START		
DB, PC, OL, PG, RCT Adult patients with mild asthma 52 weeks	**Annualized exacerbation* rate:** • Albuterol 100mcg as needed: 0.400 • Budesonide 200mcg twice daily + as needed albuterol: 0.175 • Budesonide 200mcg/ formoterol 6 mcg as needed: 0.195 Budesonide/formoterol vs. albuterol: RR 0.49; 95% CI, 0.33 to 0.72; P<0.001 Budesonide/formoterol vs. budesonide: RR 1.12; 95% CI, 0.70 to 1.79; P = 0.65	Low
O'Byrne,et al[8] (n=3836), SYGMA 1		
DB, PG RCT Patients 12 and older with mild asthma 52 weeks	**Mean percentage of weeks with well controlled asthma per patient†:** • Placebo twice daily + terbutaline 0.5mg as needed: 31.1% • Placebo twice daily + budesonide 200mcg/ formoterol 6 mcg as needed: 34.4% • Budesonide 200mcg twice daily + terbutaline 0.5mg as needed: 44.4% Budesonide-formoterol vs. terbutaline: OR 1.14; 95% CI, 1.00 to 1.30; P=0.046	Moderate
Bateman, et al[9] (n=4176), SYGMA 2		
DB, PG, Phase 3, RCT Patients 12 and older with mild asthma 52 weeks	**Annualized rate of severe exacerbations:** • Placebo twice daily + budesonide 200mcg/ formoterol 6mcg as needed: 0.11 • Budesonide 200mcg twice daily + terbutaline 0.5mg as needed: 0.12 Noninferiority margin was set at 1.2 Rate ratio: 0.97; upper one-sided 95% confidence limit 1.16	Low
Key: * Exacerbation that required one or more of the following: an urgent medical care consultation, a prescription of systemic glucocorticoids, or an episode of high beta-agonist use; † As needed therapy was used to determine symptom control as measured via an electronic patient diary with asthma symptom scores, night-time awakenings, morning peak expiratory flow, inhaler-monitor data, and		

an electronic case-report form for the additional use of inhaled or systemic glucocorticoids.
Abbreviations: CI = confidence interval; DB = double blind; OL = open-label; PC = placebo controlled; PG = parallel group; RCT = randomized controlled trial; RR = relative rate.

Budesonide/formoterol reduced exacerbation rates as demonstrated by the primary endpoint in the START and SYGMA 2 studies and as a secondary endpoint in the SYGMA 1 study, which found a reduction with the use of low dose budesonide/formoterol compared to as-needed SABA (relative rate [RR] 0.40; 95% confidence interval [CI], 0.18 to 0.86; p<0.05).[7] Scheduled maintenance budesonide therapy was more effective in reducing asthma exacerbations compared to as-needed budesonide-formoterol.[7,8]

The START trial results are limited by a high chance of performance bias, due to the open label design. SYGMA 2 was a noninferiority trial that started out as a superiority trial; however, a change in trial design was made due to exacerbation rates which were lower than expected and high adherence to maintenance therapy. The primary endpoint was calculated based on the full analysis set; however, use of the per protocol population is a more accurate assessment of efficacy in a noninferiority trial. Both SYGMA trials and the START trial were funded by AstraZeneca, the manufacturer of Symbicort (budesonide/formoterol) and Pulmicort (budesonide).

Budesonide/formoterol Policies and Best Practices

- Adolescent and adult dose of budesonide/formoterol:
  - **Reliever therapy**: 160/4.5 mcg as needed
  - **MART**: up to 54 mcg metered dose of formoterol
- Budesonide/formoterol should not be used with other LABAs or ICS/LABA combination products
- Budesonide/formoterol is a preferred therapy for Fee-for-Service (FFS) Oregon Health Plan (OHP) patients

Guideline Recommendations

Treatment recommendations for individuals with asthma are based on symptoms and divided into steps. Asthma guidelines recommend therapies based on intermittent or persistent symptoms; however, preferred therapy for each step may differ according to the guideline in which recommendations are based (**Table 2**).

Table 2. Asthma Treatment Guideline Recommendations for Adolescents and Adults*[5,10,11]

Steps	Guideline	Treatment Recommendations
Step 1	GINA	As-needed low dose ICS-formoterol or As-needed SABA with ICS
	NAEPP	SABA as-needed
	NICE+	SABA as-needed
Step 2	GINA	As-needed low dose ICS-formoterol or low-dose maintenance ICS
	NAEPP	Low-dose ICS and SABA as-needed OR Concomitant ICS and SABA as-needed
Step 3	GINA	Low dose maintenance ICS-formoterol or ICS/LABA with SABA as-needed
	NAEPP	Daily and as-needed combination low-dose ICS-formoterol
	NICE+	Daily ICS with SABA as-needed
Step 4	GINA	Medium dose maintenance ICS-formoterol or ICS/LABA with SABA as-needed
	NAEPP	Daily and as-needed combination medium-dose ICS-formoterol
	NICE+	MART regimen with low-dose ICS
Step 5	GINA	Add-on LAMA Consider high dose ICS-formoterol
	NAEPP	Daily medium- to high-dose ICS/LABA + LAMA and SABA as needed
	NICE+	Increase ICS dose to moderate maintenance dose
Step 6	NAEPP	Daily high-dose ICS/LABA + oral systemic corticosteroids + SABA as needed

Key: * Alternative treatment options are available in full guidelines; + Correlation of NICE recommendations to steps defined by other guidelines.
Abbreviations: GINA - Global Initiative for Asthma; ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; MART - maintenance reliever therapy; NAEPP - National Asthma Education and Prevention Program; NICE - National Institute for Health and Care Excellence; SABA – short-acting beta-agonist.

Recent GINA recommendations separate reliever therapy recommendations for adults and adolescents with asthma into two tracks (**Table 3**).[5] The change was prompted by evidence that the risk of severe asthma exacerbations exists in individuals with intermittent symptoms and this population experiences risk reduction with ICS-containing treatment. For individuals requiring daily controller therapy, MART is recommended.[5] For children 6-11 years, an ICS is recommended whenever a SABA is used, if not taking a daily maintenance ICS.[5]

Table 3. Asthma Reliever Therapy Recommendations for Adults and Adolescents[5]

Track	Therapy	Rationale
Track 1	Low-dose ICS-formoterol as reliever therapy	Risk reduction in severe exacerbations with ICS-formoterol compared to SABA reliever alone*
Track 2	SABA as reliever therapy with instructions to take ICS when SABA is used†	Alternate approach if patient has no exacerbations on current therapy and is likely to be adherent to controller therapy

Key: * Preferred therapy; † If not taking daily maintenance ICS
Abbreviations: ICS = inhaled corticosteroid; SABA = short-acting beta-agonist

The National Institute for Health and Care Excellence (NICE) provides guidance on asthma treatment based on symptoms but does not base recommendations on steps, as designated by other guidelines. Short-acting beta-agonist monotherapy is recommended NICE for reliever therapy and for those with infrequent, short-lived wheeze and normal lung function in adult patients.[10] NICE recommends daily ICS treatment as first-line maintenance therapy for adult patients with asthma.[10] MART is recommended for adult patients who have uncontrolled asthma on low-dose ICS and LABA, with or without a leukotriene receptor antagonist (LTRA), as maintenance therapy.

In 2020 the National Asthma Education and Prevention Program (NAEPP) updated treatment recommendations for adolescents and adults based on a review done by the Agency for Healthcare Research and Quality (AHRQ).[11] No changes to the recommendations were made for individuals with intermittent asthma (Step 1) for the use of as-needed SABA. Daily low-dose ICS with a SABA or as-needed concomitant ICS and SABA is recommended for mild persistent asthma (Step 2). MART therapy is recommended as the preferred therapy for moderate persistent asthma (Step 3 and Step 4) as daily and for as-needed treatment.[11] This was a strong recommendation based on moderate certainty of evidence.[11]

Considerations for implementing MART therapy based on NAEPP recommendations[11]:

- Individual is taking Step 3 (low-dose ICS) or Step 4 (medium-dose ICS) treatment
- The dose of MART maintenance therapy is ICS/formoterol 1-2 puffs once or twice daily and 1-2 puffs as needed for asthma symptoms
- The recommended formoterol dose is 4.5 mcg/inhalation, based on trial data

Conclusion

There is evidence for improved symptom control with the use of budesonide/formoterol as reliever therapy and as MART in adolescent and adult patients with asthma. Guideline recommendations vary on the level of asthma symptoms necessitating the use of MART therapy. Benefits of MART include a reduced risk of severe exacerbations, reduced steroid exposure and less reliance on compliance to daily maintenance treatments.

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References

1. Centers for Disease Control and Prevention. Most Recent Asthma State or Territory Data. 2019. Available at: cdc.gov/astha/most_recent_data_states.htm. Accessed February 9, 2022.
2. Oregon Health Authority. Asthma Among Oregon Health Plan Members. October 2017. Available at: www.oregon.gov/oha. Accessed February 11, 2022.
3. Centers for Disease Control and Prevention. Asthma Emergency Department (ED) Visits 2010-2018. Available at: cdc/gov/asthma/asthma_stats/asthma-ed-visits_2010-2018.html. Accessed February 11, 2022.
4. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008-2013. *Ann Am Thorac Soc*. 2018;15(3):348-356. doi:10.1513/AnnalsATS.201703-259OC
5. Global Initiative for Asthma. Global Strategy for Asthma Managment and Prevention, 2021. Available at: www.ginasthma.org. Accessed February 11, 2022.
6. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. *JAMA*. 2018;319(14):1485-1496. doi:10.1001/jama.2018.2769.
7. Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. *N Engl J Med*. 2019;380(21):2020-2030. doi:10.1056/NEJMoa1901963
8. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med*. 2018;378(20):1865-1876. doi:10.1056/NEJMoa1715274.
9. Bateman ED, Reddel HK, O'Byrne PM, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. *N Engl J Med*. 2018;378(20):1877-1887. doi:10.1056/NEJMoa1715275.
10. National Institute for Health and Care Excellence. Athma: diagnosis, monitoring and chronic asthma managment. NICE Guideline. November 2017. Available at: nice.org.uk/guidance/ng80. Acessed November 15, 2018.
11. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF, Pace W, Schatz M. Managing Asthma in Adolescents and Adults: 2020 Asthma Guideline Update From the National Asthma Education and Prevention Program. *JAMA*. 2020;324(22):2301-2317. doi:10.1001/jama.2020.21974.

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May 2022 Volume 12 Issue 4

Population Trends in the Use of Migraine Preventative Treatments

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Introduction

Migraine is a disorder characterized by recurrent attacks of headaches of moderate to severe intensity, often accompanied by photophobia, phonophobia, nausea, and vomiting.[1] A migraine headache condition can be classified as chronic if occurring on 15 or more days per month with migraine features on 8 or more days.[2] Episodic migraine is a similar condition, but headaches occur less frequently, typically between 4 to 14 days per month.[2] The prevalence and burden of self-reported migraine and severe headache in the United States (US) adult population is high, affecting roughly 1 out of every 6 Americans and 1 in 5 women over a 3-month period.[3]

In 2015, the prevalence of self-reported migraine or severe headache was highest in American Indian or Alaska Natives (18%) compared with Blacks (16%), Whites (15%), and Hispanics (15%) with the lowest prevalence in Asians (11%).[3] There is a higher burden of migraine in those aged 18 to 44 (18%), unemployed people (21%), those with family income less than $35,000 per year (20%), and the elderly and disabled (16%).[3] The percentage of persons with migraine with Medicaid health insurance coverage (26%) and uninsured people (17%) was higher than those with private insurance (15%).[3] In reproductive aged women, headache is the third leading cause of emergency department (ED) visits.[3]

Patients affected by frequent migraines may need preventive treatment in order to reduce the frequency and severity of attacks. This newsletter will describe population trends in use of migraine preventative agents and discuss a drug use evaluation (DUE) that analyzed the use of guideline-recommended migraine preventative therapy in the Oregon Medicaid Fee-For-Service (FFS) population.[4]

Oral Migraine Preventative Agents

Preventative therapy is indicated for people who experience 4 or more migraine headaches per month or if headaches last longer than 12 hours.[5] The 2012 American Academy of Neurology (AAN) and American Headache Society guideline recommends divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol and timolol as first-line therapies for migraine prevention (**Table 1**).[5]

Table 1. Classification of Migraine Preventative Therapies[5]

Level A: Medications with Established Efficacy	Divalproex Sodium, Sodium Valproate, Topiramate, Metoprolol, Propranolol, Timolol
Level B: Medications which are Probably Effective	Amitriptyline, Venlafaxine, Atenolol, Nadolol
Level C: Medications which are Possibly Effective	Lisinopril, Candesartan, Clonidine, Guanfacine, Carbamazepine, Nebivolol, Pindolol

High-quality evidence shows these agents should be offered to patients with episodic or chronic migraine to reduce migraine attack frequency and severity, improve function, and reduce disability.[5] Dosing should be initiated at a low dose and gradually increased as tolerated. An adequate trial to determine efficacy requires at least 8 weeks at goal dose range.[6] The full effect of prophylactic therapy may take up to 6 months. Due to the risk of congenital birth defects, valproate and topiramate should not be prescribed to women of childbearing potential who are not using reliable methods of birth control.[5]

The recently FDA-approved small molecule, oral calcitonin gene-related peptide (CGRP) inhibitors for migraine prevention, rimegepant and atogepant, have not been included in high-quality guidelines as of 2022. Approval for rimegepant as preventative therapy in adults with episodic migraine was based on one phase 2/3 study.[7] The mean number of migraine days per month at baseline was 7.8 days.[7] In this 12-week trial, rimegepant 75 mg every other day reduced the mean migraine days per month by -0.8 more than placebo (-4.3 versus -3.5 days; 95% confidence interval [CI], -1.46 to -0.20; p=0.0099).[7] Adverse events occurring in at least 2% of rimegepant-treated participants were nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection.[7] Seven (2%) participants who received rimegepant and 4 (1%) who received placebo discontinued the study due to an adverse event.[7]

A phase 3 trial also showed atogepant was more effective than placebo in reducing the mean number of migraine days per month over 12 weeks.[8] The mean number of migraine days per month at baseline ranged from 7.5 to 7.9 in the four groups (10 mg, 30 mg, 60 mg and placebo).[8] The mean differences from placebo in the change from baseline were −1.2 days with 10 mg atogepant (95% Confidence Interval [CI], −1.8 to −0.6), −1.4 days with 30 mg atogepant (95% CI, −1.9 to −0.8), and −1.7 days with 60 mg atogepant (95% CI, −2.3 to −1.2) (P<0.001 for all comparisons with placebo).[8] The most common adverse events in patients taking atogepant were constipation, nausea, and upper respiratory tract infections.[9] Nine (4%) participants who received atogepant 10 mg, 4 (1.8%) people who received atogepant 30 mg, 6 (2.6%) people who received atogepant 60 mg, and 6 (2.7%) participants who received placebo discontinued the study due to an adverse event.[8] Dosing of atogepant ranges from 10 mg to 30 mg to 60 mg per day depending on renal function and possible drug interactions with concomitant medications.[9]

Epidemiologic studies suggest approximately 38% of adults with migraines need preventive therapy, but only 3% to 13% currently use it.[10] Studies have shown oral preventive therapies are associated with a high degree of non-adherence (approximately 35–50%) mainly due to bothersome side effects and relatively low and inconsistent efficacy.[11,12] A 2014 systematic review assessed oral prophylaxis medication adherence and persistence among patients with migraine.[13] Adherence refers to the extent to which a patient follows prescribed directions with respect to timing, dose, and frequency.[13] Persistence refers to the time during which a patient remains on a prescribed medication after initiating therapy.[13] This review demonstrated a downward trend in migraine

prophylaxis adherence and persistence over time.[13] Observational studies (n=14) showed migraine preventative adherence ranges of 41% to 95% at 2 months, 21% to 80% at 6 months, and 35% to 56% at 12 months.[13] Persistence ranges of 41% to 88% at 2 months, 19% to 79% at 6 months, and 7% to 55% at 12 months were also reported.[13] There was a substantially lower rate of discontinuation among trials evaluating propranolol compared with amitriptyline or topiramate.[13] Adverse events including cognitive effects, somnolence, and weight gain, were the most common reason for discontinuation (24% for topiramate, 17% for amitriptyline, and 8% for propranolol).[13]

Injectable Migraine Preventative Agents: OnabotulinumtoxinA and CGRP Antagonists

OnabotulinumtoxinA is indicated for the prophylaxis of headaches in adults with chronic migraine who have headaches that occur at least 15 days per month and last four hours a day or longer.[14] The recommended re-treatment schedule is every 12 weeks.[14] Safety and efficacy of botulinum toxin have not been established for prophylaxis of episodic migraine.[14,15] The 2016 AAN guideline on therapeutic uses of botulinum toxin recommends onabotulinumtoxinA as a safe and effective treatment for chronic migraine to reduce the number of headache days (Level A effective).[15] OnabotulinumtoxinA is probably effective and should be considered to improve health-related quality of life (Level B effective).[15]

A 2018 Cochrane review assessed the effects of botulinum toxin for the prevention or reduction in frequency of chronic migraine in adults.[16] The number of chronic migraine days at baseline ranged from 12 to 20 days.[16] Pooled data from 2 trials (n=1384) showed that compared to placebo, botulinum toxin may reduce the number of migraine days per month in patients with chronic migraine by 2 days at 12 weeks post-treatment (95% CI -2.8 to -1.1, moderate-quality evidence).[16] Analysis of adverse events showed an increase in the risk ratio with treatment with botulinum toxin over placebo 30% (RR 1.28, 95% CI 1.12 to 1.47, moderate-quality evidence).[16] For every 100 participants, 60 experienced an adverse event in the botulinum toxin group compared with 47 in the placebo group.[16]

Three trials compared botulinum toxin with 2 alternative oral prophylactic medications (topiramate 100 to 200 mg/day and sodium valproate 250 mg twice daily).[16] Meta-analyses were not possible for number of migraine days, number of headache days or number of migraine attacks due to insufficient data, but individual trials reported no differences between groups for a variety of efficacy measures in the population of both chronic and episodic migraine participants (low-quality evidence).[16] In the botulinum toxin group 73 in every 100 people experienced any adverse event, and in the alternative oral treatment group 86 in every 100 treated people experienced an adverse event.[16] The difference in risk between groups of any adverse event was not statistically significant (P=0.67, low-quality evidence).[16] There was a difference in favor of botulinum toxin in the relative risk of withdrawing due to adverse events of 0.28 compared with the alternative prophylactic agents (95% CI 0.10 to 0.79, low-quality evidence).[16] The proportion of patients discontinuing treatment with botulinum toxin compared to alternative prophylactic agents was low (7%).[16]

Medications targeting CGRP or its receptor approved for migraine prevention include atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab and rimegepant. Atogepant and rimegepant are available as oral tablets. Eptinezumab is administered via intravenous infusion. Erenumab, fremanezumab and galcanezumab can be self-administered via subcutaneous injection. There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab and galcanezumab reduce the number of chronic migraine days per month (decrease of 1.8 to 3.5 days a month) compared to placebo.[17] For episodic migraine prevention, the number of migraine days per month were reduced with eptinezumab, erenumab, fremanezumab and galcanezumab compared to placebo, with a difference ranging from -0.7 to -2.8 days (moderate quality of evidence).[17] Evidence for CGRP inhibitors is limited to indirect treatment comparisons which prevents comparative efficacy assessment. These brand name medications are more costly compared to the generic availability of most of the oral prophylaxis agents.

Medicaid FFS Prior Authorization Requirements for CGRP antagonists:
Patient must have an adequate trial (at least 6 weeks) without response or have contraindications to 1 medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants.

Oregon FFS Medicaid Drug Use Evaluation Results

The purpose of a 2021 DUE was to determine what percentage of the Oregon FFS Medicaid population chronically utilized triptans and evaluate use of preventative migraine therapy for these patients.[4] Chronic use of triptans was defined as any three FFS claims within a 120-day period to indicate fills of triptan for three consecutive months.[4] In addition, the number of emergency department (ED) visits, and hospitalizations was assessed.[4] From October 2018 through September 2019, only a small percentage (1%) of Oregon FFS Medicaid patients had at least one triptan claim (n=1,178 patients).[4] Even fewer were chronic triptan users (n=169).[4] With an estimated 26% prevalence of Medicaid patients with migraines,[3] this finding may suggest: 1) the Oregon FFS Medicaid population has a lower prevalence of patients with migraines; 2) Medicaid patients are utilizing non-triptan therapies (such as acetaminophen or NSAIDs) more often;3) patients are not staying enrolled in FFS long enough to accurately identify patients with migraines based on claims data alone; or 4) FFS patients often have other insurance which may result in gaps in pharmacy claims data.[4] The majority of chronic triptan users were female and between the ages of 18 and 44 years old, which matches the expected demographics of patients with migraines based on self-reported data.[3]

Based on guideline recommendations, all patients meeting the definition of chronic triptan use would qualify for preventative migraine treatment.[4] However, only about half (54%) of chronic triptan users were prescribed an oral guideline-recommended prophylaxis agent.[4] When a prophylaxis agent was initiated, the majority of patients had at least 2 consecutive months of claims for that agent, which follows guideline recommendations of at least 8

weeks of prophylactic therapy to determine efficacy.[4] Anticonvulsants (47%) and beta-blockers (46%) were used more frequently than antidepressants (36%).[4] This is consistent with guidelines that do not recommend one specific prophylaxis agent over another, and instead recommend that patient-specific factors and comorbidities should be taken into account when choosing an appropriate agent.[4] Regardless of the specific medication being utilized, the majority of patients were prescribed medications with Level A evidence (**Table 1**).[4]

Because there were so few chronic triptan users (n=169) and even fewer who were also prescribed a preventative agent (n=92), the impact of prophylaxis therapy on triptan utilization, ED visits, and hospitalizations is unclear.[4] However, prophylaxis users did appear to use slightly less triptans (6.8 claims per year versus 7.1 claims per year for non-prophylaxis users).[4] Decreased triptan utilization implies fewer migraine days per month (a marker of prophylaxis agent efficacy).[4] Very few patients (4 to 5%) sought ED care for migraines.[4]

Oregon FFS Medicaid Drug Use Evaluation Limitations

The main limitation of this analysis is that there was no guaranteed way to ensure that the oral agents assessed for migraine prophylaxis were prescribed for migraine prophylaxis since all of these agents have other indications, including pain management for other chronic conditions.[4] Another limitation of this analysis is that it did not assess non-triptan abortive therapy use (such as non-steroidal anti-inflammatory drugs or acetaminophen) since these agents can be obtained over the counter and their use would have been difficult to identify.[4] Because this analysis only included patients with triptan claims, this population may under-represent the number of patients treated for migraine in the Oregon FFS Medicaid population.[4] For patients prescribed triptans, there may have been a gap in true representation of triptan utilization if patients paid cash for the triptan (rather than using their Oregon FFS Medicaid benefits).[4] The primary reason a patient might pay cash rather than using insurance is to by-pass the quantity limits imposed by the preferred drug list.[4] Additionally, using claims data alone to identify chronic triptan users may inherently exclude patients due to the nature of Medicaid patients entering and exiting Oregon FFS Medicaid over time by joining and leaving coordinated care organizations.[4]

Conclusion

In summary, the use of preventative therapy to reduce the frequency and severity of migraine attacks is supported by clinical guidelines.[5] A recent DUE using pharmacy claims in the Oregon Medicaid FFS population revealed that 54% of chronic triptan users were prescribed a guideline-recommended oral preventative medication.[4] Although this percentage appears higher than national statistics, there is an opportunity to improve utilization of migraine preventative therapies to reduce the frequency of severe migraine headaches in the Medicaid population. Injectable options for migraine prophylaxis include onabotulinumtoxinA and 4 of the recently approved CGRP antagonists. Prior authorization criteria have been implemented to ensure appropriate utilization of the injectable agents.

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References:

1. Sprenger T, Viana M, Tassorelli C. Current Prophylactic Medications for Migraine and Their Potential Mechanisms of Action. Neurotherapeutics. 2018;15(2):313-323.
2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
3. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. Headache. 2018;58(4):496-505.
4. Bartholomew, R., et al. Drug Use Evaluation: Migraine Prophylaxis. Presented to the Oregon Pharmacy and Therapeutics Committee June 2021. https://www.orpdl.org/durm/meetings/meetingdocs/2021_06_03/finals/2021_06_03_PnT_Complete.pdf. Accessed April 19, 2022.
5. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78(17):1337-1345.
6. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache. 2019;59(1):1-18.
7. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2021;397(10268):51-60.
8. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the Preventive Treatment of Migraine. N Engl J Med. 2021;385(8):695-706.
9. QULIPTA (atogepant) tablets Prescribing Information. Dublin, Ireland; Forest Laboratories Ireland Ltd. and Abbvie. October 2021.
10. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-349.
11. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478-488.
12. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache. 2013;53(4):644-655.
13. Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. J Manag Care Pharm. 2014;20(1):22-33.
14. BOTOX (onabotulinumtoxinA) for injection. Prescribing Information. Madison, NJ; Allergan Pharmaceuticals. July 2021.
15. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(19):1818-1826.
16. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. Cochrane Database Syst Rev. 2018;6(6):Cd011616.

17. Drug Effectiveness and Review Project (DERP). Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention. Center for Evidence-based Policy OH.

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Drug Use Evaluation: Duplicate Drug Therapy

Plain Language Summary: Do Medicaid providers regularly prescribe two or more similar medicines together that do not have additional health benefits?

- Medicines that work in a similar way are grouped together under one drug class name (for example, "statins" and "beta-blockers"). Providers often prescribe medicines from different drug classes to treat their patient's health condition. There is usually no good reason to use two medicines from the same class because there is no added health benefit and it may increase harmful side-effects. Using two medicines at once from the same drug class to treat a health condition is known as "duplicate drug therapy."
- In Oregon Medicaid, most patients do not have duplicate drug therapy. Only 1.3% of Oregon Medicaid patients regularly received 2 or more medicines from the same drug class.
- When patients had 2 or more prescribers, it was more common to see patients being treated with duplicate drug therapy compared to one drug therapy.
- When prescriptions were filled at more than one pharmacy, it was more common to see patients being treated with duplicate drug therapy compared to one drug therapy.
- Average healthcare costs (Medical, Pharmacy, and Total) were about twice as much for patients who regularly received duplicate drug therapy compared to those being treated with single drug therapy.

Research Questions:

1. In the Oregon Health Plan (OHP), how many patients are prescribed chronic duplicate drug therapies compared to patients receiving monotherapy?
2. How often is duplicate drug therapy prescribed from more than one provider for 90 days or longer?
3. How often is duplicate drug therapy dispensed from more than one pharmacy for 90 days or longer?
4. Do patients on chronic duplicate drug therapy have a higher impact on healthcare resource utilization compared to patients receiving monotherapy?

Conclusions:

- Patients prescribed chronic duplicate drug therapy compared to patients receiving monotherapy:
    - Only 1.3% of patients from select therapeutic drug classes had chronic duplicate therapy compared to chronic monotherapy.
    - About 9% of patients with chronic duplicate therapy were American Indian or Alaska Native.
    - The relative proportion of American Indian or Alaska Native persons with chronic duplicate therapy compared chronic monotherapy was slightly higher than those without tribal affiliation (1.7% vs 0.3%, respectively).
    - Among standard therapeutic classes, skeletal muscle relaxants had the highest rates of duplicate therapy (8.5%) but the total number of individuals on chronic therapy with SMRs was relatively low (117 patients) over the course of a year.
    - Among drug classes with similar pharmacology, the incretin-based therapies had the highest relative percentage of individuals on chronic duplicate therapy (6%), but the overall number of individuals on chronic incretin therapies was relatively low (47 patients) over the one-year timeframe.

- Patients prescribed chronic duplicate drug therapy from more than one provider:
    - About 59% of patients prescribed chronic duplicate therapy had their prescriptions written by a single prescriber.
    - More patients with 2 or more prescribers had duplicate therapy compared to monotherapy (41% vs. 23%, respectively).
    - Only about 2% of FFS patients had duplicate therapy from 2 or more prescribers.
- Patients prescribed chronic duplicate drug therapy dispensed from more than one pharmacy:
    - About 82% of patients prescribed chronic duplicate therapy had their prescriptions filled at a single pharmacy.
    - More patients who went to 2 or more pharmacies were on duplicative therapy than patients on monotherapy (18% vs. 13%, respectively)
    - Only about 2% of duplicate therapy FFS claims were dispensed from 2 or more pharmacies.
- Patients prescribed chronic duplicate drug therapy and impact on healthcare resource utilization:
    - Mean healthcare costs for patients with chronic duplicate therapy were about twice as much as those with monotherapy within most major categories (Medical, Pharmacy, and Total).
    - Mean costs for outpatient services were about 50% higher for chronic duplicate therapy patients compared to monotherapy.

Recommendations:

- No policy changes recommended.

Current Policy

The Oregon Health Authority's (OHA) Division of Medical Assistance Programs routinely reviews the drug therapy profiles of OHP FFS clients for clinically appropriate drug utilization. The purpose of the polypharmacy profiling program is to work with the client's prescribing practitioner to improve the health and safety of recipients and offer opportunities to enhance continuity and coordination of care in the use of prescription drugs. A key component in the assessment of appropriate drug therapy criteria includes, but is not limited to, therapeutic drug duplication.

Background

It is estimated that about half of the U.S. population has used one or more prescription drugs in the past 30 days.[1] The most commonly prescribed drug classes in adults are lipid-lowering agents, beta-blockers, anti-diabetic drugs, antidepressants, and analgesics.[1] In 2020, U.S. pharmaceutical expenditures grew to $535 billion, an increase of almost 5% compared to the year before.[2] As more prescription drugs are consumed, the risk of medication-related harms may be exacerbated by increased patient complexity, disjointed care, multiple prescribers, and low health literacy.[3] Medication errors have been defined as a failure in the treatment process that leads to, or has the potential to lead to, patient harm.[4] A medication error may occur in any part of the medication process including prescribing a patient the wrong type, incorrect dose, route, or preparation of medication, or even a failure to properly monitor the effects and safety of an administered or prescribed medication.[4] Outpatient medication errors may lead to adverse events that require emergency department visits or unplanned hospitalizations.[4] It has been estimated that medication-related adverse events (MRAEs) in the U.S. have a healthcare economic impact between $77 to $177 billion.[4]

Duplicate prescriptions or written orders for the same or similar medication not intended to be taken simultaneously by the patient may be considered an inappropriate medication error.[4] However, there are instances when multiple medications prescribed for a patient may be clinically appropriate if each drug has a clear indication, and the regimens are well tolerated and cost-effective.[5] The use of multiple drugs by an individual is known as polypharmacy.[6,7] There is no standardized definition for what constitutes polypharmacy but literature consistently suggests the threshold is at least 5 or more medications.[6-8] Although polypharmacy may or may not be appropriate, studies in older adults have shown that as the number of drugs prescribed increases, the chance of potentially serious drug-drug interactions (DDI) increase exponentially.[9] With an excessive number of drugs present on the patient profile, it is a challenge for clinicians to

distinguish between agents prescribed to treat an underlying disease versus those prescribed to treat medication-related side-effects.[3] Routine polypharmacy as a result of overprescribing, under-prescribing, or mis-prescribing is clinically inappropriate due to its potential negative impact on adverse drug events, medication adherence, emergency department visits, hospitalizations, and increased direct and indirect healthcare costs. [3,6,10-12] Some of the most frequently prescribed drugs in a patient with polypharmacy include cardiovascular and metabolic agents.[6] Age and comorbidity status are common determinants of polypharmacy; however, other sociodemographic factors such as gender, race, ethnicity, place of residence, income level, and behavior may also be key contributors.[8]

Many professional organizations have increasingly recognized the need to promote provider awareness of inappropriate prescribing.[5,13-15] For patients with advanced age, inappropriate prescribing has been addressed through criterion-based process measures such as the Beers criteria which can be applied to large scale prescribing databases but often lack detail or fail to provide useful clinical alternatives.[5,13,14] The *Screening Tool of Older Persons potentially inappropriate Prescriptions* (STOPP) is a more comprehensive, physiological-based screening tool which addresses drug-drug and drug-disease interactions, appropriate doses, and treatment duration.[13] Although the STOPP tool may not be quite as useful for clinicians attempting to optimize drug therapy for younger adults and/or children, it does address important aspects of therapy such as clinical effectiveness and makes suggestions for removal of potentially unnecessary drugs and drug duplications.[13]

In recent years, there has been stronger attempts to reduce unnecessary polypharmacy through deprescribing.[8] Deprescribing is the planned and supervised process of dose reduction or discontinuing medications that may be causing harm or no longer providing benefit.[8] Some prescribers may be reluctant to deprescribe based on clinical complexity and fear of destabilizing their patient.[15] When patient care is shared among multiple providers, there may be an unwillingness to deprescribe without awareness of past rationale or due to an incomplete patient history. Other prescribers may still subscribe to a "more is better" treatment philosophy with the belief that deprescribing is denying the patient effective treatment. However, deprescribing considers the potential benefits and harms of each individual drug on the patient's profile as well as the cumulative risk of multiple drugs used simultaneously.[15,16] There is mounting evidence to suggest that deprescribing is safe, practical, beneficial, and helps reduce inappropriate drug therapy.[15,16]

Some types of electronic prescribing software can help alert prescribers to potential inappropriate therapy (i.e., medications prescribed outside of normal age-dose parameters, potentially harmful drug-drug interactions, or possible drug-disease concerns) before the prescription goes to the pharmacy.[4,17,18] These screening tools may also be designed to alert providers to duplicate drug therapy if present.[11] Therapeutic duplication occurs when 2 or more medications from the same therapeutic class are prescribed.[1,18] Whether simultaneous use of agents from the same drug class or simultaneous use of medications with the same therapeutic effect, duplicate therapy can be dangerous or even deadly for a patient.[18] Studies have reported that therapeutic duplication comprises roughly 6% of all prescribing errors.[19] When patients undergo cross tapers or multiple prescribers become involved in their care, there is a higher potential for unintended therapeutic duplication.[20] Medications with different mechanisms from within certain classes such as insulins, antimicrobials, and immunosuppressants may be appropriate; however, other types of therapeutic duplications can present serious problems. For example, duplicate therapy with angiotensin-converting enzyme (ACE) inhibitors may increase the risk of hypotensive symptoms and renal dysfunction without an increase in clinical benefit.[21] Patients on multiple selective serotonin reuptake inhibitors (SSRIs) or SSRI combined with a selective norepinephrine inhibitor may place the patient at risk of developing anticholinergic effects (urinary retention, constipation, dry mouth, etc.) or even serotonin toxicity.[22] Oral anticoagulants have long been ranked among the highest priority for drug safety as well.[4,23] The Centers for Disease Control and Prevention (CDC) has reported that anticoagulants account for a significant proportion of all emergency department (ED) visits, with typically half of the visits resulting in hospitalization.[23-25] Unintended duplicate therapy with anticoagulants can magnify the risks of dangerous hemorrhage especially in patients with advanced age.[25] GLP-1 agonists and DPP-4 inhibitors are incretin-based therapies which have not been FDA-approved for combined use, and there are no treatment guidelines or high-quality evidence to recommend additional

benefits of combination therapy.[26] With rare cases of acute pancreatitis reported in patients treated with certain incretin-based therapies, it is unknown if duplicate therapy might increase the risk of significant adverse effects.[27]

Pharmacy claims processing tools are available to help screen profiles to minimize the possibility of dangerous drug duplications.[17] However, pharmacists may not be able to rely exclusively on drug review software to highlight all potentially inappropriate drug therapy duplications.[17] Since computerized claims processing systems often function independently, prescriptions filled at more than one pharmacy increase the risk that therapy duplication will not be identified, especially if multiple prescribers are involved.[28] If a therapeutic duplication is identified, the severity or clinical implication may not be available which can hider pharmacist ability to make informed benefit-risk assessments. Other claims processing software may be programmed with such high sensitivity that legitimate warnings may be ignored due to alert fatigue.[27] Whether undetected, overridden or ignored, duplicate therapy of agents with no established clinical benefit is a potential waste of healthcare resources and possibly dangerous.[12,17,18]

In the fee-for-service (FFS) Medicaid population, studies have reported that almost 50% of members meet the traditional definition of polypharmacy as simultaneous use of 5 or more drugs for a consecutive period of 60 days.[6] Polypharmacy has been significantly associated with multimorbidity and may result in poorer outcomes and the need for more frequent healthcare utilization.[29] The risk of polypharmacy with inappropriate therapeutic duplication may dramatically increase when patient care involves multiple prescribers and pharmacies.[28] Certain categories of medications such as antidepressants, anticoagulants, and analgesics may be more prone to duplicate therapy prescribing than others.[11] Prior authorizations (PAs) are tools created and enforced by payers to help ensure safe, appropriate, and cost-effective prescribing. However, there may be certain medications or medication-related procedures with clinical, administrative, and/or legal constraints which make the use of PA impractical or inappropriate.[30] The purpose of this drug use evaluation (DUE) is to determine how often therapeutic duplication occurs in the Oregon Health Plan (OHP)-FFS population, whether multiple prescribers and or pharmacies are involved, and its impact on overall healthcare costs.

Methods:

This analysis included 2 distinct populations of patients. The first population included any patient with chronic duplicate therapy defined as at least 90 days who were:

a) covered by 2 or more drugs (based on HSN) within the same specific therapeutic class or
b) covered by 2 or more agents (HSN) from different specific therapeutic classes (STCs) that have similar mechanisms with no more than a 7-day gap between the dates of service.

The second population included patients with chronic monotherapy with the same definitions except for coverage by only one drug (based on HSN) within the selected specific therapeutic class. The chronic monotherapy population was chosen to provide context for the relative frequency of prescribing for the drug classes of interest.

The primary analysis included continuously eligible FFS and Coordinated Care Organization (CCO) patients with paid FFS claims for drugs of interest (see **Appendix 1, Table A1**) between 1/01/2021 and 12/31/2021.

Patients were excluded if they had primary insurance coverage (i.e., third party liability [TPL]) at any time within the primary analysis period, if they had 75% or less Medicaid eligibility, limited or no Medicaid drug benefit, or Medicare part D coverage at any time during the analysis period. Patients were identified based on the following benefit packages:

Excluded

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

Claims data for these patients may be incomplete. Patients were excluded from the monotherapy group if at any time they had duplicate therapy.

The number of patients prescribed chronic duplicate therapy by a single versus multiple prescribers were evaluated as well as the number of patients with duplicate therapy claims from a single versus multiple pharmacies. Lastly, average patient healthcare costs while on duplicate or monotherapy were assessed for all FFS and CCO claims (pharmacy and medical) paid by Medicaid for a given member during the eligibility period while on duplicate or monotherapy between 01/01/2021 and 12/31/2021.

Results:

Demographics

There were a total of 62,931 patients who were included in these study populations based on paid FFS claims for a drug of interest. Overall for the selected drug classes, there were relatively few patients identified who had chronic duplicate therapy (n=816; 1.3%). Most patients in the primary analysis were between the ages of 19 and 64 years of age. About 9% of all the patients with chronic duplicate therapy were American Indian or Alaska Native (HNA). A larger proportion of members who identified as American Indian/Alaska Native had chronic duplicate therapy compared to the non-HNA population (1.7% vs 0.3%, respectively). Of all the included classes of medications, the SMRs had the highest relative percentage of chronic duplicate therapy (8.5%) but the total number of individuals on chronic therapy with SMRs was relatively low in the FFS population (117 patients). When classes were grouped by similar mechanism, the incretin-based therapies had the highest frequency of chronic duplicate therapy (3 patients; 6%), but only 47 total FFS patients on incretin therapy were identified over a one-year period.

Table 1 - Baseline Therapy Comparison

	# Patients with Chronic Duplicate Therapy		# Patients with Chronic Monotherapy		Percent of Patients on Chronic Duplicate Therapy Relative to Monotherapy (%)
N=	**816**	**%**	**62,115**	**%**	**1.3%**
American Indian/Alaska Native (HNA)	70	8.6%	4,000	6.4%	1.7%
Non-HNA	746	91.4%	58,115	93.6%	0.3%

Age					
Avg (min-max)	45.9	(10-67)	39.7	(4-91)	
0-12	1	0.1%	1,338	2.2%	0.1%
13-18	16	2.0%	4,828	7.8%	0.3%
19-64	796	97.5%	55,525	89.4%	1.4%
≥65	3	0.4%	424	0.7%	0.7%
Specific Therapeutic Class					
Inhibitors of RAAS					
A4D		0.0%	572	0.9%	0.0%
A4F		0.0%	262	0.4%	0.0%
A4L		0.0%		0.0%	-
A4T		0.0%		0.0%	-
Incretin based therapies					
C4F		0.0%	1	0.0%	0.0%
C4I		0.0%	34	0.1%	0.0%
C4J		0.0%	9	0.0%	0.0%
Statins (HMG-CoA Reductase Inhibitors)					
M4D	1	0.1%	551	0.9%	0.2%
Statins & Combos (HMG-CoA Reductase Inhibitors and ezetimibe)					
M4M		0.0%		0.0%	-
Beta-Blockers, Oral					
J7A		0.0%	93	0.1%	0.0%
J7C	4	0.5%	314	0.5%	1.3%
Anticoagulants, Oral and SQ					
M9K		0.0%	5	0.0%	0.0%
M9L		0.0%	10	0.0%	0.0%
M9T		0.0%	1	0.0%	0.0%
M9V		0.0%	36	0.1%	0.0%
Antidepressants, SSRIs					
H2S	94	11.5%	44,620	71.8%	0.2%
Antidepressants, SNRIs					

H7C	75	9.2%	15,767	25.4%	0.5%
Muscle Relaxants, Oral					
H6H	10	1.2%	107	0.2%	8.5%
General Mechanism					
Inhibitors of RAAS		0.0%	834	1.3%	0.0%
Incretin-based therapies	3	1.5%	44	0.1%	6.4%
HMG-CoA Reductase Inhib.		0.0%	551	0.9%	0.0%
Beta-blockers	1	0.1%	407	0.7%	0.2%
Anticoagulants		0.0%	52	0.1%	0.0%
Antidepressants	628	77.0%	60,387	97.2%	1.0%

Prescribers

Of the patients identified with chronic duplicate therapy, most (59%) had their prescriptions written by a single prescriber. However, when comparing claims written by 2 or more prescribers, there was a higher percentage of patients with duplicate therapy than monotherapy (41% vs. 23%, respectively). Nonetheless, the occurrence of duplicate therapy with 2 or more prescribers involved was relatively low overall at just over 2% compared to monotherapy with the same agents.

Table 2 - Claims from Single vs. Multiple Prescribers

	# Patients with Chronic Duplicate Therapy		# Patients with Chronic Monotherapy		Percent of Patients on Chronic Duplicate Therapy Relative to Monotherapy (%)
N=	**816**	**%**	**62,115**	**%**	**1.3%**
Patients with single prescriber	483	59.2%	47,695	76.8%	1.0%
Patients with ≥2 prescribers	333	40.8%	14,420	23.2%	2.3%

Pharmacies

Most of the patients with chronic duplicate therapy had their prescriptions filled at a single pharmacy (82%). However, there was a relatively higher proportion of patients with duplicate therapy (18%) who filled prescriptions at 2 or more pharmacies than those on monotherapy (13%). Overall, the percentage of duplicate therapy claims dispensed from 2 or more pharmacies appeared to be relatively low (2%) compared to the monotherapy group.

Table 3 - Claims from Single vs. Multiple Pharmacies

	# Patients with Chronic Duplicate Therapy		# Patients with Chronic Monotherapy		Percent of Patients on Chronic Duplicate Therapy Relative to Monotherapy (%)
N=	**816**	**%**	**62,115**	**%**	**1.3%**
Patients with single pharmacy	666	81.6%	54,259	87.4%	1.2%
Patients with ≥2 pharmacies	150	18.4%	7,856	12.6%	1.9%

Healthcare Utilization

Mean healthcare costs for patients with chronic duplicate therapy were roughly twice as much as those with monotherapy within most major categories (Medical, Pharmacy, and Total). Outpatient services mean costs were about 50% more for chronic duplicate therapy compared to monotherapy.

Table 4 - Healthcare Resource Utilization while on Duplicate or Monotherapy

	Mean Costs for Patients on Chronic Medications	
	Duplicate Therapy	**Monotherapy**
Paid Medical Claims		
Emergency Department	$1,163	$617
Inpatient Hospitalizations	$1,048	$660
Outpatient Services (all other medical claims)	$21,870	$14,079
Paid Pharmacy Prescription Claims*	$2,392	$1,314
Average Total Costs**	$26,473	$16,670

*=Prescription claims include amount paid to pharmacies minus rebates.

**=Average Total Costs include all FFS and CCO claims (pharmacy and medical) paid by Medicaid for a given member category during eligibility period while on duplicate or monotherapy between 01/01/2021 and 12/31/2021.

Limitations:

Data presented in this report is based on OHP claims history and has several inherent limitations.

- The evaluation provides a short "snapshot" in time for agents within a limited number of specific therapeutic classes.
- Data were based on claims history which may not accurately reflect true medication use.
- Patients may elect to pay cash rather than navigate the PA process for certain agents. This evaluation only included claims paid by OHP, and any potential cash claims are not included.
- Medical claims for non-pharmacological services: Due to delays in submission of medical claims and billing mechanisms for non-pharmacological therapies, the mean costs of healthcare resource utilization are difficult to evaluate. Often billing for medical visits is significantly delayed and claims data may not accurately capture all visits. For patients enrolled in a CCO, non-pharmacological treatments, hospitalizations, and ED visits are paid for by the CCO while medication therapy for carve-out medications are paid by FFS.
- Some duplicate therapy claims may have represented dose titrations or specific doses that could not be attained by one commercially available strength or formulation. The DUE did not distinguish whether prescriptions were written by more than one provider while the patient was under transitional care.
- Tribal affiliated claims that received all-inclusive rate (AIR) for reimbursement were not excluded from the total cost figures. Duplicate therapy was identified at a higher frequency in the HNA population. It is unknown as to what extent HNA claims may have resulted in higher pharmacy costs in the duplicate therapy group compared to monotherapy.

References:

1. Martin CB, Hales CM, Gu Q, et al. Prescription drug use in the United States, 2015–2016. National Center for Health Statistics. NCHS Data Brief, no 334. Hyattsville, MD; 2019. Accessed online June 1, 2022.
2. Tichy EM, Hoffman JM, Suda KJ, et al. National trends in prescription drug expenditures and projections for 2021. *Am J Health Syst Pharm.* 2021;78(14):1294-1308.
3. Talebreza S, McPherson ML. Recognizing and Managing Polypharmacy in Advanced Illness. *Medical Clinics of North America*. 2020;104(3):405-413.
4. Laatikainen O, Sneck S, Turpeinen M. Medication-related adverse events in health care-what have we learned? A narrative overview of the current knowledge. *Eur J Clin Pharmacol.* 2022;78(2):159-170.
5. O'Mahony D, Gallagher PF. Inappropriate prescribing in the older population: need for new criteria. *Age and Ageing*. 2008;37(2):138-141.
6. Feng X, Tan X, Riley B, et al. Polypharmacy and Multimorbidity Among Medicaid Enrollees: A Multistate Analysis. *Popul Health Manag*. 2018;21(2):123-129.
7. Petrovic M, O'Mahony D, Cherubini A. Inappropriate prescribing: hazards and solutions. *Age and Ageing.* 2022;51(2):afab269.
8. Talebreza S, McPherson ML. Recognizing and Managing Polypharmacy in Advanced Illness. Medical Clinics of North America. 2020;104(3):405-413.
9. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf.* 2007;30(10):911-918.
10. Valuck RJ, Morrato EH, Dodd S, et al. Medicaid Pharmacotherapy Research Consortium. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. *Curr Med Res Opin*. 2007 Oct;23(10):2567-76.
11. Almodóvar AS, Nahata MC. Associations Between Chronic Disease, Polypharmacy, and Medication-Related Problems Among Medicare Beneficiaries. *Journal of Managed Care & Specialty Pharmacy.* 2019;25(5):573-577.
12. Davies LE, Spiers G, Kingston A, et al. Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. *Journal of the American Medical Directors Association.* 2020;21(2):181-187
13. Bradley MC, Motterlini N, Padmanabhan S, et al. Potentially inappropriate prescribing among older people in the United Kingdom. *BMC Geriatrics*. 2014;14:72.
14. Opondo D, Eslami S, Visscher S, et al. Inappropriateness of Medication Prescriptions to Elderly Patients in the Primary Care Setting: A Systematic Review. *PLOS ONE*. 2012;7(8):e43617.
15. Reeve E, Moriarty F, Nahas R, et al. A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf*. 2018;17(1):39-49.
16. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA internal medicine.* May 2015;175(5):827-34.
17. Trygstad TK, Christensen D, Garmise J, et al. Pharmacist response to alerts generated from Medicaid pharmacy claims in a long-term care setting: results from the North Carolina polypharmacy initiative. *Journal of Managed Care Pharmacy*. 2005;11(7):575-583.
18. Lee H, Song I, Shin SM, et al. Regulatory effect of decreasing therapeutic duplication of respiratory drugs using a prescription database between 2012 and 2015. *Regulatory Toxicology & Pharmacology*. 2019;103:218-228.
19. Shao SC, Lai EC, Chan YY, et al. Therapeutic Duplication of Long-Acting Injectable Drugs. *Journal of patient safety*. 2018;14(3):e74-e75.
20. Tamblyn RM, McLeod PJ, Abrahamowicz M, et al. Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. *Can Med Assoc J* 1996; 154:1177-84.
21. Yusuf S, Teo K, Pogue J, et al. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *New England Journal of Medicine.* 2008;358(15):1547-1559.
22. Palaniyappan L, Insole L, Ferrier N. Combining antidepressants: a review of evidence. *Advances in Psychiatric Treatment*. 2009;15(2):90-99.

23. Centers for Disease Control and Prevention. Adverse Drug Events from Specific Medicines. 2019. Available from https://www.cdc.gov/medicationsafety/adverse-drug-events-specific-medicines.html. Accessed June 1, 2022.
24. Geller AI, Shehab N, Lovegrove MC et al. Emergency Visits for Oral Anticoagulant Bleeding. *J GEN INTERN MED* 35, 371–373 (2020).
25. Rahmanzade, R., Cabrera Diaz, F., Zaugg, C. et al. Therapeutic duplication of anticoagulants: a retrospective study of frequency and consequences in a tertiary referral hospital. *Thrombosis J* 18, 14 (2020).
26. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008;32(Suppl 1):S1-S201.
27. Singh AK, Gangopadhyay KK, Singh R. Risk of acute pancreatitis with incretin-based therapy: a systematic review and updated meta-analysis of cardiovascular outcomes trials. *Expert Rev Clin Pharmacol.* 2020;13(4):461-468.
28. Martin CB, Wiley-Exley EK, Richards S et al. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Annals of Pharmacotherapy*. 2009;43(1):36-44.
29. Priya K, Sreshta M, Philip S. Cost-saving medication therapy management for outpatients. *Perspectives in Clinical Research*. 2021;12(1):14-20.
30. Prada SI, Loaiza JS. Comparing the Medicaid Prospective Drug Utilization Review Program Cost-Savings Methods Used by State Agencies in 2015 and 2016. *American Health & Drug Benefits*. 2019;12(1):7-12.

Appendix 1: Coding Information

Table A1. Codes for Standard Therapeutic Classes

Class	HIC3	HSN	Brand	Generic	PDL
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6113	BENAZEPRIL HCL	benazepril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6113	LOTENSIN	benazepril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	128	CAPOTEN	captopril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	128	CAPTOPRIL	captopril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	130	ENALAPRIL MALEATE	enalapril maleate	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	130	EPANED	enalapril maleate	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	130	VASOTEC	enalapril maleate	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6106	FOSINOPRIL SODIUM	fosinopril sodium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6106	MONOPRIL	fosinopril sodium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	LISINOPRIL	lisinopril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	PRINIVIL	lisinopril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	QBRELIS	lisinopril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	ZESTRIL	lisinopril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	9934	MOEXIPRIL HCL	moexipril HCl	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	9934	UNIVASC	moexipril HCl	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	13911	PERINDOPRIL ERBUMINE	perindopril erbumine	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	7631	ACCUPRIL	quinapril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	7631	QUINAPRIL HCL	quinapril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6080	ALTACE	ramipril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6080	RAMIPRIL	ramipril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	8991	MAVIK	trandolapril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	8991	TRANDOLAPRIL	trandolapril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	37444	EDARBI	azilsartan medoxomil	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	16913	ATACAND	candesartan cilexetil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	16913	CANDESARTAN CILEXETIL	candesartan cilexetil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	16920	TEVETEN	eprosartan mesylate	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	15576	AVAPRO	irbesartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	15576	IRBESARTAN	irbesartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	9829	COZAAR	losartan potassium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	9829	LOSARTAN POTASSIUM	losartan potassium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	23490	BENICAR	olmesartan medoxomil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	23490	OLMESARTAN MEDOXOMIL	olmesartan medoxomil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	18839	MICARDIS	telmisartan	Y

Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	18839	TELMISARTAN	telmisartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	12204	DIOVAN	valsartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	12204	VALSARTAN	valsartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4L	42256	ENTRESTO	sacubitril/valsartan	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4T	34493	ALISKIREN	aliskiren hemifumarate	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4T	34493	TEKTURNA	aliskiren hemifumarate	N
Diabetes, DPP-4 Inhibitors	C4F	39970	ALOGLIPTIN-METFORMIN	alogliptin benz/metformin	N
Diabetes, DPP-4 Inhibitors	C4F	34665	JANUMET	sitagliptin phos/metformin	Y
Diabetes, DPP-4 Inhibitors	C4F	34665	JANUMET XR	sitagliptin phos/metformin	N
Diabetes, DPP-4 Inhibitors	C4F	38464	JENTADUETO	linagliptin/metformin HCl	N
Diabetes, DPP-4 Inhibitors	C4F	38464	JENTADUETO XR	linagliptin/metformin HCl	N
Diabetes, DPP-4 Inhibitors	C4F	39970	KAZANO	alogliptin benz/metformin HCl	N
Diabetes, DPP-4 Inhibitors	C4F	37246	KOMBIGLYZE XR	saxagliptin HCl/metformin HCl	N
Diabetes, GLP-1 Receptor Agonists	C4I	40782	ADLYXIN	lixisenatide	N
Diabetes, GLP-1 Receptor Agonists	C4I	38451	BYDUREON BCISE	exenatide microspheres	N
Diabetes, GLP-1 Receptor Agonists	C4I	38451	BYDUREON PEN	exenatide microspheres	N
Diabetes, GLP-1 Receptor Agonists	C4I	32893	BYETTA	exenatide	Y
Diabetes, GLP-1 Receptor Agonists	C4I	44675	OZEMPIC	semaglutide	N
Diabetes, GLP-1 Receptor Agonists	C4I	44675	RYBELSUS	semaglutide	N
Diabetes, GLP-1 Receptor Agonists	C4I	41421	TRULICITY	dulaglutide	Y
Diabetes, GLP-1 Receptor Agonists	C4I	36436	VICTOZA 2-PAK	liraglutide	Y
Diabetes, GLP-1 Receptor Agonists	C4I	36436	VICTOZA 3-PAK	liraglutide	Y
Diabetes, DPP-4 Inhibitors	C4J	39968	ALOGLIPTIN	alogliptin benzoate	N
Diabetes, DPP-4 Inhibitors	C4J	34126	JANUVIA	sitagliptin phosphate	Y
Diabetes, DPP-4 Inhibitors	C4J	39968	NESINA	alogliptin benzoate	N
Diabetes, DPP-4 Inhibitors	C4J	36471	ONGLYZA	saxagliptin HCl	Y
Diabetes, DPP-4 Inhibitors	C4J	37576	TRADJENTA	linagliptin	N
Antidepressants	H2S	10321	CELEXA	citalopram hydrobromide	Y
Antidepressants	H2S	10321	CITALOPRAM HBR	citalopram hydrobromide	Y
Antidepressants	H2S	24022	ESCITALOPRAM OXALATE	escitalopram oxalate	Y
Antidepressants	H2S	1655	FLUOXETINE DR	fluoxetine HCl	V
Antidepressants	H2S	1655	FLUOXETINE HCL	fluoxetine HCl	Y
Antidepressants	H2S	6338	FLUVOXAMINE MALEATE	fluvoxamine maleate	Y
Antidepressants	H2S	6338	FLUVOXAMINE MALEATE ER	fluvoxamine maleate	V
Antidepressants	H2S	24022	LEXAPRO	escitalopram oxalate	Y
Antidepressants	H2S	7344	PAROXETINE CR	paroxetine HCl	V
Antidepressants	H2S	7344	PAROXETINE ER	paroxetine HCl	V
Antidepressants	H2S	7344	PAROXETINE HCL	paroxetine HCl	Y
Antidepressants	H2S	7344	PAXIL	paroxetine HCl	Y
Antidepressants	H2S	7344	PAXIL CR	paroxetine HCl	V
Antidepressants	H2S	25796	PEXEVA	paroxetine mesylate	V

Antidepressants	H2S	1655	PROZAC	fluoxetine HCl	Y
Antidepressants	H2S	6324	SERTRALINE HCL	sertraline HCl	Y
Antidepressants	H2S	6324	TRAZODONE HCL	sertraline HCl	Y
Antidepressants	H2S	6324	ZOLOFT	sertraline HCl	Y
Antidepressants	H7C	26521	CYMBALTA	duloxetine HCl	Y
Antidepressants	H7C	40202	DESVENLAFAXINE ER	desvenlafaxine	V
Antidepressants	H7C	35420	DESVENLAFAXINE SUCCINATE ER	desvenlafaxine succinate	Y
Antidepressants	H7C	26521	DRIZALMA SPRINKLE	duloxetine HCl	V
Antidepressants	H7C	26521	DULOXETINE HCL	duloxetine HCl	Y
Antidepressants	H7C	8847	EFFEXOR	venlafaxine HCl	Y
Antidepressants	H7C	8847	EFFEXOR XR	venlafaxine HCl	Y
Antidepressants	H7C	40632	FETZIMA	levomilnacipran HCl	V
Antidepressants	H7C	35420	PRISTIQ	desvenlafaxine succinate	Y
Antidepressants	H7C	8847	VENLAFAXINE HCL	venlafaxine HCl	Y
Antidepressants	H7C	8847	VENLAFAXINE HCL ER	venlafaxine HCl	Y
Muscle Relaxants, Oral	H6H	1950	AMRIX	cyclobenzaprine HCl	N
Muscle Relaxants, Oral	H6H	1949	BACLOFEN	baclofen	Y
Muscle Relaxants, Oral	H6H	1944	CARISOPRODOL	carisoprodol	N
Muscle Relaxants, Oral	H6H	1942	CARISOPRODOL COMPOUND	carisoprodol/aspirin	N
Muscle Relaxants, Oral	H6H	1941	CHLORZOXAZONE	chlorzoxazone	N
Muscle Relaxants, Oral	H6H	1950	CYCLOBENZAPRINE HCL	cyclobenzaprine HCl	Y
Muscle Relaxants, Oral	H6H	1950	CYCLOBENZAPRINE HCL ER	cyclobenzaprine HCl	N
Muscle Relaxants, Oral	H6H	1947	DANTRIUM	dantrolene sodium	N
Muscle Relaxants, Oral	H6H	1947	DANTROLENE SODIUM	dantrolene sodium	N
Muscle Relaxants, Oral	H6H	1950	FEXMID	cyclobenzaprine HCl	N
Muscle Relaxants, Oral	H6H	1949	FLEQSUVY	baclofen	N
Muscle Relaxants, Oral	H6H	1950	FLEXERIL	cyclobenzaprine HCl	Y
Muscle Relaxants, Oral	H6H	1941	LORZONE	chlorzoxazone	N
Muscle Relaxants, Oral	H6H	1949	LYVISPAH	baclofen	N
Muscle Relaxants, Oral	H6H	1945	METAXALL	metaxalone	N
Muscle Relaxants, Oral	H6H	1945	METAXALONE	metaxalone	N
Muscle Relaxants, Oral	H6H	1938	METHOCARBAMOL	methocarbamol	Y
Muscle Relaxants, Oral	H6H	1936	METHOCARBAMOL W/ASPIRIN	methocarbamol/aspirin	N
Muscle Relaxants, Oral	H6H	1906	NORFLEX	orphenadrine citrate	N
Muscle Relaxants, Oral	H6H	1791	NORGESIC FORTE	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1906	ORPHENADRINE CITRATE	orphenadrine citrate	N
Muscle Relaxants, Oral	H6H	1906	ORPHENADRINE CITRATE ER	orphenadrine citrate	N
Muscle Relaxants, Oral	H6H	1791	ORPHENADRINE-ASPIRIN-CAFF	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1791	ORPHENGESIC	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1791	ORPHENGESIC FORTE	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1949	OZOBAX	baclofen	N

Muscle Relaxants, Oral	H6H	1941	PARAFON FORTE DSC	chlorzoxazone	N
Muscle Relaxants, Oral	H6H	1938	ROBAXIN-750	methocarbamol	Y
Muscle Relaxants, Oral	H6H	1936	ROBAXISAL	methocarbamol/aspirin	N
Muscle Relaxants, Oral	H6H	1945	SKELAXIN	metaxalone	N
Muscle Relaxants, Oral	H6H	1944	SOMA	carisoprodol	N
Muscle Relaxants, Oral	H6H	11582	TIZANIDINE HCL	tizanidine HCl	Y
Muscle Relaxants, Oral	H6H	1944	VANADOM	carisoprodol	N
Muscle Relaxants, Oral	H6H	11582	ZANAFLEX	tizanidine HCl	Y
Beta-Blockers, Oral	J7A	13795	CARVEDILOL	carvedilol	Y
Beta-Blockers, Oral	J7A	34245	CARVEDILOL ER	carvedilol phosphate	N
Beta-Blockers, Oral	J7A	13795	COREG	carvedilol	Y
Beta-Blockers, Oral	J7A	34245	COREG CR	carvedilol phosphate	N
Beta-Blockers, Oral	J7A	2095	LABETALOL HCL	labetalol HCl	Y
Beta-Blockers, Oral	J7A	2095	TRANDATE	labetalol HCl	Y
Beta-Blockers, Oral	J7C	2107	ACEBUTOLOL HCL	acebutolol HCl	Y
Beta-Blockers, Oral	J7C	2104	ATENOLOL	atenolol	Y
Beta-Blockers, Oral	J7C	4791	BETAPACE	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	BETAPACE AF	sotalol HCl	N
Beta-Blockers, Oral	J7C	5168	BETAXOLOL HCL	betaxolol HCl	N
Beta-Blockers, Oral	J7C	7396	BISOPROLOL FUMARATE	bisoprolol fumarate	N
Beta-Blockers, Oral	J7C	2105	BLOCADREN	timolol maleate	N
Beta-Blockers, Oral	J7C	16740	BYSTOLIC	nebivolol HCl	N
Beta-Blockers, Oral	J7C	2103	CORGARD	nadolol	N
Beta-Blockers, Oral	J7C	2101	HEMANGEOL	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	INDERAL LA	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	INDERAL XL	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	INNOPRAN XL	propranolol HCl	N
Beta-Blockers, Oral	J7C	6323	KAPSPARGO SPRINKLE	metoprolol succinate	N
Beta-Blockers, Oral	J7C	5168	KERLONE	betaxolol HCl	N
Beta-Blockers, Oral	J7C	2102	LOPRESSOR	metoprolol tartrate	Y
Beta-Blockers, Oral	J7C	6323	METOPROLOL SUCCINATE	metoprolol succinate	
Beta-Blockers, Oral	J7C	2102	METOPROLOL TARTRATE	metoprolol tartrate	Y
Beta-Blockers, Oral	J7C	2103	NADOLOL	nadolol	N
Beta-Blockers, Oral	J7C	16740	NEBIVOLOL HCL	nebivolol HCl	N
Beta-Blockers, Oral	J7C	2106	PINDOLOL	pindolol	N
Beta-Blockers, Oral	J7C	2101	PROPRANOLOL HCL	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	PROPRANOLOL HCL ER	propranolol HCl	N
Beta-Blockers, Oral	J7C	4791	SORINE	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	SOTALOL	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	SOTALOL AF	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	SOTYLIZE	sotalol HCl	N

Beta-Blockers, Oral	J7C	2104	TENORMIN	atenolol	Y
Beta-Blockers, Oral	J7C	2105	TIMOLOL MALEATE	timolol maleate	N
Beta-Blockers, Oral	J7C	6323	TOPROL XL	metoprolol succinate	Y
Statins & Combos	M4D	2793	ALTOPREV	lovastatin	N
Statins & Combos	M4D	12404	ATORVASTATIN CALCIUM	atorvastatin calcium	Y
Statins & Combos	M4D	25009	CRESTOR	rosuvastatin calcium	Y
Statins & Combos	M4D	25009	EZALLOR SPRINKLE	rosuvastatin calcium	N
Statins & Combos	M4D	6312	FLOLIPID	simvastatin	N
Statins & Combos	M4D	8946	FLUVASTATIN ER	fluvastatin sodium	N
Statins & Combos	M4D	8946	FLUVASTATIN SODIUM	fluvastatin sodium	N
Statins & Combos	M4D	8946	LESCOL	fluvastatin sodium	N
Statins & Combos	M4D	8946	LESCOL XL	fluvastatin sodium	N
Statins & Combos	M4D	12404	LIPITOR	atorvastatin calcium	Y
Statins & Combos	M4D	36983	LIVALO	pitavastatin calcium	N
Statins & Combos	M4D	2793	LOVASTATIN	lovastatin	Y
Statins & Combos	M4D	6227	PRAVACHOL	pravastatin sodium	Y
Statins & Combos	M4D	6227	PRAVASTATIN SODIUM	pravastatin sodium	Y
Statins & Combos	M4D	25009	ROSUVASTATIN CALCIUM	rosuvastatin calcium	Y
Statins & Combos	M4D	6312	SIMVASTATIN	simvastatin	Y
Statins & Combos	M4D	6312	ZOCOR	simvastatin	Y
Statins & Combos	M4D	44422	ZYPITAMAG	pitavastatin magnesium	N
Statins & Combos	M4M	26505	EZETIMIBE-SIMVASTATIN	ezetimibe/simvastatin	N
Statins & Combos	M4M	41633	ROSUVASTATIN-EZETIMIBE	ezetimibe/rosuvastatin cal	N
Statins & Combos	M4M	41633	ROSZET	ezetimibe/rosuvastatin cal	N
Statins & Combos	M4M	26505	VYTORIN	ezetimibe/simvastatin	N
Anticoagulants, Oral and SQ	M9K	23233	ARIXTRA	fondaparinux sodium	N
Anticoagulants, Oral and SQ	M9K	7878	ENOXAPARIN SODIUM	enoxaparin sodium	Y
Anticoagulants, Oral and SQ	M9K	23233	FONDAPARINUX SODIUM	fondaparinux sodium	N
Anticoagulants, Oral and SQ	M9K	7429	FRAGMIN	dalteparin sodium,porcine	N
Anticoagulants, Oral and SQ	M9K	8989	INNOHEP	tinzaparin sodium,porcine	N
Anticoagulants, Oral and SQ	M9K	7878	LOVENOX	enoxaparin sodium	Y
Anticoagulants, Oral and SQ	M9L	2812	COUMADIN	warfarin sodium	Y
Anticoagulants, Oral and SQ	M9L	2812	JANTOVEN	warfarin sodium	Y
Anticoagulants, Oral and SQ	M9L	2812	WARFARIN SODIUM	warfarin sodium	Y
Anticoagulants, Oral and SQ	M9T	35604	PRADAXA	dabigatran etexilate mesylate	Y
Anticoagulants, Oral and SQ	M9V	37792	ELIQUIS	apixaban	Y
Anticoagulants, Oral and SQ	M9V	41672	SAVAYSA	edoxaban tosylate	Y
Anticoagulants, Oral and SQ	M9V	35915	XARELTO	rivaroxaban	Y

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Prior Authorization Criteria Update: Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Program

Plain Language Summary:

- What is changing? Beginning in 2023, members who are covered in the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program may be qualified for treatment of some conditions not normally covered under the Oregon Health Plan (OHP) fee-for-service (FFS) program.
- The EPSDT program covers healthcare services for people under 21 years old who are enrolled in the Medicaid. For people enrolled in the FFS program (Medicaid Open Card), the OHP determines coverage of treatment on a case-by-case basis.
- We recommend policy updates to support an individual review for members covered under the EPSDT program.

Purpose of Update:

The EPSDT program is intended to provide comprehensive coverage of healthcare services for people up to their 21st birthday. Services include exams, screenings, diagnostics, and medically necessary and appropriate treatment. Determination of whether a service meets definitions for medically appropriate and medically necessary use are made on an individual case-by-case basis. Medically appropriate and medically necessary services are defined in Oregon Administrative Rule (OAR) 410-120-0000.

(146) "Medically Appropriate" means health services, items, or medical supplies that are:

(a) Recommended by a licensed health provider practicing within the scope of their license;

(b) Safe, effective, and appropriate for the patient based on standards of good health practice and generally recognized by the relevant scientific or professional community based on the best available evidence;

(c) Not solely for the convenience or preference of an OHP client, member, or a provider of the service item or medical supply; and

(d) The most cost effective of the alternative levels or types of health services, items, or medical supplies that are covered services that can be safely and effectively provided to a Division client or member in the Division or MCE's judgment;

(e) All covered services must be medically appropriate for the member or client but not all medically appropriate services are covered services.

(147) "Medically Necessary" means health services and items that are required by a client or member to address one or more of the following:

(a) The prevention, diagnosis, or treatment of a client or member's disease, condition, or disorder that results in health impairments or a disability;

(b) The ability for a client or member to achieve age-appropriate growth and development;

(c) The ability for a client or member to attain, maintain, or regain independence in self-care, ability to perform activities of daily living or improve health status; or

(d) The opportunity for a client or member receiving Long Term Services & Supports (LTSS) as defined in these rules to have access to the benefits of non-institutionalized community living, to achieve person centered care goals, and to live and work in the setting of their choice;

(e) A medically necessary service must also be medically appropriate. All covered services must be medically necessary but not all medically necessary services are covered services.

Beginning in January 2023, Oregon elected to not renew their waiver for the prioritized list for members covered under the EPSDT benefit. Subsequently, the following policy updates are recommended to accommodate individualized review based on medical necessity and appropriateness for members enrolled in FFS who are under 21 years of age. These changes are intended to continue to support the current prioritized list for members at least 21 years of age.

Recommendation:

- Update all prior authorization criteria to support individualized review of drugs based on medically appropriate and necessary use for members younger than 21 years of age (up to their 21st birthday) who have an unfunded diagnosis.
- In the absence of more specific criteria already approved by P&T, standard definitions for medically appropriate and necessary use will include:
    - FDA-approved or compendia-supported indication;
    - Trial and failure, contraindication, or intolerance to at least 2 preferred products (when available in the class); and
    - Documentation that the disease is of sufficient severity that it impact's the patient's health

Acne Medications

Goal(s):

- Ensure that medications for acne are used appropriately for OHP-funded conditions for adults.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 months

Requires PA:

- All drugs in the Acne medications class

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 an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP? HERC guideline notes 65 and 132 describe funding status based on disease severity: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-132.docx https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-065.docx	**Yes:** Approve for 12 months. ~~Go to #4~~	**No: For current age ≥ 21 years:** Pass to RPh. Deny; not funded by the OHP **For current age < 21 years:** Go to #4.

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

P&T/DUR Review: 12/22; 02/21 (SF); 06/2020 (SF); 11/18 (JP)
Implementation:TBD; 7/1/20; 1/1/1

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):
- Ensure that non-preferred drugs are used appropriately for OHP-funded conditions in adults.
- Allow case-by-case review for members covered under the EPSDT program.

Initiative:
- PDL: Preferred Drug List

Length of Authorization:
- Up to 6 months

Requires PA:
- Non-preferred drugs

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org

- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4	**No**: **For current age ≥ 21:** Pass to RPh. Deny; not funded by the OHP **For current age <21 years:** Go to #5.
4. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
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 #5	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
6. 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.
~~5. RPh only: All other indications need to be evaluated for funding status on the OHP prioritized list~~ ~~• If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.~~ ~~• If not funded and patient is over 21 years of age or older: Deny; not funded by the OHP.~~ ~~• If not funded and patient is less than 21 year of age or less: Approve for 6 months, or for length of the prescription, whichever is less if treatment has or is expected to improve the patient's ability to grow, develop or participate in school.[1] If no documentation is provided: Deny; not funded by the OHP.~~		

~~1. *Statement of intent 4:* https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-SOI-004.docx~~

P&T / DUR Review: *12/23; 4/22; 7/15, 9/10; 9/09; 5/09*
Implementation: *TBD; 5/1/22; 10/13/16; 8/25/15; 8/15; 1/1/11, 9/16/10*

Analgesics, Non-Steroidal Anti-Inflammatory Drugs

Goal(s):
- To ensure that non-preferred oral and nasal spray NSAIDs are used for conditions funded by the OHP.
- Restrict ketorolac to short-term use (5-day supply every 60 days) per the FDA black boxed warning.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred oral and nasal spray NSAIDs.

- Ketorolac: Maximum of one claim per 60 days, with a maximum 20 tablets/5-day supply or 126 mg/day for nasal spray (maximum 5-day combined duration of treatment every 60 days).

Preferred 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		
~~5.~~6. What diagnosis is being treated?	Record ICD10 code.	
~~6.~~7. Is the diagnosis funded by the Oregon Health Plan?	**Yes:** Go to #~~43~~	**No:** Current Age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: go to #3.
8. Is there documentation of medical appropriateness and medical necessity? Definitions for medical appropriateness include use for an FDA indication AND use, contraindication, or intolerance to preferred agents in the class. Medical necessity includes documentation that the diagnosis impacts the patient's health.	**Yes:** Go to #4	**No:** Pass to RPh; deny medical appropriateness or medical necessity
~~7.~~9. Is this a request for ketorolac, new or continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	**Yes:** Document prior therapy in PA record. Go to #5~~4~~.	**No:** Go to #6~~5~~
~~8.~~10. Is request for more than a 5-day supply of ketorolac within 60 days (200 mg total over 5 days for tablets, 630 mg total over 5 days for the nasal spray)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6~~5~~

Approval Criteria		
~~9.~~11. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based and reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for up to 12 months.

P&T Review: *2/21 (KS), 3/16 (MH); 11/14; 9/13; 2/12; 9/09; 2/06*
Implementation: *1/1/15, 1/1/14, 5/14/12, 1/1/10*

Tetracyclines (Oral)-Quantity Limit

Goal(s):
- Restrict use of oral tetracyclines to OHP-funded diagnoses in adults. Allow case-by-case review for members covered under the EPSDT program.
- Prevent inappropriate use beyond two, 14-day supplies within a 3-month time period
- Approve long-term use only for indications supported by the medical literature.

Length of Authorization:
- Up to 6 months

Requires PA:
- Long-term use of oral tetracyclines beyond two, 14-day supplies in a 3-month timeframe

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 an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. If clinic provides supporting literature: Go to #3 If not supported by literature: Deny; medical appropriateness
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4	**No: For current age ≥ 21 years:** Pass to RPh. Deny; not funded by the OHP. **For current age < 21 years:** Go to #6. ~~**No**: Go to #6~~
4. Is the requested agent a preferred product?	**Yes:** Approve for duration of prescription or up to 6 months, whichever is less.	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
6. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
7. 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.

~~6. RPh only: All other indications need to be evaluated for funding status on the OHP prioritized list~~

- ~~If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.~~
- ~~If not funded and patient is over 21 years of age or older: Deny; not funded by the OHP.~~
- ~~If not funded and patient is less than 21 year of age or less: Approve for 6 months, or for length of the prescription, whichever is less if treatment has or is expected to improve the patient's ability to grow, develop or participate in school.[1] If no documentation is provided: Deny; not funded by the OHP.~~

1. ~~Statement of intent 4: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-SOI-004.docx~~

P&T / DUR Review: *12/22; 5/17 (MH)*
Implementation: *TBD; 7/1/17*

Drugs for Non-funded Conditions

Goal:

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

Length of Authorization:

- Up to 6 months.

Requires PA:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No: For current age ≥ 21 years:** Pass to RPh. Deny; not funded by the OHP. **For current age < 21 years:** Go to #3
3. I~~I~~s there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?~~Is the patient less than 21 years of age or younger AND is there documentation that the therapy is expected to improve the patient's ability to grow, develop or participate in school?~~	**Yes:** Approve for 6 months, or for length of the prescription, whichever is less	**No:** Pass to RPh; Deny; ~~not funded by the OHP~~medical necessity.
4. Pass to RPh. The prescriber must provide documentation of therapeutic failure, adverse event, or contraindication alternative drugs approved by FDA for the funded condition. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.		

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

Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Restrict use of targeted immune modulators to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence. Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:
- All targeted immune modulators with indications for severe asthma, atopic dermatitis, or other indications (see **Table 2** below) for both pharmacy and physician-administered claims.
- This PA does not apply to topical agents for inflammatory skin conditions which are subject to separate clinical PA criteria.

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. Maximum Adult Doses for Inhaled Corticosteroids

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Armonair (fluticasone propionate)	232 mcg BID
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
AirDuo Digihaler (fluticasone/salmeterol)	232/14 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	232/14 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 2. FDA-approved Indications and Ages

Generic Name/ BRAND NAME	**Eosinophilic Asthma**	**Moderate to Severe Allergic Asthma**	**Difficult To Treat, Severe Asthma***	**Hypereosinophilic Syndrome (HES)**	**Eosinophilic Granulomatosis with Polyangiitis (EGPA)**	**Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)**	**Eosinophilic Esophagitis**	**Atopic Dermatitis (AD)**	**Other**

Abrocitinib CIBINQO								≥18 years	
Benralizumab FASENRA	≥12 years								
Dupilumab DUPIXENT	≥6 years (or with oral corticosteroid dependent asthma)					≥18 years	≥12 years and weighing at least 40 kilograms	≥6 months	PN ≥18 years
Mepolizumab NUCALA	≥6 years			≥ 12 years	≥18 years	≥18 years			
Omalizumab XOLAIR		≥6 years				≥18 years			CSU ≥ 12 years
Reslizumab CINQAIR	≥18 years								
Tezepelumab TEZSPIRE			≥ 12 years						
Tralokinumab ADBRY								≥18 years	
Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS).									
Abbreviations: CSU = Chronic spontaneous urticarial; PN = prurigo nodularis									

Table 3. Abrocitinib Dosing Adjustments for Atopic Dermatitis

Assessment	Recommended Dose
CYP2C19 Poor Metabolizer	50 mg once daily and may increase to 100 mg once daily after 12 weeks if inadequate response to 50 mg once daily
GFR 30 to 59 mL/min	Start with 50 mg once daily and may increase to 100 mg once daily after 12 weeks if inadequate response to 50 mg once daily
GFR < 30 mL/min	Use is not recommended
Severe hepatic impairment (Child-Pugh Class C)	Use is not recommended

Table 4. FDA-Approved Dosing for Monoclonal Antibodies Used to Treat Severe Asthma Phenotypes

Generic Name	Brand Name	Asthma Indication	Initial Dose and Administration Route	Maintenance Dose and Administration Route
Benralizumab	FASENRA	Severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks for the first 3 doses	30 mg SC every 8 weeks

Dupilumab	DUPIXENT	Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Pediatrics (6 to 11 yo)**:** An initial loading dose is not necessary Adults and Adolescents ≥ 12 yo : 400 mg to 600 mg SC x 1 dose	Ages 6 – 11 yo (weight 15 to 30 kg) 100 mg SC every 2 weeks OR 300 mg SC every 4 weeks Adults and Adolescents ≥ 12 yo: 200 to 300 mg SC every 2 weeks
Mepolizumab	NUCALA	Severe asthma with an eosinophilic phenotype	N/A	Ages ≥ 6 – 11 yo: 40 mg SC every 4 weeks Ages ≥ 12 yo: 100 mg SC every 4 weeks
Omalizumab	XOLAIR	Moderate to severe persistent asthma and positive allergy testing	N/A	75 to 375 mg SC every 2 to 4 weeks based on weight and serum IgE levels
Reslizumab	CINQAIR	Severe asthma with an eosinophilic phenotype	N/A	3 mg/kg IV infusion every 4 weeks
Tezepelumab	TEZSPIRE	Severe asthma	N/A	210 mg SC every 4 weeks
Abbreviations: IgE = immunoglobulin E; IV = intravenous; kg = kilogram; mg = milligram; N/A = Not Applicable; SC = subcutaneous; yo = years old				

Table 5. Dupilumab Dosing by Indication

Indication	**Dose (Subcutaneous)**
Atopic Dermatitis in adults	600 mg followed by 300 mg every 2 weeks
Atopic Dermatitis in pediatric patients (aged 6 to 17 years)	600 mg followed by 300 mg every 4 weeks (15 to 29 kg) 400 mg followed by 200 mg every 2 weeks (30 to 59 kg) 600 mg followed by 300 mg every 2 weeks (≥ 60 kg)
Asthma in adults and adolescents (aged 12 years and older)	400 mg followed by 200 mg every 2 weeks or 600 mg followed by 300 mg every 2 weeks
Asthma in pediatric patients (aged 6 to 11 years)	100 mg every 2 weeks or 300 mg every 4 weeks (15 to 29 kg) 200 mg every 2 weeks (≥ 30 kg)
Chronic rhinosinusitis with nasal polyps in adults	300 mg every other week
Eosinophilic esophagitis in adults and adolescents (aged 12 years and older)	300 mg once a week

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication and indications (**Table 2**)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes:** Go to #4	**No:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. Current Age < 21 years: Go to #4
4. Is the request for dupilumab?	**Yes:** Go to # 5	**No:** Go to #6
5. If the request is for dupilumab, is the dose appropriate for the indication (**Table 5**)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7
7. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the diagnosis Severe Atopic Dermatitis (AD)? Severe disease is defined as:[1] • 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: ○ At least 10% body surface area involved, or ○ Hand, foot, face, or mucous membrane involvement	**Yes:** Go to #9	**No:** Go to #17

Approval Criteria		
9. Is the medication being prescribed by or in consultation with a dermatologist, allergist, or a provider who specializes in care of atopic dermatitis?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for abrocitinib?	**Yes:** Go to #11	**No:** Go to #16
11. Are baseline labs (platelets, lymphocytes, lipids) documented? *Note: Abrocitinib therapy should not be initiated if platelet count is < 150,000/mm^3, absolute lymphocyte count is < 500/mm^3, absolute neutrophil count is < 1,000/mm^3, or hemoglobin is < 8 g/dL	**Yes:** Go to #12 Document Lab and Date Obtained: Platelets:_____ Lymphocytes:_____ Lipids:_____ Hemoglobin:_____	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the patient currently taking other targeted immune modulators or oral immunosuppressants?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. If the patient has renal or hepatic impairment has the dose been adjusted as described in Table 3?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Is the patient taking a strong CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2C9 inducer, CYP2C19 inducer, or antiplatelet inhibitor?	**Yes:** Go to # 15	**No:** Go to # 16

Approval Criteria		
15. If the patient is taking a strong CYP2C19 inhibitor (e.g., fluvoxamine, fluoxetine), or CYP2C9 inhibitor (e.g., fluconazole, amiodarone), or CYP2C9 inducer (e.g., rifampin, phenobarbital), or CYP2C19 inducer (carbamazepine), or antiplatelet agent has the abrocitinib dose been adjusted in Table 3 or has the interacting drug been discontinued if necessary? *Note: agents with antiplatelet properties (NSAIDs, SSRIs, etc.) should not be used during the first 3 months of abrocitinib therapy. Do not use aspirin at doses ≥ 81 mg/day with abrocitinib during the first 3 months of therapy.	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
17. Is the request for eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #18

Approval Criteria		
18. Is the request for the treatment of a patient with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #19
19. Is the request for treatment of nasal polyps?	**Yes:** Go to #20	**No:** Go to #22
20. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to #21	**No:** Pass to RPh. Deny; medical appropriateness
21. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
22. Is the request for treatment of severe asthma?	**Yes:** Go to #23	**No:** Go to #30
23. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #24	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
24. Has the patient experienced one of the following: • at least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR • taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR • at least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #25 Document number asthma exacerbations over the previous 12 months or oral corticosteroid dose over the previous 6 months or number of hospitalizations or ED visits in the past 12 months _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
25. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #26	**No:** Pass to RPh. Deny; medical appropriateness.
26. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, tezepelumab etc.)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #27
27. Is the request for tezepelumab?	**Yes:** Approve for up to 12 months.	No: Go to #28
28. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #29

Approval Criteria		
29. If the request is for asthma with an eosinophilic phenotype, can the prescriber provide documentation of one of the following biomarkers: • severe eosinophilic asthma, confirmed by blood eosinophil count ≥150 cells/µL OR • fractional exhaled nitric oxide (FeNO) ≥25 ppb in the past 12 months?	**Yes:** Approve up to 12 months, based on dosing outlined in **Table 4**. Document eosinophil count (or FeNO date):_____	**No:** Pass to RPh. Deny; medical appropriateness.
30. Is the request for treatment of eosinophilic esophagitis?	**Yes:** Go to #31	**No:** ~~Pass to RPh. Deny; medical appropriateness.~~Go to #321
31. Does the patient have a documented contraindication or failed trial of the following treatments: • Proton pump therapy for at least 8 weeks OR • Corticosteroid therapy with local administration of fluticasone multi-use inhaler for at least 8 weeks (use nasal inhaler and swallow contents of the spray).	**Yes**: Document drug and dates trialed and intolerances (if applicable): _____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
32. 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 #2733	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
33. Is there documentation from the provider that alternative treatments for the condition are inappropriate, unavailable, or ineffective?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with targeted immune modulator 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) from when treatment started OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for asthma?	**Yes:** Go to #4	**No:** Go to #6
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the number of emergency department (ED) visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
6. Is the request to renew therapy for another FDA approved indication~~eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndrome (HES), or eosinophilic esophagitis~~?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports.* *http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed March 1, 2022.*
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.
3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021
4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

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P&T Review: *10/22 (DM) 6/22 (DM); 8/21 (DM); 10/20 (KS),7/19; 7/18; 7/16*
Implementation: *1/1/23; 7/1/22; 1/1/22; 9/1/21; 8/19/19, 8/15/18, 8/16*

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 www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Examples of FUNDED indications (12/16/21)

ICD-10	Description
B37.3	Candidiasis of vulva and vagina
B37.1	Candidiasis of the lung
B37.7	Disseminated Candidiasis
B37.5-37.6, B37.81-37.84, B37.89-37.90	Candidiasis of other specified sites
B38.0-B38.4, B38.7, B38.9	Coccidiomycosis various sites
B39.0-39.5, B39.9, G02, I32, I39, J17	Histoplasmosis
B40.9,B41.0, B41.9, B48.0	Blastomycosis
B42.0-42.9,, B43.9, B44.9-45.0, B45.7, B45.9, B46.9, B48.1-48.2, B48.8, B49	Rhinosporidiosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycosis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
B48.8	Mycosis, Opportunistic
B44.81	Bronchopulmonary Aspergillus, Allergic
N73.9-75.1, N75.9, N76.0-N77.1	Inflammatory disease of cervix vagina and vulva
L03.019,L03.029, L03.039, L03.049	Cellulitis and abscess of finger and toe
P37.5	Neonatal Candida infection
B37.42,B37.49	Candidiasis of other urogenital sites

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

ICD-10	Description
L2.083, L2.10-2.11, L21.8-21.9,	Erythematosquamous dermatosis
L22	Diaper or napkin rash
L20.0-20.84, L20.89-20.9	Other atopic dermatitis and related conditions
L24.0-24.2, L25.1-25.5, L57.8, L57.9,	Contact dermatitis and other eczema

L23.0, L23.81, L24.81, L25.0, L25.2, L25.8-25.9, L55.1-55.2 , L56.8, L58.9	
L53.0-53.2, L51.0, L51.8-51.9, L52, L71.0-71.1, L71.8, L93.0, L93.2, L49.0-L49.9, L26, L30.4, L53.8, L92.0, L95.1, L98.2, L53.9	Erythematous conditions
L43.8,L44.1-44.3, L44.9,L66.1	Lichen Planus
L70.0-70.2, L70.8	Rosacea or acne
B35.1	Tinea unguium (onychomycosis)
B36.0	Pityriasis versicolor
B36.2	Tinea blanca
B36.3	Black piedra
B36.8, B36.9	Mycoses, superficial
B37.2	Cutaneous candidiasis
B37.9	Candidiasis, unspecified
R21	Rash and other nonspecific skin eruption

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

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

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

Approval Criteria		
2. Is the diagnosis funded by OHP? (See examples in Table 1).	**Yes:** Go to #3	**No:** Go to #4
3. 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.
4. 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 #5
5. Is the diagnosis not funded by OHP? (see examples in Table 2).	**Yes:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by OHP Current age < 21: Go to #9	**No:** Got to #6
6. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	**Yes:** Go to #7	**No:** Go to #119

Approval Criteria		
7. 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 #8
8. 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, basiliximab, cyclophosphamide, cyclosporine, etanercept, everolimus, hydroxychloroquine, infliximab, leflunomide, mercaptopurine, methotrexate, mycophenolate, rituximab, sirolimus, tacrolimus	**Yes:** Approve as follows: (immunocompromised patient) ORAL & TOPICAL • Course of treatment. • If length of therapy is unknown, approve for 3 months.	**No:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #9

Approval Criteria		
9. 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 #10	**No:** Pass to RPh. Deny; medical necessity.
10. 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.

~~9.~~ 11. 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: Deny; not funded by the OHP.
  ○ Deny non-fungal diagnosis (medical appropriateness)
  ○ Deny fungal ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP).
  ○ Forward any fungal ICD-10 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.		

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

Antihistamines

Goals:

- Approve antihistamines only for conditions funded by the OHP in adults. Allow case-by-case review for members covered under the EPSDT program.
- Allergic rhinitis treatment is covered by the OHP only when complicated by other diagnoses (e.g. asthma, sleep apnea).
- Promote use that is consistent with Oregon Asthma Guidelines and medical evidence. http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx

Length of Authorization:

- 6 months

Requires PA:

- Non-preferred oral antihistamines and combinations

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does patient have a diagnosis of allergic rhinitis, allergic conjunctivitis, or chronic rhinitis/pharyngitis/nasopharyngitis?	**Yes:** Go to #4	**No:** Go to #8

Approval Criteria		
4. Does the patient have asthma or reactive airway disease exacerbated by chronic/allergic rhinitis or allergies?	**Yes:** Go to #5	**No:** Go to #6
5. Does the drug profile show an asthma controller medication (e.g. ORAL inhaled corticosteroid, leukotriene antagonist, etc.) and/or inhaled rescue beta-agonist (e.g. albuterol) within the last 6 months? *Keep in mind: albuterol may not need to be used as often if asthma is controlled on other medications.*	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness. *Oregon Asthma guidelines recommend all asthma clients have access to rescue inhalers and those with persistent disease should use anti-inflammatory medicines daily (preferably orally inhaled corticosteroids).*
6. Does patient have other co-morbid conditions or complications that are funded? • Acute or chronic inflammation of the orbit • Chronic Sinusitis • Acute Sinusitis • Sleep apnea • Wegener's Granulomatosis	**Yes:** Document ICD-10 codes. Go to #7	**No:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #10
7. Does patient have contraindications (e.g. pregnancy), or had insufficient response to available treatment alternatives for the funded condition? Document.	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the diagnosis COPD or Obstructive Chronic Bronchitis?	**Yes:** Pass to RPh. Deny; medical appropriateness. Antihistamine not indicated.	**No:** Go to #9

Approval Criteria		
9. Is the diagnosis funded? Note: Chronic Bronchitis, acute upper respiratory infections, and urticarial are not funded by the OHP~~?~~	**Yes:** Pass to RPh. Deny; ~~not funded by the OHP~~medical appropriateness	**No:** Current age ≥ 21 years: Pass to RPh. ~~Go to #10~~Deny; not funded by the OHP Current age < 21 years: Go to #10
10. 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 #11	**No:** Pass to RPh. Deny; medical necessity.
11. 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.
~~9. RPh only: Is the diagnosis above the line or below the line?~~ ~~10.~~ ~~11. Above: Deny; medical appropriateness~~ ~~Below: Deny; not funded by the OHP (e.g., acute upper respiratory infections or urticaria).~~		

P&T Review: *12/22; 5/15 (AG); 9/10; 9/08; 2/06; 9/04; 5/04; 2/02*
Implementation: *TBD; 5/1/16; 7/15, 1/11, 7/09, 7/06, 3/06, 10/04, 8/02, 9/06*

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Prior Authorization Criteria Update: Sedatives

Plain Language Summary:

- How does new guidance affect the current Medicaid Open Card policy?
- Guidance was recently published from the Oregon Health Evidence Review Commission (HERC). They recommend coverage of cognitive behavioral therapy for sleep disorders starting January 2023. This is supported by current recommendations from the American Academy of Sleep Medicine and European Sleep Research Society.
- The American Academy of Sleep Medicine and the European Sleep Research Society recommend cognitive behavioral therapy (CBT) for sleep disorders:
    - that make it difficult to fall asleep or stay asleep *and*
    - where lack of sleep creates difficulty doing activities during the day.
- Providers can prescribe medicines for sleep disorders when cognitive behavioral therapy does not improve patient sleep.
- The Oregon Health Evidence Review Commission recommended that Medicaid cover sedatives for only 30 days because of side effects with longer use.
    - Side effects include increased risk of memory problems, falls, broken bones, inability to sleep without use of these medicines, and daytime sleepiness.
    - Risk of side effects may increase as people get older, particularly if over 65 years of age and when combined with other medicines that have similar side effects.
- Providers must explain to the Oregon Health Authority why someone needs a sedative before Medicaid will pay for it. This process is called prior authorization.
- Medicaid Open Card will pay for melatonin without prior authorization when prescribed for children. Melatonin is not covered for adults.
- The Drug Use Research Management program recommends policy updates to match HERC guidance.

Purpose of Update:

Beginning on January 1, 2023, the Health Evidence Review Commission (HERC) adopted a new guideline which addresses treatments for insomnia. This new policy pairs cognitive behavioral therapy for treatment of insomnia on a funded line and recommends limitation of sedative-hypnotics to short-term use only (1 month per year) in patients who are currently participating in or have previously failed to have benefit with cognitive behavioral therapy (CBT). The specific duration of treatment was recommended due to concerns with long-term risks of sedative hypnotics and increasing risk of dependence with longer-term use. Previously, both medical and pharmacological treatments for insomnia had been unfunded.

Evidence for this class was last reviewed by the Pharmacy and Therapeutics Committee in August 2022. Cognitive Behavioral Therapy (CBT) is recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine[1] and the European Sleep Research Society[2] based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.[1,2] Evidence supports efficacy of both brief CBT interventions and longer therapy.[2] Orexin receptor antagonists (suvorexant), benzodiazepines (triazolam and temazepam only), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), doxepin, and ramelteon all have weak recommendations to treat sleep onset and/or sleep maintenance insomnia based on low-quality evidence.[1] However,

long-term treatment of chronic insomnia with a sedative (≥12 weeks) is not recommended because of lack of evidence and possible adverse effects based on low-quality evidence.[2] FDA labeling for most sedative drugs indicated for insomnia recommends re-evaluation of comorbid diagnoses which could be contributing to symptoms if insomnia persists for more than 7-10 days of treatment. Trazodone, quetiapine, and diphenhydramine are not recommended due to adverse effects and lack of efficacy, and there is insufficient evidence for use of melatonin in adults.[1]

Common adverse effects associated with sedative medications include dizziness, daytime drowsiness, and somnolence. Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia. The risk of fracture may depend on the length of time people used the drugs, with new users of these drugs at greatest risk of hip fracture.[3] FDA labeling for non-benzodiazepine sedatives includes warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions. Risk for daytime impairment may be higher in women or elderly who metabolize and eliminate sedative medications more slowly from the body.[4] The FDA warns that high levels of a sedative in the bloodstream can result in impairment even if patients feel fully awake.[4] Benzodiazepine sedatives are also associated with physical dependence and a taper plan is usually recommended to minimize withdrawal symptoms and facilitate discontinuation after routine, long-term use. Provider resources and best practices for benzodiazepine tapers were recently published by the Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG).[5] Taper schedules be individualized based on patient circumstances, diagnoses, dose, and length of benzodiazepine use. Many patients may benefit in switching, or cross-tapering, to a longer-acting benzodiazepine like diazepam before reducing their total benzodiazepine dose.[5]

Recommendation:

- Update prior authorization criteria to limit sedative use to 30 days and encourage use of cognitive behavioral therapy for insomnia.

References:

1. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;13(2):307-349.
2. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26(6):675-700.
3. Oregon State University Drug Use Research and Management Program. Drug Class Update with New Drug Evaluation: Sedatives. December 2020. https://www.orpdl.org/durm/meetings/meetingdocs/2020_12_03/archives/2020_12_03_Sedatives_ClassUpdate.pdf Accessed April 12, 2022.
4. Mental Health Problems in People with Learning Disabilities: Prevention, Assessment and Management. NICE Guideline, No. 54. National Guideline Alliance (UK). London: National Institute for Health and Care Excellence (UK); 2016 Sep. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089546/. Accessed 10/27/17.
5. Oregon Health Authority. Mental Health Clinical Advisory Group. How to approach a benzodiazepine taper. May 2022. Available online at https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Tapering-Benzodiazepines.pdf. Accessed June 15, 2022.

Appendix 1. Proposed Safety Edits

Sedatives

Goals:

- Restrict use of sedatives to OHP-funded conditions. Long-term treatment of~~uncomplicated~~ insomnia is not funded~~; insomnia contributing to covered co-morbid conditions is funded.~~ .

- Encourage use of cognitive behavioral therapy for insomnia.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Limit daily zolpidem dose to the maximum recommended daily dose by the FDA.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives (e.g., sedative hypnotics, hypnotics-melatonin agonists) except melatonin in children and adolescents. Melatonin is not covered for adults over 18 years of age.

Covered Alternatives:

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

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose
Zolpidem	Ambien	10 mg
Zolpidem ER	Ambien CR	12.5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for melatonin in an adult over 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. 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 and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class. Go to #5	**No:** Go to #5

Approval Criteria		
5. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for lifetime.	**No:** Go to #6
6. Has the patient been treated with a different non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #7	**No:** Go to #9
7. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Go to #9 Document reason for switch ~~and approve duplication for 30 days~~.	**No:** Go to #8
8. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient on CPAP?	**Yes:** Go to # 11~~Approve for up to 12 months.~~	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated due to depressant effect.
11. Is the request for treatment of insomnia?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Is the patient currently engaged in cognitive behavioral therapy focused on insomnia treatment OR failed to have benefit in symptoms after 5-6 CBT interventions focused on treatment of insomnia?	**First request:** Sedative treatment can be approved for 30 days. Long-term treatment must document that benefits outweigh risks. **Subsequent request:** Go to **Renewal Criteria**	**No:** Pass to RPh. Deny; medical appropriateness.
~~11. Is the patient being treated for co-morbid:~~ ~~• Depression;~~ ~~• Anxiety or panic disorder; or~~ ~~• Bipolar disorder?~~ ~~**AND**~~ ~~Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?~~	~~**Yes:** Approve for up to 12 months.~~	~~**No:** Pass to RPh; Go to #12~~
~~12.~~13. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve ~~up to 6 months~~30 days with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** ~~Go to #13~~Deny; not funded by OHP.
~~13. RPh only: Is this a request for continuation therapy for a patient with a history of chronic benzodiazepine use where discontinuation would be difficult or unadvisable?~~	~~**Yes:** Document length of treatment and last follow-up date. Approve for up to 12 months.~~	~~**No:** Deny; medical appropriateness~~

Renewal Criteria		
1. Is the request for a slow taper plan?	**Yes:** Approve for duration of taper (not to exceed 3 months). Subsequent requests should document progress toward discontinuation,	**No:** Go to #2
~~1.~~2. Is there documentation that benefits of ongoing benefits (hospitalizations, function, quality of life), outweigh risks (memory problems, dementia, cognitive impairment, daytime sedation, falls, fractures, dependence, and reduced long-term efficacy)?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *8/22 (SS); 12/20; 7/18; 3/17; 11/14, 3/14, 5/06, 2/06, 11/05, 9/05, 2/04, 2/02, 9/01*
Implementation: *10/1/22; 1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

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Prior Authorization Criteria Update: Growth Hormones

PLAIN LANGUAGE SUMMARY:

- This review was written because the Health Evidence Review Commission (HERC) recently made changes to allow the Oregon Health Plan (OHP) to fund limited coverage of human growth hormone (HGH) for adults and to support a case-by-case review for HGH treatment in children and young adults.
- HGH is used as a medicine in people that do not make enough in their own body naturally. HGH is approved by the Food and Drug Administration to treat specific medical conditions that affect a person's ability to grow and develop. HGH is also a medication that may be illegally used to improve athletic performance or in body building. HGH should be prescribed by a doctor with special training for treating children and adults with a medical need for growth hormone.
- HGH treatment may be covered by OHP when it is medically necessary. Providers must submit documentation to support use before OHP Open Card will pay for this medicine through a process called prior authorization.

Purpose of Update:

The purpose of this prior authorization (PA) update is to align fee-for-service PA criteria with new Health Evidence Review Commission (HERC) guidance for use of human growth hormones (HGH) and their FDA-approved indications. HGH is supplied in several formulations for the treatment of a limited number of pediatric and adult conditions (see **Appendix 1** - **table 1**). HERC recently updated its guidance to allow limited coverage of HGH for adults and allow individualized review for HGH needs for children.[1]

Prior to the update, guideline note 74 restricted use of growth hormone (HGH) to children until they achieved "adult height as determined by bone age."[2] As a result, some FDA-approved indications related to pediatric-onset endocrine or developmental syndromes were not covered by the Oregon Health Plan (OHP) once adult bone age was achieved.[1] HERC has authorized use of GH to treat diagnoses with medical evidence of effectiveness and safety such as for the treatment of panhypopituitarism, iatrogenic, and other pituitary disorders (Line 40), and pituitary dwarfism (Line 386).[1] HERC guidance specified that treatment of children and adolescents with growth hormone (for any indication) must be evaluated for medical appropriateness and medical necessity on a case-by-case basis.[1] HGH therapy for children and adolescents must be initiated by and continued in consultation with a pediatric endocrinologist.[1]

Guideline note 74 also specified the conditions under which hypopituitarism (E23.0) was considered above or below the funding line.[1] Prior to the update, treatment for isolated deficiency of human growth hormone in adults was not covered.[2] Beginning in January 2023, HGH treatment may be covered for adults with hypopituitarism under the following circumstances:

1) HGH must be prescribed by or in consultation with an endocrinologist AND

2) Either of the following:

a) Growth hormone deficiency is confirmed by a negative response to a growth hormone stimulation test (e.g., serum GH levels of <5 ng/ml on stimulation testing with either of the following: glucagon or insulin); OR

b) Patient has had the pituitary removed or destroyed or has had panhypopituitarism since birth; AND

3) The prescriber certifies that the growth hormone is not being prescribed for anti-aging therapy or to enhance athletic ability or body building

If these conditions do not apply, then the adult HGH deficiency falls on Line 652 and would not be covered by OHP. However, funded conditions such as HIV associated with cachexia and short bowel syndrome are still covered for adults by FDA-approved GH agents.[1]

The growth hormone class was last reviewed in December 2021. An updated literature search did not identify any new literature that qualified for inclusion. Previous reviews have reported that somatropin (i.e., Growth Hormone, GH) is recommended as treatment option for children with growth failure associated with growth hormone deficiency (GHD), Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, and those born small for gestational age with subsequent growth failure at four years of age or later, and short stature homeobox-containing gene deficiency.[3-14] High-quality guidelines identified from previous reviews have recommended that GH be initiated and monitored by a pediatrician with specialist expertise in managing growth hormone disorders in children and that the choice of brand name product should be made on an individual basis after consideration of likelihood of adherence to treatment and cost.[13-15] In addition, it was reported that the treatment of somatropin should be discontinued if growth velocity increases less than 50% from baseline in the first year of treatment, final height is approached and growth velocity is less than 2 cm total growth in 1 year, adherence issues, or if final height is attained.[13,14] No new evidence has been found to support of any difference in efficacy/effectiveness or safety between the different somatropin products and formulations for any population or subgroup.[13-15] Previous reviews did find low quality evidence that use of GH in childhood may increase all-cause mortality as an adult and may increase incidence of cancer as an adult and increase secondary malignancies in cancer survivors.[15] Lastly, evidence was insufficient to identify a clinically meaningful benefit for GH treatment in adults.[15]

Recommendation:

- Update the growth hormone prior authorization criteria to align with HERC coverage guidance and FDA-approved indications.
- Evaluate costs in the executive session to inform PDL status.

References:

1. Health Evidence Review Commission. HERC Prioritized List of Health Services. October 1, 2022. https://www.oregon.gov/oha/HPA/DSI-HERC/PrioritizedList/10-1-2022%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed 10/18/2022.
2. Health Evidence Review Commission. HERC Prioritized List of Health Services. January 1, 2022. https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List-Archives.aspx#d152c280-dd0c-4b58-86ee-da303b826eee. Accessed 10/18/2022.
3. Genotropin® (somatropin) [prescribing information]. Pfizer, Inc.; New York (NY); 2016 Sep.
4. Humatrope® (somatropin) [prescribing information]. Lilly USA, LLC: 2016 Dec.
5. Norditropin® (somatropin) [prescribing information]. Novo Nordisk Inc.; Plainsboro (NJ); 2018 Feb.
6. Nutropin AQ® (somatropin) [prescribing information]. Genentech, Inc.; San Francisco (CA); 2016 Dec.

7. Omnitrope® (somatropin) [prescribing information]. Sandoz, Inc.; Princeton (NJ); 2016 Dec.
8. Saizen® (somatropin) [prescribing information]. EMD Serono, Inc.; Rockland (MA); 2018 May.
9. Serostim® (somatropin) [prescribing information]. EMD Serono, Inc.; Rockland (MA); 2018 May.
10. Zomacton® (somatropin) [prescribing information]. Ferring Pharmaceuticals, Inc.; Parsippany (NJ); 2018 Jan.
11. Zorbtive® (somatropin) [prescribing information]. EMD Serono, Inc.; Rockland (MA); 2017 May.
12. Skytrofa (lonapegsomatropin subcutaneous injection) [Prescribing Information]. Palo Alto, CA. Ascendis Pharma, Inc. August 2021.
13. Drug Use Research & Management Program. Drug Class Update: Growth Hormones. 2012; http://www.orpdl.org/durm/meetings/meetingdocs/2012_09_27/archives/2012_09_27_GH_Scan.pdf. Accessed October 18, 2022.
14. Drug Use Research & Management Program. Drug Class Update with New Drug Evaluation: Growth Hormones. 2021; http://www.orpdl.org/durm/meetings/meetingdocs/2021_12_02/archives/2021_12_02_GH_ClassUpdate.pdf. Accessed October 18, 2022.
15. Drug Use Research & Management Program. Literature Scan: Growth Hormones. 2017; http://www.orpdl.org/durm/meetings/meetingdocs/2017_09_28/archives/2017_09_28_Growth_Hormone_LitScan.pdf. Accessed October 18, 2022.

Appendix 1: Prior Authorization Criteria

Growth Hormones

Goal(s):

- Restrict use of growth hormone (GH) in adults for where there is medical evidence of effectiveness and safety and supported by expert guidelines.

NOTE: Treatment with GH in children and adolescents (for any indication) must be evaluated for medical appropriateness and medical necessity on a case-by-case basis.

Length of Authorization:

- Up to 12 months

Requires PA:

- All GH products require prior authorization for OHP coverage. Treatment is not included for use in antiaging therapy or to enhance athletic ability or for body building.

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. Pediatric and Adults FDA Approved Indications for Growth Hormone

	somatropin									Lonapeg-somatropin
	Genotropin	**Norditropin**	**Nutropin AQ**	Humatrope	Omnitrope	Saizen	Serostim	Zorbtive	Zomacton	Skytrofa
Pediatric Indications										
GHD	X	X	X	X	X	X			X	X
Prader-Willi Syndrome	X	X			X					
Noonan Syndrome		X								
Turner Syndrome	X	X	X	X	X				X	
Idiopathic Short Stature	X	X	X	X	X				X	
SHOX Deficiency				X					X	
Growth Failure Secondary to CKD			X							
Small for Gestational Age	X	X		X	X				X	
HIV Associated Cachexia							X			
Adult Indications										
GHD	X	X	X	X	X	X			X	
HIV Associated Cachexia							X			
SBS								X		

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; SBS = short bowel syndrome; SHOX = Short stature homeobox-containing gene

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #3
3. Has the provider documented goals of therapy and objective baseline assessment (e.g., quality of life, exercise capacity, height, body composition improvements, etc)? Note: these same assessments should be evaluated for continuation of treatment.	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for one of the conditions listed below? For children and adolescents age 17 and younger • Growth hormone deficiency (GHD) • Prader-Willi syndrome • Noonan syndrome • Turner syndrome • Idiopathic Short Stature • Growth Failure secondary to chronic kidney disease (CKD) • Small for gestational age • Short stature homeobox-containing (SHOX) gene deficiency • HIV Associated Cachexia For adults age 18 years and older • Growth hormone deficiency (GHD) • HIV Associated Cachexia • Short Bowel Syndrome (SBS)	**Yes:** Go to #6	**No:** Go to #5

Initial Approval Criteria		
5. Is this a request regarding an EPSDT* benefit for a patient 20 years old or younger?	**Yes:** Pass to RPh for final decision. Final denial decisions are based on case-by-case review of medical necessity and medical appropriateness, considering an individual child's needs. If supporting literature and patient history is provided, approve for up to 6 months. Otherwise, Deny; medical appropriateness.	**No:** Pass to RPh. Deny; medical appropriateness
6. Is this a request for initiation of growth hormone therapy?	**Yes:** Go to #7	**No:** Go to **Renewal Criteria**
7. Is the agent being prescribed by, or in consultation with, an appropriate specialist (e.g., an endocrinologist for adults or a pediatric endocrinologist or pediatric nephrologist for children/adolescents)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for a pediatric patient with Prader-Willi syndrome who also has: • Severe obesity? Or • A history of upper airway obstruction or sleep apnea? Or • Severe respiratory impairment? Note: Recombinant somatropin is contraindicated in these patients due to the risk of sudden death.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9

Initial Approval Criteria		
9. Is the request for treatment of hypopituitarism (E23.0)?	**Yes:** Go to #10	**No:** Go to #11
10. Is the growth hormone deficiency confirmed by a negative response to a growth hormone stimulation test (eg, serum GH levels of <5 ng/ml on stimulation testing with either glucagon or insulin)? OR Is there evidence that the patient had the pituitary removed/destroyed or has had panhypopituitarism since birth?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the requested product preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #12
12. Will the prescriber change to a preferred product that is medically appropriate for the condition? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Go to #13
13. Is the request for lonapegsomatropin?	**Yes:** Go to #14	**No:** Approve for up to 6 months
14. Is the request for a pediatric patient 1 year or older with a body weight >11.5 kg?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

*=Early and Periodic Screening, Diagnostic & Treatment

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Was treatment with this agent initiated in a patient prior to reaching adulthood (<18 years of age) to improve growth velocity or height?	**Yes:** Go to #3	**No:** Go to #5
3. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #6	**No:** Go to #4
4. Is there documentation that benefits of therapy continue to outweigh risks? Current guidelines recommend discontinuation of treatment once growth velocity is less than 2.5 cm per year. Risks, benefits, and goals of therapy should be reassessed in patients whose epiphyses are closed.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is there documentation of improvement from baseline as assessed by the prescribing provider?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #7
7. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 6 months

P&T Review: 12/22 (DE);12/21; 6/21;11/18; 9/17; 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
Implementation: 1/1/19; 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03

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Drug Class Update: Inhalers for Asthma/COPD

Date of Review: December 2022

Date of Last Review: Inhaled anticholinergics (Oct 2021)
Short-acting beta agonists (July 2019)
Other inhalers (Oct 2020)

Dates of Literature Search: 01/01/2020 - 10/03/2022

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

Plain Language Summary:

- This review looks at new evidence for medicines that are inhaled to treat people that have lung diseases called asthma and chronic obstructive pulmonary disease (COPD). These medicines work in several different ways. Groups of medicines that work the same way are put into the same category that are called classes. Classes include:
  - Medicines that help to quickly open up the lungs (called fast-acting beta-agonists [FABA])
  - Medicines that help to reduce swelling to open up the lungs (called an inhaled corticosteroid [ICS])
- New evidence shows that people who used both a FABA and ICS were able to breathe normaly, needed less additional medication to treat their asthma, and went to the hospital or urgent care for treatment less frequently than when people used placebo or other asthma treatments.
- In people with COPD, an inhaled medicine that combines three classes of medicines helped people breathe better than inhalers that contained only two classes of medicines. The product with 3 classes includes the medicines budesonide, glycopyrronium and formoterol fumarate compared to inhalers with only two of these medicines.
- New evidence shows that people with mild COVID-19 symptoms who were not vaccinated and used an ICS inhaler needed to go to the hospital less often than people who did not use an ICS.
- A new study compared 2 different FABA and ICS combination inhalers called formoterol/ICS and salmeterol/ICS. People who took these medicines had similar risk of severe side effects.
- The National Asthma Education Prevention Program Coordinating Committee (NAEPPCC) recommends that people with asthma use the combination of ICS-formoterol if they:
  - require medicine occasionally when they have trouble breathing or
  - have symptoms more often and require daily treatment with medicine.
- The Drug Use Research and Management Group (DURM) recommends no changes to our current policy for inhaled therapies used for people with asthma and COPD.

Author: Kathy Sentena, PharmD

Purpose for Class Update:
The purpose of this update is to review new literature on effectiveness and safety of asthma and COPD inhaled therapies published since the last reviews.

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

Conclusions:
- There were 4 high-quality systematic reviews, 3 new guidelines, 2 randomized controlled trials (RCTs) and 4 new formulations identified for this review.
- Evidence for the use of budesonide 182 mcg plus glycopyrronium 8.2 mcg plus formoterol fumarate 5.8 mcg (BGF) in people with COPD was evaluated by the Canadian Agency for Drugs and Technologies in Health (CADTH). There was moderate quality of evidence that BGF reduced the rate of moderate to severe COPD exacerbations compared with glycopyrronium 14.4 mcg plus formoterol fumarate 9.6 mcg (GFF) and budesonide 320 mcg plus formoterol fumarate 9.6 mcg (BFF) at 52 weeks and improved FEV_1 at 24 weeks when compared to GFF and BFF. The changes were Results were not clinically significant for this comparison.[1] There is insufficient direct evidence which compares this product to other triple therapy inhalers; however, indirect comparison suggest similar efficacy and safety.
- A high quality systematic review and meta-analysis evaluated the use of FABA and ICS inhalation in patients with mild asthma. The single combination inhaler of FABA/ICS reduced asthma exacerbations requiring steroids (high quality evidence), hospital admissions or unscheduled healthcare visits (low quality of evidenced), and exposure to systemic corticosteroids compared to FABA, taken as needed (low quality evidence). When compared to ICS, the use of FABA/ICS demonstrated reductions in asthma-related hospital admissions or unscheduled heath care visits (low quality of evidence).[2]
- Patients with mild COVID-19 treated with ICS, in addition to standard of care (e.g., antipyretics and antibiotics if bacterial pneumonia was suspected), had a reduced risk of hospital admission or death up to day 30.[3] Incidence of admission or death was 57 per 1000 people treated with ICS compared to standard of care (incidence 79 per 1000 people treated; relative risk [RR] 0.72; 95% confidence intervals [CI], 0.51 to 0.99) based on moderate quality evidence.[3]
- A high quality systematic review and meta-analysis evaluated risk of death and severe adverse reactions associated with formoterol/ICS compared to salmeterol/ICS.[4] There was insufficient evidence to make conclusions on mortality outcomes due to low incidence of events. Based on data for all-cause non-fatal serious events, there is probably no difference in safety profiles between formoterol/ICS compared to salmeterol/ICS (moderate quality evidence).
- New guidance from the National Asthma Education Prevention Program Coordinating Committee (NAEPPCC) recommends the use of single-inhaler ICS-formoterol both daily and as needed for individuals 4 years and older with moderate persistent asthma.[5] This single inhaler regimen is referred to as "single maintenance and reliever therapy (SMART)". Long acting muscarinic antagonists (LAMAs) are recommended in addition to an ICS in people 12 years and older who have uncontrolled persistent asthma who cannot tolerate ICS-long-acting beta-agonist (LABA).[5] The addition of LAMA is also indicated in individuals using ICS-LABA and still experiencing symptoms.[5]
- The Global Initiative for Asthma (GINA), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 and US Preventative Services Task Force (USPSTF) updates support current policy.[6,7,8]
- There is insufficient evidence for the use of inhaled therapies for asthma and COPD in non-white people and in Medicaid populations.

Recommendations:

- No changes recommended based on the review of the current evidence.
- The prior authorization (PA) criteria will be updated to align with current guideline recommendations. Recommend retiring the ICS/LABA specific criteria and making non-preferred therapies subject to general PA for non-preferred products.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- Literature for inhaled anticholinergics was last evaluated in October 2021. At the time, the NAEPPCC Expert Panel recommended the use of LAMAs in patients with asthma and conditionally recommended adding LAMA to ICS controller therapy instead of continuing the same dose of ICS alone (conditional recommendation; moderate certainty of evidence). After executive session Combivent®, Respimat®, and Incruse Ellipta® were made preferred.
- Evidence for short acting beta agonists (SABA) was reviewed July of 2019. In certain groups with asthma, the use of SABA with anticholinergics may reduce hospitalization rates when presenting to an emergency room compared to SABA use alone. No changes in policy were made.
- A list of preferred therapies are available in **Appendix 1**. All classes have PA criteria for non-preffered therapies. The LABAs require step-therapy prior to coverage of non-preferred LABA and LABA/ICS products for patients with asthma and COPD. There is PA criteria for all LAMA/LABA and LAMA/LABA/ICS products.
- The inhaled therapies for asthma and COPD are comprised of 7 classes: anticholinergics, SABAs, LABAs, ICS, ICS/LABAs, and LAMA/LABA combinations. The inhaled therapies account for a significant cost to the Oregon Health Authortiy. Compliane to the PDL ranges from a low of 25% for the LABA class to 100% for SABAs.

Background:

ASTHMA

Asthma is a chronic inflammatory condition of the lungs resulting in airway obstruction, bronchial hyperresponsiveness and airway edema. Genetics and environmental factors are thought to contribute to asthma development. Centers for Disease Control and Prevention data from 2018 reports the burden of asthma in Oregon to be over 11%.[9] Asthma is characterized by symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis is confirmed by spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after SABA use), airway obstruction that is at least partially reversible and exclusion of other potential diagnoses.[6] Asthma is characterized as being intermittent or persistent (and further divided into mild, moderate or severe). The underlying pathophysiology of asthma is multi-factorial and includes several phenotypes: eosinophil predominant, neutrophil predominant, and allergic asthma. In particular, those patients with eosinophil asthma Type 2 (T2)-high, which indicates high levels of T-helper type 2 lymphocytes, respond well to ICS therapy and biologic therapy if asthma remains uncontrolled. Patients with eosinophilic asthma also have high levels of sputum eosinophils, and while a correlation of blood eosinophil levels to sputum eosinophils is not well defined, guidelines typically diagnose eosinophilic asthma when blood eosinophils are greater than or equal to 150 cells/µL.[6] Studies of biologic therapies have evaluated use in patients with eosinophil levels of at least 150 cells/µL to more than 400 cells/µL.

Asthma treatment can be categorized as quick-relief medication and long-term control medications. Asthma treatment is inititated in a stepwise manner based on the severity of asthma symptoms.[6] Evidence demonstrates that even people with mild asthma can be at risk of exacerbations; therefore, several guidelines recommend the use of ICS-formoterol as a controller and reliever therapy, also referred to as SMART (single maintenance and reliever therapy) or MART (maintenance and reliever therapy).[5] ICS, alone or in combination, are the preferred maintenance therapy for all patients with persistent asthma.[5] If additional therapy is required to control asthma symptoms, LABAs are recommended in combination with ICS.[6] Other maintenance therapy options include leukotriene

inhibitors, methylxanthines, cromolyn sodium and nedocromil. Fast-acting beta-agonists, ICS-formoterol, anticholinergics and systemic corticosteroids are recommended for acute symptom management. Biologic asthma treatments are recommended for those patients with severe asthma that is unresponsive to controller-drug therapy.[6]

Outcome measures used in asthma trials are forced expiratory volume in one minute (FEV_1), asthma exacerbations, hospitalization, emergency room visits, and need for oral corticosteroids. Change from baseline in FEV_1 is a common surrogate endpoint used in clinical trials and clinical practice since it is highly reproducible. Research in COPD patients suggest that minimally important FEV_1 changes range from 100-140 mL.[6] Moderate-quality evidence suggests that targeting interventions for asthma based on sputum eosinophil levels in people with severe asthma that is difficult to treat may reduce the number and severity of asthma attacks in adults; however, additional research is needed.[6] The Asthma Control Questionnaire (ACQ) is used to determine symptom control. Scores range from 0-6 with higher scores indicative of worse asthma. The ACQ-5 consists of 5 questions that are averaged for a score. MCID for the ACQ-5 is a change of 0.5 points.[6]

COPD

Chronic obstructive pulmonary disease is a chronic respiratory disorder characterized by reduced expiratory flow due to irreversible airway inflammation. Airway narrowing, hyperinflation and impaired gas exchange are pathological changes associated with COPD. Chronic bronchitis and emphysema are often associated with COPD.[1] The most common cause of COPD is airway irritation, usually from cigarette smoking. In rare cases, alpha-1 antitrypsin (AAT) deficiency has been implicated in the development of early onset COPD.

Chronic cough or sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of $FEV_1/FVC < 0.70$), symptom severity, risk of exacerbations and comorbidities.[1] COPD is classified into four stages based on spirometric measurements of FEV_1/FVC: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (very severe). The Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) guidelines recommend therapeutic approaches based on disease burden (e.g., breathlessness, exercise limitations, health status and risk of exacerbations) as well as FEV_1. Patients are classified into groups A-D (low to high risk of symptoms and exacerbations).[1] This type of classification system shifts the focus from only FEV_1 measurements as these are not always indicative of COPD status.[7]

Common treatment options for patients with COPD are bronchodilators and antimuscarinic drugs (LABAs and LAMAs). For patients who require additional therapy, the combination of a LABA and LAMA is often used.[1] Triple therapy with a LABA, LAMA and ICS is recommended for those with COPD and sustained symptoms despite dual therapy.[1] Bronchodilators (short and long-acting) have demonstrated improvements in FEV_1 and symptom improvement. Long-acting bronchodilators (LAMAs and LABAs) improve lung function, dyspnea, health status and reduce exacerbation rates. Inhaled corticosteroids/LABAs have been shown to improve health status, reduce exacerbations and improve lung function compared to ICS monotherapy. Conclusive evidence of benefit has not been demonstrated with ICS alone in patients with COPD. Phosphodiesterase-4 inhibitors have a role in COPD management by minimizing airway narrowing and damage due to inflammation. Phosphodiesterase-4 inhibitors are used as add-on therapy for patients with COPD who have persistent symptoms or exacerbations despite optimal treatment with other COPD therapies. There is a lack of conclusive benefit for improved survival rates with any of the inhaled respiratory medications used in the management of COPD, and no medications have shown a preventative effect in the decline of lung function.[7]

Goals of therapy for COPD management are to improve symptoms, reduce frequency of exacerbations, improve exercise tolerance and daily activities and reduce mortality.[1] Important outcomes to access the effectiveness of therapies include: lung function, quality of life (QoL), dyspnea, exacerbation rate and/or severity, mortality and adverse events. FEV_1 is the most common surrogate outcome used in studies to determine therapy effectiveness. The minimal clinically

important difference (MCID) in FEV_1 values for COPD changes have not been clearly defined, but Cochrane reviews recommend a change of 100 mL.[7] Other sources suggest a change in percent predicted FEV_1 of 10.38% or more would correlate with a MCID.[7] The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on quality of life with scores ranging from 0-100 and higher scores indicative of more limitations. The MCID for the SGRQ is a change of 4 units.[7] The transitional dyspnea index (TDI) is a measurement of breathlessness in people with COPD. A score change of 1 unit has been shown to be clinically meaningful. Symptom are also accessed by the Modified British Medical Reasearch Council (mMRC) questionnaire which is a scale measuring dyspnea and the COPD Assessment Test (CAT) which evaluates a range of symptoms from cough to energy.[10] Smoking cessation is the only intervention shown to reduce the rate of lung function decline.

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

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

New Systematic Reviews:
<u>CADTH- Budesonide-Glycopyrronium-Formoterol Fumarate Reimbursement Review</u>
CADTH evaluated the clinical efficacy of the combination product budesonide, glycopyrronium and formoterol fumarate (BGF) for long-term maintenance treatment of patients with COPD.[1] A systematic review of the clinical benefits and adverse events of BGF identified 2 RCTs for evaluation (ETHOS and KRONOS).[11,12] Relevant outcomes of significance were COPD exacerbations, symptom relief, and incidence of chronic bronchitis and/or emphysema. Results for exacerbation outcomes are presented in **Table 1**. In the KRONOS study, the primary outcome was FEV_1 area under the curve (AUC) from 0-4 hours for BGF versus BFF, GFF or versus BUD-FOR comparisons. Change from baseline in morning pre-dose trough FEV_1 was higher for BGF compared to GFF and for BGF compared to BUD/FORM.[1] For the secondary outcome of use of rescue medications, the difference was not statistically different in KRONOS between groups but was reduced with the use of BGF in ETHOS when compared to GFF and BFF. Between group difference in SGRQ scores were not clinically significant. In ETHOS, there was a reduced risk of mortality with BGF compared to GFF (HR 0.51; 95% CI, 0.330 to 0.80) with no differences compared to BFF.[1] Mortality was not measured in KRONOS. Adverse events were similar between groups. The most common events were nasopharyngitis, and upper respiratory tract infection. Serious adverse events were reported in approximately 20% of patients treated in ETHOS and 9% treated in KRONOS.[1]

Both studies had high rates of discontinuations due to adverse events (6.1% in ETHOS and 4.25% in KRONOS) and missing data.[1] Additional limitations were under enrollment of females and lower use than expected of the LAMA-LABA combination inhaler (14%) at baseline and the overall magnitude of benefit was small for the use of triple inhalation combination therapy.

Table 1. Description of Randomized Comparative Clinical Trials.[1,11,12]

Study	Comparison	Population	Outcome	Results	Notes/Limitations
ETHOS DB, MC, PG	1. BGF MDI 2. GFF MDI 3. BFF MDI 52 week duration	Patients with moderate to very severe COPD and at least 1 exacerbation in the last year N=8,588	Moderate to severe COPD exacerbations*	Adjusted rate: 1. 1.08 2. 1.42 3. 1.24 <u>BGF vs. GFF</u> RR 0.76 (95% CI, 0.69 to 0.83) <u>BGF vs. BFF</u> RR 0.87 (95% CI, 0.79 to 0.95)	- BGF was more effective than GFF and GFF at reducing COPD exacerbations
			Lung function (FEV_1 AUC_{0-4h} mL)‡	<u>BGF vs. GFF</u> LSM 22 mL (95% CI, 4 to 39)	- Differences between groups were not clinically meaningful
			Symptoms (based on TDI focal score)	<u>BGF vs. GFF</u> 0.40 units (95% CI, 0.24 to 0.55) <u>BGF vs. BFF</u> 0.31 units (95% CI, 0.15 to 0.46)	- Symptom improvement was higher with BGF compared to GFF and BFF but the difference was not considered clinically meaningful
KRONOS DB, MC, PG	1. BGF MDI 2. GFF MDI 3. BFF MDI 4. BUD-FOR DPI (400 mcg-12 mcg active control) open-label 24 week duration	Symptomatic patients with moderate to very severe COPD N=1,902	Moderate to severe COPD exacerbations	Adjusted rate: 1. 0.46 2. 0.95 3. 0.56 4. 0.55 <u>BGF vs. GFF</u> RR 0.48 (95% CI, 0.37 to 0.64); P<0.0001 <u>BGF vs. BFF</u> RR 0.82 (95% CI, 0.58 to 1.17); P=0.2792 <u>BGF vs. BUD-FOR</u> RR 0.83 (95% CI, 0.59 to 1.18); P=0<0.0001 <u>BGF vs. BUD-FOR</u> RR 0.83 (95% CI, 0.59 to 1.18); P=0.3120	- All comparisons were prespecified superiority analysis with the exception of BFF MDI vs. BUD/FORM DPI which was prespecified as a non-inferiority analysis

			Lung function* (FEV_1 $AUC_{0\text{-}4h}$ mL)	1. 305 mL 2. 288 mL 3. 201 mL 4. 214 mL <u>BGF vs. GFF</u> LSM 16 mL (95% CI, -6 to 38); P=0.1448 <u>BGF vs. BFF</u> LSM 104 mL (95% CI, 77 to 131); P<0.0001 <u>BGF vs. BUD-FORM</u> LSM 91 mL (95% CI, 64 to 117); P<0.0001	- MCID for FEV_1 $AUC_{0\text{-}4h}$ mL is 0.10 L to 0.14 L so results are clinically significant for BGF vs BFF comparison BGF vs. BUD-FORM
			Change from baseline in morning pre-dose trough FEV_1*	1. 293 mL 2. 125 mL 3. 73 mL 4. 88 mL <u>BGF vs. GFF</u> LSM 22 mL (95% CI, 4 to 39); P=0.0139 <u>BGF vs. BFF</u> LSM 74 mL (95% CI, 52 to 95)†; P<0.0001 <u>BGF vs. BUD-FORM</u> LSM -10 mL (95% CI, -36 to 16); P=0.4390	- BGF increased morning pre-dose trough FEV_1 more than GFF and BFF but not more than BUD-FORM
			Symptoms (based on TDI focal score)	<u>BGF vs. GFF</u> 0.177 units (95% CI, -0.071 to 0.426) <u>BGF vs. BFF</u> 0.237 units (95% CI, -0.068 to 0.542) <u>BGF vs. BUD-FOR</u> 0.461 units (95% CI, 0.156 to 0.766)	- None of the comparison differences were clinically significant.

Key: * Primary outcome; † Prespecified secondary endpoint; ‡ Prespecified substudy population

Abbreviations: $AUC_{0\text{-}4h}$ – area under the curve in 0 to 4 hours; BFF – budesonide 320 mcg plus formoterol fumarate 9.6 mcg; BGF – budesonide 182 mcg plus glycopyrronium 8.2 mcg plus formoterol fumarate 5.8 mcg; FEV_1 – forced expiratory flow in 1 second; GFF – glycopyrronium 14.4 mcg plus formoterol fumarate 9.6 mcg; MCID – minimal clinically important difference; MDI – meter-dose inhaler; RR – rate ratio; TDI – Transitional Dyspnea Index (TDI)

Cochrane – Combination Fixed-dose Beta Agonist and Steroid Inhaler as Required for Adults or Children with Mild Asthma

The efficacy and safety of using a single combination therapy inhaler consisting of a FABA plus ICS for the treatment of mild asthma, as needed for symptoms, was evaluated by Cochrane in 2021. Studies that were at least 12 weeks in duration were included.[2] Single fixed-dose FABA/ICS inhaler as needed was compared to placebo, SABA as needed, ICS with SABA as needed, fixed-dose combination ICS/LABA, or fixed-dose combination ICS/FABA with as needed ICS/FABA. Six studies (n=9,656) were included and all studies used budesonide (200 mcg or 320 mcg) and formoterol (6 or 9 mcg) in a single dry powder inhaler.[2] Two-studies were open-label. Active comparators contained fast-acting bronchodilators terbutaline (0.5 mg per puff or 500 mcg) and formoterol (4.5 mcg per puff) or salbutamol (2 puffs of 100 mcg each/not available in the United States). Four studies included adults and 2 studies included people at least 12 years of age. The mean age of enrolled patients was 36 to 43 years. Overall, the studies were found to be at low risk of bias even with the inclusion of 2 open-label studies.

Results for the comparisons are available in **Table 2**. Combination therapy of FABA/ICS demonstrated reductions in asthma exacerbations requiring steroids, hospital admissions or unscheduled healthcare visits, and exposure to systemic corticosteroids in patients with mild asthma compared to FABA as needed. When compared to ICS the use of FABA/ICS demonstrated reductions in asthma-related hospital admissions or unscheduled heath care visits.[2] There were no clinically meaningful changes in perceived symptom control by patients, as measured by the ACQ-5, for any comparison.

Table 2. Results for Comparison of FABA/ICS to Active Comparators in Patients with Mild Asthma[2]

Treatment	Comparator	Outcome	Result	Strength of Evidence	Comments
FABA/ICS as needed (2 RCTs)	FABA as needed	Exacerbations requiring systemic steroids	OR 0.45 (95% CI, 0.34 to 0.60)	High	Equates to 109 people out of 1000 in the FABA group experiencing an exacerbation compared to 52 out of 1000 people taking FABA/ICS
		Asthma-related hospital admission or emergency-department or urgent care visit	OR 0.35 (95% CI, 0.20 to 0.60)	Low	Results favored FABA/ICS
		Asthma control (based on ACQ-5)*	MD -0.15 points (95% CI, -0.20 to -0.10)	Moderate	Results favored FABA/ICS but did not meet the MCID threshold of a difference of 0.5.
		Inhaled steroid dose	MD 76.50 mcg beclomethasone (the mean ICS dose was 18.7 mcg in the FABA as needed group)	Moderate	Patients treated with a combined therapy containing ICS have a higher daily inhaled steroid dose than those treated with FABA alone
		Total systemic steroid dose	MD 9.90 mg prednisolone lower in FABA/ICS group (the mean total dose in the FABA as needed group was 17.4 mg prednisolone)	Low	Similar between groups since both groups utilized small doses of systemic steroids

		Adverse Events	OR 0.82 (95% CI, 0.71 to 0.95)	Moderate	Fewer adverse events in those taking FABA/ICS as needed
FABA/ICS as needed (4 RCTs)	Maintenance ICS plus as needed FABA	Exacerbations requiring systemic steroids	OR 0.79 (95% CI, 0.59 to 1.07)	Low	Results favored as needed FABA/ICS but was not statistically significant
		Asthma-related hospital admission or emergency-department or urgent care visit	OR 0.63 (95% CI, 0.44 to 0.91)	Low	Results favored as needed FABA/ICS
		Asthma control (based on ACQ-5)*	MD 0.12 points higher	High	Results favored maintenance ICS but change from baseline was not clinically significant
		Inhaled steroid dose	MD 154.51 mcg lower in FABA/ICS group	Moderate	Results favored lower inhaled steroid doses in FABA/ICS group
		Total systemic steroid dose	MD 7 mg prednisolone lower in FABA/ICS group (the mean total dose in the FABA as needed group was 20.97 mg prednisolone)	Moderate	Similar between groups since both groups utilized small doses of systemic steroids
		Adverse Events	OR 0.96 (0.82 to 1.14)	Moderate	Incidence was similar between groups

Key: * Lower scores indicate better asthma control

Abbreviations: ACQ-5 – asthma control questionnaire-5; CI – confidence interval; FABA – fast-acting beta-agonist; ICS – inhaled corticosteroid; MD – mean difference; OR – odds ratio; RCTs – randomized controlled trials

Cochrane – Inhaled Corticosteroids for the Treatment of COVID-19

A 2022 Cochrane review evaluated the safety and efficacy of ICS use for the treatment of COVID-19.[3] Three RCTs, including 3,607 participants, evaluated people with confirmed mild COVID-19. The majority of participants were adults and those over 50 years of age had comorbidities such as hypertension, diabetes, or lung disease. Inhaled corticosteroids studied were budesonide (1600 mcg/day) and ciclesonide (640 mcg/day) and given in addition to usual care. Comparisons were made to standard of care (e.g., antipyretics and antibiotics if bacterial pneumonia was suspected).[3]

The most robust evidence was for the outcomes of hospital admission or death and symptom reduction (all initial symptoms resolved). The use of ICS resulted in a reduced risk of admission to the hospital or death up to day 30 by 57 per 1000 people treated compared to standard of care with 79 per 1000 people treated (RR 0.72; 95% CI, 0.51 to 0.99; moderate-quality evidence).[3] There was moderate-quality evidence that symptom resolution (all initial syptoms resolved) at day 14 occurred in 553 people per 1000 in those using an ICS compared to 465 per 1000 people treated with standard of care (RR 1.19; 95% CI, 1.09 to 1.30).[3] There was low-quality evidence that there was little difference in all-cause mortality and in duration (time) to symptom resolution upon comparison of ICS and standard of care.[3]

Results are mostly applicable to people with mild COVID-19. Studies were completed before the introduction of COVID vaccines so applicability of these results to vaccinated populations is unclear. There is insufficient evidence on adverse reactions, quality of life, and use in people with moderate to severe COVID.

Cochrane – Regular Treatment with Formoterol and an Inhaled Corticosteroid versus Regular Treatment with Salmeterol and an Inhaled Corticosteroid for Chronic Asthma: Serious Adverse Events

A systematic review and meta-analysis published in 2021 evaluated 11,572 adults and 723 children and adolescents with chronic asthma to evaluate formoterol or salmeterol, with an ICS, on mortality and non-fatal serious adverse events.[4] Included studies were at least 12 weeks in duration and randomized patients to either formoterol/budesonide, salmeterol/fluticasone, formoterol/extra-fine beclomethasone, formoterol/mometasone, or salmeterol/budesonide. Most of the included studies had low risk of bias.

There was insufficient evidence to make conclusions on mortality, as the rate of death was low in all studies. Forty-six adults experienced asthma-related severe adverse events.[4] Moderate quality evidence demonstrated no difference between formoterol/ICS versus salmeterol/ICS for the outcomes of all-cause non-fatal serious events in studies lasting 18 to 26 weeks.[4] The specific findings for all-cause non-fatal serious adverse events comparison were:

- formoterol/budesonide versus salmeterol/fluticasone odds ratio (OR) 1.14 (95% CI, 0.82 to 1.59);
- formoterol/beclomethasone versus salmeterol/fluticasone OR 0.94 (95% CI, 0.43 to 2.08) and
- formoterol/mometasone versus formoterol/salmeterol OR 1.02 (95% CI, 0.47 to 2.20).[4]

Limitations include a low number of serious adverse events related to asthma, making it difficult to have high confidence in comparative findings for patients treated with formoterol/ICS and salmeterol/ICS.

After review, nine 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).[13–21]

New Guidelines:

High Quality Guidelines:

NAEPPCC – Update on the Asthma Management Guidelines

Guidance for the management of asthma was updated in 2020 by the NAEPPCC.[5] Recommendations were formulated by an Expert Panel using the GRADE framework in conjunction with a methodology team. A systematic review was completed by the Agency for Healthcare Research and Quality Evidence-Based Practice Center. Conflicts of interest (COI) were disclosed and those with a high level of COI were excluded from the Expert Panel. Priority topics were identified and those pertaining to inhaled treatments will be presented.[5]

The intermittent use of ICS and LAMAs for asthma was one of the priority topics included in this update.[5] Recommendations are presented in **Table 3**. A change from previous guidance is the use of ICS-formoterol as a controller and reliever therapy, based on evidence that the combination therapy reduces asthma exacerbations.[5]

Table 3. NAEPP Recommendations for Asthma Management Inhaled Therapies[5]

Recommendation	Age Group	Strength of Recommendation
Recommendations for use of Intermittent ICS for Asthma		
Children that have recurrent wheezing triggered by respiratory tract infections and no wheezing between infections should receive a short course of daily ICS at the onset of a respiratory tract	0-4 years of age	Conditional recommendation, high strength of evidence

infection with an as-needed SABA for quick-relief therapy compared to an as needed SABA only for quick-relief therapy		
Individuals with mild persistent asthma should receive either of the following treatments as part of Step 2 therapy for worsening asthma: 1. Daily low-dose ICS and as-needed SABA for quick-relief therapy OR 2. Intermittent* as-needed SABA and an ICS used concomitantly	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
Individuals with mild to moderate persistent asthma who are likely to be adherent to daily ICS, short-term increases in the ICS dose for increased symptoms or decreased peak flow are NOT recommended	Ages 4 years and older	Conditional recommendation, low strength of evidence
Individuals with moderate to severe persistent asthma should receive ICS-formoterol in a single inhaler‡ used as both daily controller and reliever therapy† compared to either a higher-dose ICS as daily controller therapy and SABA for quick-relief therapy or the same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy	Ages 4 years and older	High certainty of evidence for ages 12 years and older, moderate certainty of evidence for ages 4 to 11 years
Individuals with moderate to severe persistent asthma should receive ICS-formoterol‡ in a single inhaler used as both daily controller and reliever therapy compared to higher-dose ICS-LABA as daily controller therapy and SABA for quick relief therapy	Ages 12 years and older	Conditional recommendation, high strength of evidence
Recommendations for the use of LAMAs for Asthma		
In individuals with uncontrolled persistent asthma, it is not recommended to add LAMA to ICS compared to adding LABA to ICS	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
In individuals not using LABA for uncontrolled persistent asthma, adding a LAMA to ICS controller therapy is recommended over continuing the same dose of ICS	Ages 12 years and older	Conditional recommendation, moderate strength of evidence
In individuals with uncontrolled persistent asthma, adding LAMA to ICS-LABA compared to continuing the same dose of ICS-LABA is recommended	Ages 12 years and older	Conditional recommendation, moderate certainty of evidence

Key: * intermittent therapy is defined as temporary use of ICS in those not regularly using ICS controller therapy; † Single-inhaler ICS-formoterol both daily and as needed is referred to as "single maintenance and reliever therapy (SMART)"; ‡ The maximum recommended formoterol dose is 12 puffs (54 mcgs) for those 12 years and older and 8 puffs (36 mcgs) for children 4 to 11 years.

GINA – Global Strategy for Asthma Management and Prevention

The Global Initiative for Asthma published an update in 2022 for the management of asthma. GINA updates their recommendations on an annual basis to guide diagnosis and management of asthma in adults and adolescents.[6] Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D (**Table 4**) .[6] Guideline limitations included to the guidelines were lack of reporting for conflicts of interest and limited discussion on barriers to implementing ecommendations.[6]

Table 4. GINA Guidance Levels of Evidence[6]

Evidence Categories	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs)	Evidence from well designed RCTs

	• High quality evidence without significant limitations	
B	• Randomized controlled trials with important limitations • Limited body of evidence	Evidence from RCTs that include only a limited number of patients, post-hoc, or subgroup analyses of RCTs or meta-analyses of RCTs
C	• Non-randomized trials • Observational studies	Evidence is from outcomes of uncontrolled or non-randomized tirlas or from observational studies
D	• Panel consensus judgement	Provision of guidance is deemed valuable but clinical literature on the subject matter is insufficient

Pharmacotherapy used to treat people with asthma is based off of asthma severity (**Table 5**). A substantial change in treatment recommendations is that monotherapy with SABAs in adults and adolescents is no longer recommended for asthma management. GINA guidelines recommend that all adults and adolescents with asthma receive an ICS-containing controller treatment.[6] Therapy can be given as a regular daily treatment for people with persistent symptoms or as-needed in people with mild asthma for symptom relief. Recommendations are divided into treatment tracks based on *the choice of reliever therapy*: Track 1 and Track 2.

- Track 1: Low dose ICS -formoterol. Preferred option due to exacerbation reduction compared to SABA monotherapy.
- Track 2: SABA for reliever therapy

Initial treatment recommendations for adults and adolescents with asthma are presented in **Table 6**. Track 1 is the preferred treatment option. Recommendations for children 6-11 years old are in **Table 7**.

Table 5. Asthma Severity Directing Therapy[6]

Mild Asthma	*Step 1* – Symptoms less than twice a month
	Step 2 – Symptoms twice a month or more, but less than daily
Moderate Asthma	*Step 3* – Symptoms most days or waking with asthma once a week or more
Severe Asthma	*Step 4* – Symptoms most days or waking with asthma once a week or more or low lung function
	Step 5 – Severely uncontrolled asthma

Table 6. GINA Recommendations for Starting Treatment in Adults and Adolescents with Asthma[6]

STEP	Treatment Recommendation Track 1*	Treatment Recommendation Track 2†
STEP 1	-As-needed low dose ICS-formoterol	-Low dose ICS whenever a SABA is taken
STEP 2	-As-needed low dose ICS-formoterol	-Low dose maintenance ICS
STEP 3	-Low dose maintenance ICS-formoterol (MART)	-Low dose maintenance ICS/LABA
STEP 4	-Medium dose maintenance ICS-formoterol (MART)	-Medium/high dose maintenance ICS/LABA
STEP 5	-Add-on LAMA -Refer for phonotypic assessment -Consider high dose maintenance ICS-formoterol +/- other pharmacotherapy	-Add-on LAMA -Refer for phonotypic assessment -Consider high dose maintenance ICS-LABA +/- other pharmacotherapy

Key: * Reliever is as-needed low-dose ICS-formoterol; † Reliever is as-needed SABA
Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MART – maintenance and reliever therapy with ICS-formoterol; SABA – short-acting beta agonist

Table 7. GINA Recommendations for Starting Treatment in Children 6-11 years with Asthma[6]

STEP	Preferred Controller Therapy *	Alternate Controller Therapy Options*
STEP 1	- Low dose ICS whenever a SABA is taken	- Consider low dose daily ICS
STEP 2	- Daily low dose ICS	- Daily LTRA *or* - Low dose ICS taken whenever a SABA is used
STEP 3	- Low dose ICS-LABA *or* - Medium dose ICS *or* - Very low dose ICS-formoterol maintenance and reliever (MART)	- Low dose ICS + LTRA
STEP 4	- Medium dose ICS-LABA *or* - Low dose ICS-formoterol maintenance and reliever therapy (MART)	- Add tiotropium *or* - Add LTRA
STEP 5	- Refer for phonotypic assessment *+/-* - Higher dose ICS-LABA *or* - Other add-on pharmacotherapy	- Add-on anti-IL5 *or* - As a last resort, consider add-on low dose OCS but consider side effects
Key: *As-needed SABA (or low dose ICS-formoterol reliever for MART) Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta agonist; IL-5 – interleukin 5; LTRA - leukotriene receptor antagonist; MART – maintenance and reliever therapy with ICS-formoterol; OCS – oral corticosticosteroids; SABA – short-acting beta agonist		

GOLD – Global Strategy for Diagnosis, Management, and Prevention of COPD

The Global Initiative for Chronic Obstructive Lung Disease updated recommendations for managing COPD in 2022.[7] A systematic review was undertaken to evaluate new literature. Guidelines are based on a systematic search of the literature and publications are reviewed for acceptance by at least two committee members that are without conflicts of interest. Evidence is graded based on criteria developed by the National Heart Lung and Blood Institute which ranks the level of evidence from A to D (**Table 8**) . Conflict of interest were documented for 76% of the committee. Other limitations include no discussion on resource implications/barriers to implementation of recommendations.

Table 8. GOLD Guidance Levels of Evidence

Evidence Categories	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs) • High quality evidence without significant limitations	Evidence from well designed RCTs
B	• Randomized controlled trials with important limitations • Limited body of evidence	Evidence from RCTs that include only a limited number of patients, post-hoc, or subgroup analyses of RCTs or meta-analyses of RCTs
C	• Non-randomized trials • Observational studies	Evidence is from outcomes of uncontrolled or non-randomized tirlas or from observational studies
D	• Panel consensus judgement	Provision of guidance is deemed valuable but clinical literature on thee subject matter is insufficient

COPD is classified based on FEV_1 and symptoms/risk of exacerbations as described in **Table 9 and Table 10**.[7] Exacerbations are also an important component of managing symptoms in people that have COPD. Exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy. Mild exacerbations are those that require treatment with SABA only, moderate require treatment with SABA and antibiotics and/or oral corticosteroids, and severe exacerbations are those that require the patient be hospitalized or visits the ER. The combination of symptomatic assessment, spirometry, and risk of exacerbations helps to determine the impact of COPD on the patient.

Table 9. Classification of Airflow Limitation for Patients wit COPD Based on 2022 GOLD Guidelines*[7]

Classification	Severity	Post-Bronchodilator FEV_1
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

* For patients with a FEV1/FVC < 0.70

Table 10. Classification of Symptoms/Exacerbation Risk for Patients wit COPD Based on 2022 GOLD Guidelines[7]

Classification	Assessment Test	Exacerbations
GOLD Category A	mMRC 0-1 or CAT <10	History of 0-1 moderate to severe exacerbations*
GOLD Category B	mMRC ≥2 or CAT ≥10	History of 0-1 moderate to severe exacerbations*
GOLD Category C	mMRC 0-1 or CAT <10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)
GOLD Category D	mMRC ≥2 or CAT ≥10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)

Key: * Not leading to hospital admission
Abbreviations: CAT – COPD Assessment Test; MRC – modified Medical Research Counsel questionnaire

Inhaled bronchodilators are recommended for regular use in people with COPD for the prevention and reduction of symptoms. Specific evidence related to their use is presented in **Table 11**.[7] Generally long-acting bronchodilators are preferred to short-acting therapies. Inhaled anti-inflammatory use is also an important component in the management of COPD (**Table 12**).[7] The use of ICS is not recommended in patients with COPD that have repeated pneumonia, blood eosinophils <100 cells/microliter or history of mycobacterial infection. Long-term ICS monotherapy is not recommended; however, long-term ICS with LABAs may be appropriate in people with a history of exacerbations despite appropriate treatment with long-acting bronchodilators.[7] There is some evidence to suggest the use of LABA/LAMA combination may have beneficial mortality effect in people with symptomatic COPD and a history of frequent or severe exacerbations.

Table 11. Evidence for the Use of Bronchodilators in COPD[7]

Recommendation	Evidence level
Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms	A
Combination of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms	A
LABAs and LAMAs significantly improve lung function, dyspnea, health status and reduce exacerbations rates	A
LAMAs have greater effect on exacerbation reduction* and decreased hospitalizations† compared with LABAs	A* and B†
Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy	A
Combination treatment with LABA/LAMA reduces exacerbations compared to monotherapy	B
Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance	B

Table 12. Evidence for the Use of Inhaled Anti-inflammatory Therapies in COPD[7]

Recommendation	Evidence level
The combination of an ICS and LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to severe COPD	A
Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease	A
Triple inhaled therapy of LABA/LAMA/ICS improves lung function symptoms, improves health status, and reduces exacerbations compared to LABA/ICS, LABA/LAMA, or LAMA monotherapy	A

Treatments for COPD should be initiated in people based on symptoms and exacerbation risk. There is no high quality evidence to guide initial therapy; however, **Figure 1** recommends treatment options based on available evidence.

Figure 1. Initial Pharmacological Management of COPD[7]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** * Consider if highly symptomatic (e.g., CAT > 20) ** Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator (short or long-acting) mMRC 0-1 CAT <10	**Group B** A Long Acting Bronchodilator (LABA or LAMA) mMRC ≥ 2 CAT ≥ 10

Abbreviations: EOS = blood eosinophil count in cells per microliter; mMRC = modified Medical Research Council dyspnea questionnaire; CAT = COPD assessment test

US Preventative Services Task Force – COPD Updated Evidence Report and Systematic Review

In 2022 the USPSTF updated treatment recommendations for the screening and management of COPD.[8] The guidance was based off of a systematic review and meta-analysis done by the Agency for Heatlhcare Research and Quality (AHRQ).[10] There were 3 new trials (n=20,058) included in the updated analysis on the use of pharmacological therapies for the treatment of COPD.[8]

There was moderate quality of evidence that the use of LABA, LAMA, ICS or LABA/ICS reduces the risk of exacerbations in people with moderate COPD.[8] Tiotropium demonstrated reduction in deterioration in people with moderate COPD and exacerbations in people with minimally symptoms and moderate airflow obstruction. Harms data from new evidence is consistent with previous findings from trials that show no serious adverse reactions from the use of LAMA, LABAs or ICS.[8] Data from observations trials suggest that there may be a increased risk of cardiovascular disease with LABA use and long-term use of ICS may affect bone health negatively.

After review, no guidelines were excluded due to poor quality.

New Formulations or Indications:

Breztri Aerosphere (budesonide 160 mcg, glycopyrrolate 9 mcg, and formoterol fumarate 4.8 mcg inhalation aerosol) – In July of 2020 a triple combination product of budesonide, glycopyrrolate, and formoterol was approved for the maintenance treatment of patients with COPD.[22] The approved dose is 2 inhalations twice daily. Two studies evaluated the use of Breztri in patients with COPD and history of previous LAMA, LABA and ICS use. Breztri reduced COPD exacerbation more than combination therapy with 2 agents over 52 weeks in trial 1 and over 24 weeks in trial 2 (**Table 13**).[22]

Table 13. Rate of Moderate to Severe Exacerbations[22]

Treatment	Mean Annual Rate	Rate Ratio vs. Comparator
Trial 1 (52 weeks, n=6388)		
Breztri Aerosphere*	1.08	N/A
GFF MDI	1.42	RR 0.76 (95% CI, 0.69 to 0.83); p<0.0001
BFF MDI	1.24	RR 0.87 (95% CI, 0.79 to 0.95); p=0.0027
Trial 2 (24 weeks, n=1,896)		
Breztri Aerosphere	NR	
GFF MDI	NR	RR 0.48 (95% CI, 0.37 to 0.64); p<0.05
BFF MDI	NR	RR 0.82 (95% CI, 0.58 to 1.17); p>0.05

Key: * budesonide 320 mcg/glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg

Abbreviations: BFF – budesonide/formoterol fumarate 320 mcg/9.6 mcg; GFF – glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg; MDI – meter dose inhaler; NR – not reported; RR – rate ratio.

ArmonAir Respiclick (fluticasone propionate) – Prescribing information for Armonair Respiclick® formulation of fluticasone was updated in April of 2022 to include the addition of a new 30 mcg strength.[23]

ArmonAir Respiclick (fluticasone propionate) – In July of 2021, ArmonAir Respiclick® received the approval for use as maintenance treatment for asthma as prophylactic therapy in pediatric patients ages 4 to 11 years.[23]

Trelegy Ellipta (fluticasone furoate-umeclidinium-vilanterol) – In September of 2022, Trelegy Ellipta® received an expanded indication from the FDA for maintenance treatment in people 18 years and older with asthma. A new dosage form of fluticasone furoate 200 mcg-umeclidinium 62.5 mcg-vilanterol 25 mcg was approved.[24]

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

Randomized Controlled Trials:
A total of 160 citations were manually reviewed from the initial literature search. After further review, 158 citations were excluded because of wrong study design (e.g., observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining two trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 14. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Papi, et al[25] DB, MC, Phase 3, RCT	1. Albuterol 180 mcg -budesonide 160 mcg as needed 2. Albuterol 180 mcg -budesonide 80 mcg as needed 3. Albuterol 180 mcg as needed	Patients (4 years and older) with uncontrolled moderate to severe asthma receiving inhaled glucocorticoid-containing maintenance therapy N=3132	The first event of severe asthma exacerbation in a time-to-event analysis	Annualized Rate Ratio: 1. 0.43 2. 0.48 3. 0.59 Albuterol 180 mcg/budesonide 160 mcg vs. Albuterol 180 mcg: HR 0.74 (95% CI, 0.62 to 0.89); P=0.001 Albuterol 180 mcg/budesonide 80 mcg vs. Albuterol 180 mcg: HR 0.84 (95% CI, 0.71 to 1.0); P=0.052	As needed albuterol 180 mcg/budesonide 160 mcg was more effective than albuterol 180 mcg in reducing the risk of severe asthma exacerbations. A majority of patients were white (81.1%) and 25.9% were Latinx or Hispanic.
Clemency, et al[26] DB, MC, Phase 3, RCT	1. Ciclesonide 320 mcg 2. Placebo 30 days	Non-hospitalized participants with symptomatic COVID-19 infection N=413	Time to alleviation of all COVID-19-related symptoms by day 30	1. 19.0 days 2. 19.0 days OR 1.28 days (95% CI, 0.84 to 1.97)	There was no difference between ciclesonide and placebo in reducing symptoms of COVID-19

Abbreviations: CI = confidence intervals; DB = double-blind; HR = hazard ratio; MC = multicenter; OR = odds ratio; RCT = randomized clinical trial.

References:

1. Canadian Agency for Drugs and Technologies in Health. Budesonide-glycopyrronium-formoterol fumarate dihydrate (Breztri Aerosphere). CADTH Reimbursement Review. 2021;Volume 1 Issue 11:144.

2. Crossinham I, Turner S, Ramakrishnan S, et al. Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. *Cochrane Database of Systematic Reviews.* 2021 May 4;5(5).CD013518.

3. Griesel M, Wagner C, Mikolajewska A, et al. Inhaled corticosteroids for the treatment of COVID-19. *Cochrane Database of Systematic Reviews.* 2022 Mar 9;3(3).CD015125.

4. O'Shea O, Stovold E, Cates CJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews*. 2021 April 14;4(4): CD007694.

5. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC). 2020 Focused updates to the asthma management guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217-1270. doi:10.1016/j.jaci.2020.10.003.

6. Global Initiative for Asthma. Global Initiative for Asthma Managment and Prevention, 2022. Available from: www.ginasthma.org. Accessed September 10, 2022.

7. Global Strategy for the Diagnosis, Managment, and Prevention of Chronic Obstructive Pulmonary Disease. Global Inititative for Chronic Obstructive Lung Disease. 2022 Report. Available at: https://goldcopd.org/2022-gold-reports-2/. Accessed September 15, 2022.

8. Webber EM, Lin JS, Thomas RG. Screening for chronic obstructive pulmonary disease: updated evidence report and systematic review for the us preventive services task force. *JAMA*. 2022;327(18):1812-1816. doi:10.1001/jama.2022.4708

9. Centers for Disease Control and Prevention. Most recent asthma data. May 2018. Available at: https://www.cdc.gov/asthma/most_recent_data.htm. Accessed February 23, 2019.

10. Lin JS, Webber EM, Thomas RG. Screening for chronic obstructive pulmonary disease: a targeted evidence update for the U.S. Preventive Services Task Force. Evidence Synthesis No. 215. AHRQ Publication No. 21-05287-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2022.

11. Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med*. 2018;6(10):747-758. doi:10.1016/S2213-2600(18)30327-8.

12. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *New England Journal of Medicine*. Published online June 24, 2020. doi:10.1056/NEJMoa1916046.

13. Pitre T, Kiflen M, Ho T, et al. Inhaled corticosteroids, COPD, and the incidence of lung cancer: a systematic review and dose response meta-analysis. *BMC Pulmonary Medicine*. 2022;22(1):275. doi:10.1186/s12890-022-02072-1.

14. Beasley R, Harrison T, Peterson S, et al. Evaluation of budesonide-formoterol for maintenance and reliever therapy among patients with poorly controlled asthma: a systematic review and meta-analysis. *JAMA Network Open*. 2022;5(3):e220615. doi:10.1001/jamanetworkopen.2022.0615.

15. Gong Y, Lv Y, Liu H, et al. Quantitative analysis of efficacy and safety of LABA/LAMA fixed-dose combinations in the treatment of stable COPD. *Therapeutic Advances in Respiratory Disease*. 2022;1:17534666211066068. doi:10.1177/17534666211066068.

16. Suzuki Y, Sato S, Sato K, et al. Treatment efficacy of LAMA versus placebo for stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Respiratory Investigation*. 2022;60(1):108-118. doi:10.1016/j.resinv.2021.08.002.

17. Zhou XJ, Qin Z, Lu J, Hong JG. Efficacy and safety of salmeterol/fluticasone compared with montelukast alone (or add-on therapy to fluticasone) in the treatment of bronchial asthma in children and adolescents: a systematic review and meta-analysis. *Chinese Medical Journal*. 2021;134(24):2954-2961. doi:10.1097/CM9.0000000000001853.

18. Lee HW, Kim HJ, Jang EJ, Lee CH. Comparisons of efficacy and safety between triple (inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta-agonist) therapies in chronic obstructive pulmonary disease: systematic review and bayesian network meta-analysis. *Respiration*. 2021;100(7):631-643. doi:10.1159/000515133.

19. Zhang Q, Li S, Zhou W, et al. Risk of pneumonia with different inhaled corticosteroids in COPD patients: a meta-analysis. *Copd: Journal of Chronic Obstructive Pulmonary Disease*. 2020;17(4):462-469. doi:10.1080/15412555.2020.1787369.

20. Rogliani P, Ritondo BL, Zerillo B, et al. Adding a second bronchodilator in COPD: A Meta-analysis on the risk of specific cardiovascular serious adverse events of tiotropium/olodaterol fixed-dose combination. *Copd: Journal of Chronic Obstructive Pulmonary Disease*. 2020;17(2):215-223. doi:10.1080/15412555.2020.1749252.

21. Guan R, Liu Y, Ren D, et al. The efficacy and safety of fluticasone propionate/formoterol compared with fluticasone propionate/salmeterol in treating pediatric asthma: a systematic review and meta-analysis. *Journal of International Medical Research*. 2020;48(3):300060519889442. doi:10.1177/0300060519889442.

22. Breztri Aerosphere (budesonide, glycopyrrolate, and formoterol) [prescribing Information]. AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2020.

23. Armonair Respiclick (fluticasone propionate) [prescribing information]. Parsippany, NJ; Teva Respiratory. Apri 2022.

24. Trelegy Ellipta (fluticasone furoate, umeclidinium, vilanterol) [prescribing Information]. GlaxoSmithKline. Research Triangle Park, NC. 2019.

25. Papi A, Chipps BE, Beasley R, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. *New England Journal of Medicine*. 2022;386(22):2071-2083. doi:10.1056/NEJMoa2203163.

26. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: A Randomized Clinical Trial. *JAMA Intern Med*. 2022;182(1):42-49. doi:10.1001/jamainternmed.2021.6759.

Appendix 1: Current Preferred Drug List

Anticholinergics, Inhaled

Generic	Brand	Form	PDL
ipratropium bromide	ATROVENT HFA	HFA AER AD	Y
ipratropium bromide	IPRATROPIUM BROMIDE	SOLUTION	Y
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	AMPUL-NEB	Y
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	MIST INHAL	Y
tiotropium bromide	SPIRIVA HANDIHALER	CAP W/DEV	Y
umeclidinium bromide	INCRUSE ELLIPTA	BLST W/DEV	Y
aclidinium bromide	TUDORZA PRESSAIR	AER POW BA	N
glycopyrrol/nebulizer/accessor	LONHALA MAGNAIR STARTER	VIAL-NEB	N
glycopyrrolate/neb.accessories	LONHALA MAGNAIR REFILL	VIAL-NEB	N
revefenacin	YUPELRI	VIAL-NEB	N
tiotropium bromide	SPIRIVA RESPIMAT	MIST INHAL	N

Beta agonists, Inhaled Long-acting

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

Beta-agonists, Inhaled Short-acting

Generic	Brand	Form	PDL
albuterol sulfate	ALBUTEROL SULFATE HFA	HFA AER AD	Y
albuterol sulfate	PROAIR HFA	HFA AER AD	Y
albuterol sulfate	PROVENTIL HFA	HFA AER AD	Y
albuterol sulfate	VENTOLIN HFA	HFA AER AD	Y
albuterol sulfate	ALBUTEROL SULFATE	SOLUTION	Y

albuterol sulfate	ALBUTEROL SULFATE	VIAL-NEB	Y
albuterol	ALBUTEROL	AER REFILL	N
albuterol sulfate	PROAIR RESPICLICK	AER POW BA	N
albuterol sulfate	PROAIR DIGIHALER	AER PW BAS	N
levalbuterol HCl	LEVALBUTEROL CONCENTRATE	VIAL-NEB	N
levalbuterol HCl	LEVALBUTEROL HCL	VIAL-NEB	N
levalbuterol HCl	XOPENEX	VIAL-NEB	N
levalbuterol HCl	XOPENEX CONCENTRATE	VIAL-NEB	N
levalbuterol tartrate	LEVALBUTEROL TARTRATE HFA	HFA AER AD	N
levalbuterol tartrate	XOPENEX HFA	HFA AER AD	N

Corticosteroids, Inhaled

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

Corticosteroid/LABA Combination Inhalers

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

LAMA/LABA Combination Inhalers

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

Appendix 2: Abstracts of Comparative Clinical Trials

Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial

Objective: To determine the efficacy of the inhaled steroid ciclesonide in reducing the time to alleviation of all COVID-19-related symptoms among nonhospitalized participants with symptomatic COVID-19 infection.

Design, setting, and participants: This phase 3, multicenter, double-blind, randomized clinical trial was conducted at 10 centers throughout the US and assessed the safety and efficacy of a ciclesonide metered-dose inhaler (MDI) for treating nonhospitalized participants with symptomatic COVID-19 infection who were screened from June 11, 2020, to November 3, 2020.

Interventions: Participants were randomly assigned to receive ciclesonide MDI, 160 µg per actuation, for a total of 2 actuations twice a day (total daily dose, 640 µg) or placebo for 30 days.

Main outcomes and measures: The primary end point was time to alleviation of all COVID-19-related symptoms (cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell) by day 30. Secondary end points included subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19.

Results: A total of 413 participants were screened and 400 (96.9%) were enrolled and randomized (197 [49.3%] in the ciclesonide arm and 203 [50.7%] in the placebo arm; mean [SD] age, 43.3 [16.9] years; 221 [55.3%] female; 2 [0.5%] Asian, 47 [11.8%] Black or African American, 3 [0.8%] Native Hawaiian or other Pacific Islander, 345 [86.3%] White, and 1 multiracial individuals [0.3%]; 172 Hispanic or Latino individuals [43.0%]). The median time to alleviation of all COVID-19-related symptoms was 19.0 days (95% CI, 14.0-21.0) in the ciclesonide arm and 19.0 days (95% CI, 16.0-23.0) in the placebo arm. There was no difference in resolution of all symptoms by day 30 (odds ratio, 1.28; 95% CI, 0.84-1.97). Participants who were treated with ciclesonide had fewer subsequent emergency department visits or hospital admissions for reasons related to COVID-19 (odds ratio, 0.18; 95% CI, 0.04-0.85). No participants died during the study.

Conclusions and relevance: The results of this randomized clinical trial demonstrated that ciclesonide did not achieve the primary efficacy end point of reduced time to alleviation of all COVID-19-related symptoms.

Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi , Bradley E Chipps , Richard Beasley, Reynold A Panettieri Jr, Elliot Israel , Mark Cooper , Lynn Dunsire , Allison Jeynes-Ellis , Eva Johnsson , Robert Rees , Christy Cappelletti , Frank C Albers

Background: As asthma symptoms worsen, patients typically rely on short-acting β_2-agonist (SABA) rescue therapy, but SABAs do not address worsening inflammation, which leaves patients at risk for severe asthma exacerbations. The use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, as rescue medication might reduce the risk of severe asthma exacerbation.

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

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

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

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 03, 2022
Search Strategy:

#	Searches	Results
1	Ipratropium/ or ipratropium.mp.	2660
2	tiotropium.mp. or Tiotropium Bromide/	1986
3	umeclidinium.mp.	309
4	glycopyrrolate.mp. or Glycopyrrolate/	1674
5	revefenacin.mp.	41
6	salmeterol.mp. or Salmeterol Xinafoate/	3153
7	arformoterol.mp. or Formoterol Fumarate/	1910
8	formoterol.mp. or Formoterol Fumarate/	2878
9	olodaterol.mp.	252
10	albuterol.mp. or Albuterol/	11071
11	levalbuterol.mp. or Levalbuterol/	156
12	Budesonide/ or budesonide.mp.	6988
13	Fluticasone/ or fluticasone.mp.	5025
14	mometasone.mp. or Mometasone Furoate/	1309
15	beclomethasone.mp. or Beclomethasone/	3952
16	Budesonide/ or budesonide.mp.	6988
17	ciclesonide.mp.	458
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	30459
19	limit 18 to (english language and humans and yr="2020 -Current")	1721
20	limit 19 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	160

Appendix 4: Key Inclusion Criteria

Population	People with asthma and chronic obstructive pulmonary disease (COPD)
Intervention	Inhaled therapies for people with asthma or COPD
Comparator	Active therapies or placebo
Outcomes	Lung function, symptoms, hospitalizations and mortality
Timing	NA
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Long-acting Beta-agonists (LABA)

Goals:

- To optimize the safe and effective use of LABA therapy in patients with asthma and COPD.
- ~~Step-therapy required prior to coverage of non-preferred LABA products:~~
    - ~~Asthma: inhaled corticosteroid, short-acting beta-agonist.~~
    - ~~COPD: inhaled short-acting bronchodilator.~~

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA products

Covered Alternatives:

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease?	**Yes:** Go to #56	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Approve for up to 12 months ~~**Yes:** Go to #5~~	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded
5. ~~Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?~~	~~**Yes:** Approve for up to 12 months~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
6. ~~Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?~~	~~**Yes:** Go to #7~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
5. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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

Long-acting Beta-agonist/Corticosteroid Combination (LABA/ICS)

Goals:

- To optimize the safe and effective use of LABA/ICS therapy in patients with asthma and COPD.
- ~~Step-therapy required prior to coverage:~~
  - ~~Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.~~
  - ~~COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist).~~ ~~Preferred LABA/ICS products do NOT require prior authorization.~~

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA/ICS products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the provider consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease?	**Yes:** Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers. ~~**Yes:** Go to #7~~	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers. ~~**Yes:** Go to #5~~	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. ~~Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?~~	~~**Yes:** Go to #6~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
6. ~~Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?~~	~~**Yes:** Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
7. ~~Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?~~	~~**Yes:** Go to #8~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
8. ~~Is there a documented trial of an inhaled corticosteroid (ICS) or does the patient have moderate or severe persistent asthma?~~	~~**Yes:** Approve for up to 12 months. Stop coverage of all other ICS and LABA inhalers.~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

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

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

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

Length of Authorization:
- Up to 12 months

Requires PA:
- All LAMA/LABA and LAMA/LABA/ICS products

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Go to #8~~9~~	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
~~5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?~~	~~**Yes:** Go to #6~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~10.~~5. Is the request for a LAMA/LABA combination product?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).~~**Yes:** Go to #7~~	**No:** Go to #6~~8~~
~~11. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol), or ≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization?~~	~~**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~15.~~6. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Go to #7~~Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~16.~~7. Is there documentation that the prescriber is willing to stop coverage of all other LAMA, LABA, and ICS inhaler combination products?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~17.~~8. Does the patient have an active prescription for an on-demand short-acting acting beta-agonist (SABA) and/or for ICS-formoterol?	**Yes:** Go to #~~910~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~18.~~9. Is the request for Trelegy Ellipta (ICS/LAMA/LABA) combination product and is there a documented trial of an ICS/LABA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers (with the exception of ICS-formoterol which may be continued)~~.~~	**No:** Pass to RPh. Deny; medical appropriateness.

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

Inhaled Corticosteroids (ICS)

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

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred ICS products

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for treatment of asthma or reactive airway disease?	**Yes:** Go to #6~~7~~	**No:** Go to #4
4. Is the request for treatment of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an inhaled long-acting ~~n on-demand short-acting~~ bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months ~~**Yes:** Go to #6~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~6. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?~~	~~**Yes:** Approve for up to 12 months~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~10.~~6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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Drug Class Update: Influenza

Date of Review: December 2022

Date of Last Review: Jan 2019
Dates of Literature Search: 11/01/2018 - 10/07/2022

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

Plain Language Summary:

- This review looks at new evidence for medicines that are used to treat or prevent seasonal flu (influenza).
- New evidence shows that:
  - People treated with peramivir or oseltamivir for seasonal flu had similar rates of poor outcomes and of pneumonia.
  - Children between 1 year and 12 years old taking oseltamivir for seasonal flu had slightly more side effects compared to baloxavir. Side effects of oseltamivir were usually mild.
  - People 12 years and older prescribed baloxavir or oseltamivir to treat seasonal flu had similar rates of side effects. These medicines also had the same impact on the time it takes for flu symptoms to disappear.
- The Food and Drug Administration (FDA) has updated the approved reasons to use certain medications for seasonal flu.
  - Peramivir can now be used to treat seasonal flu in people as young as 6 months.
  - Baloxavir can now be used to treat seasonal flu in people as young as 5 years.
  - Baloxavir can now be used to prevent seasonal flu in people as young as 5 years if they are in close contact with someone who has seasonal flu.
- The Infectious Diseases Society of America (IDSA) recommends medications called neuraminidase inhibitors (NAI) to treat and prevent seasonal flu, especially in people who are most likely to become very unwell from seasonal flu because of other health conditions. Oseltamivir is a common neuraminidase inhibitors.
- Under the current policy, providers must explain to the Oregon Health Authority why someone needs a non-preferred flu medicine or a preferred flu medicine for more than 5 days before Medicaid will pay for it. This process is called prior authorization (PA). We recommend changes to this policy to match new FDA indications and age ranges.

Purpose for Class Update:
The purpose of this class update is to review the literature for new comparative evidence since the last class update for influenza antivirals.

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Research Questions:

1) Is there new comparative evidence related to efficacy for the influenza antivirals for important outcomes (e.g., clinical cure, hospitalizations, mortality)?
2) Is there new comparative evidence for harms for the influenza antivirals?
3) Are there any subpopulations which would receive more benefit or suffer more harm from specific influenza antivirals?

Conclusions:

- There are 1 guideline[1], 1 systematic review[2], and 3 new comparative randomized controlled trials (RCTs)[3-5] included in this review.
- Guidelines from the Infectious Diseases Society of America (IDSA) include recommendations for influenza treatment, post-exposure prophylaxis, and in rare cases pre-exposure prophylaxis.[1]
    - Treatment for outpatients at higher risk of influenza complications are supported by high quality evidence, while treatment for those at lower risk, even if symptomatic and likely to come into contact with higher risk individuals, is supported by low-quality evidence.
    - Neuraminidase inhibitors (NAI) are recommended for influenza treatment. Combination NAI and routine use of doses higher than Food and Drug Administration (FDA) approval are not recommended (high quality evidence)
    - Short-term and longer term (duration of season) preexposure prophylaxis with oseltamivir or zanamivir should be considered in select groups of patients at high risk for morbidity and mortality (evidence level varies by patient group).
    - Postexposure prophylaxis starting within 48 hours of exposure and continuing 7 days can be considered in select patient populations at high risk for morbidity and mortality. (moderate-quality evidence)
- A high-quality systematic review comparing a single dose of intravenous (IV) peramivir 600 mg to oral oseltamivir 75 mg twice daily for 5 days found no statistical differences in rate of influenza complications (peramivir 2.5% vs. oseltamivir 4.1%; relative risk [RR]=0.70; 95% confidence interval [CI] 0.36 to 1.38; I^2=0%) or pneumonia (peramivir 2.2% vs oseltamivir 2.7%; RR=0.74; 95% CI 0.37 to 1.51; I^2=0%).[2]
- A single randomized controlled trial (RCT) of weight-based, single dose baloxavir versus weight based, twice daily oseltamivir given for 5 days for influenza treatment in children aged 1 year to less than 12 years (N=176) which looked at safety as the primary outcome, found slightly higher rates of adverse events (AE) in oseltamivir (2.6% vs. 8.6%, statistics not performed). There were no deaths, serous AEs, or hospitalizations.[3]
- A single RCT of baloxavir (single, weight-based 40 mg or 80 mg dose) versus oseltamivir 75 mg twice daily for 5 days for influenza treatment in patients 12 years and older (N=1163) found no statistical difference in time to symptom improvement (baloxavir 73.2 hours vs. oseltamivir 81.1 hours; median difference -7.7 hours; 95% CI -7.9 to 22.7) and similar AE rate (25% vs. 28%, respectively).[4]
- A single open-label, randomized trial of IV peramivir 600 mg daily for two days (P600), IV peramivir 300 mg as a single dose (P300), or oseltamivir 75 mg twice daily for 5 days (O75) in patients 16 to 70 years with influenza and pre-existing chronic respiratory diseases (N=214) found no statistical difference in the cumulative rate of time versus symptoms (CATVS; an index area under the curve of the total score of cough, sore throat, and nasal congestion for 2 weeks) for the higher peramivir dose (P600 vs. O75, estimated difference -78.36; 95% CI -215.69 to 58.96), although the lower dose did reach statistical significance (P300 vs O75 estimated difference -145.07; 95% CI -284.57 to -5.56; p=0.0416). The AE rate was highest with high-dose peramivir (25.7%) compared to lower-dose peramivir (13.4%) or oseltamivir (13.9%).[5] Neither of these peramivir dosing strategies are FDA approved.
- High quality direct comparisons between various antiviral agents remains limited.
- There is insufficient evidence to support combination therapy of NAIs and other antivirals in outpatients.
- Peramivir (RAPIVAB) received an expanded FDA-approved indication for treatment of acute uncomplicated influenza in patients as young as 6 months.[6]
- Baloxavir marboxil (XOFLUZA) has a new suspension formulation, received an expanded indication for postexposure prophylaxis, and expanded age indications down to 5 years for both postexposure prophylaxis and for influenza treatment in otherwise healthy patients.[7]

Recommendations:

- No changes to preferred drug list (PDL) are recommended based on the review of clinical evidence.
- Update prior authorization (PA) criteria with expanded indications and age ranges for peramivir and baloxavir (**Appendix 5**).
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- Evidence assessment of antivirals for treatment of influenza with a new drug evaluation for baloxavir marboxil was presented to the Pharmacy and Therapeutics (P & T) Committee in 2019. At that time, there was no new comparative evidence assessing the efficacy or safety of antivirals for treatment or prevention of influenza. Low strength evidence found that baloxavir marboxil reduced the median time to symptom improvement by 26.5 hours compared to placebo. There was insufficient evidence in patients with comorbid medical conditions or patients with severe influenza. Adverse events observed with baloxavir are similar to influenza disease and include diarrhea, bronchitis, nausea, nasopharyngitis, and headache. Resistance mutations were documented in 11% of patients in clinical trials.
- Prior reviews found insufficient direct comparative evidence between NAIs to assess the comparative efficacy or safety of these drugs. Compared to placebo, the average time to symptom improvement has been documented as 14 to 21 hours in otherwise healthy adults if NAIs were started within 48 hours of symptom onset (based on moderate-quality evidence). With prophylactic use of oseltamivir or zanamivir in adults or children, the risk of developing influenza is decreased by 2-4% compared to placebo, and there is low to insufficient quality evidence that treatment with NAIs does not impact risk of complications or rate of hospitalization. At the time of the last review, rimantadine was made non-preferred due to lack of evidence for influenza and insufficient evidence for use in other conditions. Similarly, peramivir was non-preferred due to limited available evidence.
- Prior authorization is required for all non-preferred products and for more than 5 days of preferred products to limit prophylactic use to patients at increased risk of complications from influenza. Preferred drug list (PDL) status for all influenza antivirals is presented in Appendix 1.

Background:

Influenza is a common respiratory viral infection spread through respiratory particles. Common symptoms of influenza are generally mild for many patients and include fever, chills, myalgia, headache, nausea, and fatigue. In some patients, influenza infection is severe and may result in death. It is estimated that approximately 140,000 to 710,000 yearly hospitalizations are associated with influenza, and 12,000 to 52,000 patients die from influenza yearly.[8] The 2020-2021 season had minimal influenza activity,[8] likely due to coronavirus-19 related lockdowns. Similarly, the symptomatic cases in 2021-2022 were about one-third to one-fourth of normal years, with 98.6% being influenza A and the H3N2 strain predominating.[9] Complications of influenza can include pneumonia, bronchitis, otitis media, and death. Complications may arise from the influenza virus itself or may be caused by comorbid infections or conditions which worsen with influenza infection.

Influenza viruses are classified based on viral types (influenza A and B). Influenza A is further classified into viral subtypes based on surface proteins hemagglutinin (H) and neuraminidase (N). The primary preventive treatment for influenza is vaccination. Influenza vaccines are recommended for all patients over 6 months of age who do not have contraindications to the vaccine. Formulations include inactivated vaccines, live attenuated vaccines, and recombinant vaccines. Vaccines may be administered via intradermal injection, intramuscular injection, jet injection, or nasal spray. For the 2022-2023 influenza vaccines, no changes were made to the A(H1N1)pdm09 or the B/Yamagata egg-based, cell-based, or recombinant vaccine recommended components.[9] The recommended A(H3N2) component was changed to an A/Darwin/9/2021 (H3N2)–like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)–like virus for cell-based or recombinant vaccines.[9] The B/Victoria component recommendation was changed to a B/Austria/1359417/2021–like virus.[9]

Antiviral treatment may be considered in acute uncomplicated influenza infection within 48 hours of symptom onset to reduce duration of symptoms. The Centers for Disease Control and Prevention (CDC) recommend treatment with antivirals for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated or progressive illness; or is at higher risk for influenza complications.[10] Patients considered to be at high risk for complications from influenza include patients greater than 65 years of age, children less than 2 years of age, people with chronic comorbid conditions (including those with respiratory, cardiovascular, metabolic, neurologic, immunosuppressive, endocrine, kidney or liver disease), pregnant or postpartum individuals, Native Americans, patients with BMI greater than 40, and patients residing in long-term care facilities.[10] Prophylactic treatment with antivirals is not routinely recommended by the CDC, but may be considered in the following circumstances after exposure to a person with influenza: patients at high risk of complications who cannot receive the vaccine, patients with severe immune deficiencies or those who may not respond to influenza vaccination, or patients at high risk of influenza during the first 2 weeks after vaccination.[10] Only oseltamivir, zanamivir, and baloxavir are indicated as prophylactic agents. Antivirals have the best evidence of benefit if no more than 48 hours have elapsed since the initial exposure and, if started prophylactically, should be continued for 7 days after the last known exposure.[10]

Antivirals FDA-approved for treatment of acute uncomplicated influenza include NAIs (oseltamivir, zanamivir, peramivir), adamantanes (amantadine and rimantadine), and a polymerase acidic (PA) cap-dependent endonuclease inhibitor (baloxavir marboxil).[10] Ages of approval for treatment and prophylaxis vary by agent. The CDC recommends use of oseltamivir for ages below its FDA approval for treatment in infants less than 14 days old and prophylaxis as young as 3 months. When treating pre-term infants, CDC recommends American Academy of Pediatrics (AAP) guidance for lower weight-and-gestational-age-based dosing, due to their presumed slower drug clearance due to immature renal function.[10] In persons who are pregnant, oseltamivir is the preferred antiviral treatment. Baloxavir marboxil is not recommended due to lack of evidence in pregnancy. Circulating influenza A viruses continue to have high levels of resistance to amantadine and rimantadine and these antivirals are not recommended for treatment or prevention of influenza. The CDC has tested 314 of 1782 influenza viruses genetically characterized for susceptibility to NAIs, and 3 strains (influenza A H1N1pdm09 viruses with NA-H275Y amino acid substitution known to convey oseltamivir resistance) were not inhibited normally by NAIs when tested phenotypically. When testing 535 of 1757 influenza viruses genetically characterized for susceptibility to baloxavir were tested phenotypically, one strain (influenza A H3N2 with PA-138M amino acid substitution) had reduced susceptibility.[9]

The most common outcome evaluated in influenza antiviral clinical trials is symptom improvement. Symptom severity and time to symptom improvement is often self-reported and evaluated using numeric rating scales with alleviation of symptoms defined as complete resolution or presence of only mild symptoms. Other clinically meaningful outcomes of interest include prevention of influenza complications, morbidity, mortality, hospitalizations, and serious AEs.

Usage of medications for influenza is seasonally driven and varies between years based on local and regional outbreaks. In Oregon Medicaid Fee-for-Service patients, use from October 2021 through May of 2022 varied from 6 to 60 claims in each quarter and preferred agents were most commonly used.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews.

When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

Intravenous Peramivir Versus Oseltamivir For Patients With Influenza[2]

A 2021 review compared the efficacy of IV peramivir and oral oseltamivir for treatment of polymerase chain reaction or rapid antigen test confirmed influenza. The primary outcomes of interest were incidence of complications and pneumonia. Seven RCTs with sample sizes ranging from 34 to 562 participants were included in the analysis.[2] Most studies restricted to adults or older children, and influenza clinical symptom definitions varied.[2] Peramivir dosing varied somewhat, with 4 studies using the FDA-approved 600 mg single dose regimen, while oseltamivir dosing matched standardized 75 mg twice daily for 5 days (weight based for children).[2] Four studies required symptom presentation within 48 hours, while the remaining included patients with onset 72 to 96 hours prior to enrollment.[2] There were some concerns for bias in 4 studies, low risk in 2 studies, and high risk of bias in a single study.[2] This single study had the lowest patient enrollment of any included RCT.[2]

The incidence of total complications between 600 mg peramivir and the standard oseltamivir regimen found no significant difference between the two therapies (peramivir 2.5% vs. oseltamivir 4.1%; RR=0.70; 95% CI 0.36 to 1.38; I^2=0%).[2] Meta-analysis of the 4 RCTs using the 600 mg peramivir dose compared to standard oseltamivir found no differences in overall incidence in rate of pneumonia (peramivir 2.2% vs oseltamivir 2.7%; RR=0.74; 95% CI 0.37 to 1.51; I^2=0%).[2]

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).[11-22]

New Guidelines:

High Quality Guidelines:

Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[1]

The IDSA published a December 2018 update of previous 2009 guidelines. The focus was on the care of children, pregnant and postpartum individuals, and nonpregnant adults as well as patients who are severely immunocompromised (e.g., hematopoietic stem cell and solid organ transplant recipients). Consultation is recommended with the CDC website for most up to date information regarding influenza vaccines, influenza tests, and approved antiviral medications.[1] The literature and regulatory website search was conducted through January 2018. Of note, initial baloxavir approval was in October 2018. Recommendations were graded as described in **Table 1**. Recommendations relevant to outpatient treatment and prophylaxis are summarized below.

Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines[1]

Category and Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use

B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

In patients with confirmed or suspected influenza, the following should be treated with antivirals:[1]

- Adults and children with documented or suspected influenza, irrespective of influenza vaccination history:
  - Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization *(A-II).*
  - Outpatients of any age with severe or progressive illness, regardless of illness duration *(A-III).*
  - Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients *(A-II).*
  - Children younger than 2 years and adults ≥65 years *(A-III).*
  - Pregnant individuals and those within 2 weeks postpartum *(A-III).*
- Adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history:[1]
  - Outpatients with illness onset ≤ 2 days before presentation *(C-I).*
  - Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised *(C-III).*
  - Symptomatic healthcare providers who care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised *(C-III).*

IDSA recommends that patients who meet treatment criteria should receive a NAI such as oseltamivir, inhaled zanamivir, or IV peramivir, but not a NAI combination *(A-I)* and not routinely at higher doses than FDA approved *(A-I).*[1] Uncomplicated influenza in otherwise healthy outpatients should include 5 days of oseltamivir or inhaled zanamivir, or a single IV dose of peramivir *(A-I)*.[1] Longer durations may be considered in some patients including with documented or suspected immunocompromising condition or those requiring hospitalization for severe lower respiratory tract disease *(C-III)*.[1]

Patients who should be considered for antiviral chemoprophylaxis in the absence of an exposure or institutional outbreak are included below. Oseltamivir or inhaled zanamivir should be used rather than amantadine (*A-II*).[1]

- Duration of the season (to begin as soon as influenza activity is detected in community and continued for duration of community influenza activity [A-II]).
  - Adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are severely immunocompromised) *(C-II).*
  - Adults and children aged ≥ 3 months who have the highest risk of influenza-associated complications, such as recipients of hematopoietic stem cell transplant in the first 6 to 12 months post-transplant and lung transplant recipients *(B-II*).

- Short-term duration
    - With prompt administration of inactivated influenza vaccine for unvaccinated adults and children aged ≥ 3 months who are at high risk of developing complications from influenza in whom influenza vaccination is expected to be effective when influenza activity has been detected in the community *(C-II*).
    - In unvaccinated adults, including healthcare personnel, and for children aged ≥ 3 months who are in close contact with persons at high risk of developing influenza complications during periods of influenza activity when influenza vaccination is contraindicated or unavailable and these high-risk persons are unable to take antiviral chemoprophylaxis (*C-III*).

Postexposure prophylaxis can be considered in certain non-institutionalized, asymptomatic patients detailed below. Postexposure chemoprophylaxis should begin as soon as possible after exposure, and ideally no later than 48 hours after exposure (*A-III*), and should last for 7 days in a non-outbreak setting (*A-III*).[1] After 48 hours once-daily chemoprophylaxis should not be started, but symptomatic patients should receive treatment (*A-III*).[1]

- Asymptomatic adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza (e.g., severely immunocompromised persons) and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, after household exposure to influenza *(C-II).*
- With prompt administration of influenza vaccination for adults and children aged ≥ 3 months who are unvaccinated and are household contacts of a person at very high risk of complications from influenza (e.g., severely immunocompromised persons), after exposure to influenza *(C-II).*

Additional Guidelines for Clinical Context:

<u>Recommendations for Prevention and Control of Influenza in Children 2021-2022[23]</u>

The AAP issued a technical report in 2022. Recommendations are not graded and do not include a systematic review methodology. The report focuses heavily on vaccination recommendations.

AAP defines people at high risk of influenza complications as:[23]

- Children < 5 years, and especially those < 2 years, regardless of the presence of underlying medical conditions
- Adults ≥ 50 years, and especially those ≥ 65 years
- Children and adults with chronic pulmonary disease (including asthma and cystic fibrosis); hemodynamically significant cardiovascular disease (except
- hypertension alone); or renal, hepatic, hematologic (including sickle cell disease and other hemoglobinopathies), or metabolic disorders (including diabetes mellitus)
- Children and adults with immunosuppression attributable to any cause, including that caused by medications or by HIV infection
- Children and adults with neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Children and adults with conditions that compromise respiratory function or handling of secretions (including tracheostomy and mechanical ventilation)
- Women who are pregnant or postpartum during the influenza season
- Children and adolescents < 19 years who are receiving long-term aspirin therapy or salicylate-containing medications (including those with Kawasaki disease
  and rheumatologic conditions) because of increased risk of Reye syndrome

- American Indian/Alaska Native people
- Children and adults with obesity (i.e., BMI ≥ 40 for adults and based on age for children)
- Residents of chronic care facilities and nursing homes

This report included dosing recommendations for adults, children, infants, and preterm infants (oseltamivir only for preterm infants). Preterm infant dosing has not been evaluated by the FDA, though with available pharmacokinetic and safety data the CDC and AAP recommend use in term and preterm infants as benefits of use in neonatal influenza likely outweigh risks.[1,10] Patients at higher risk of complications should be offered treatment.

Oseltamivir remains the agent of choice for treatment while inhaled zanamivir is an alternative in those who do not have chronic respiratory disease. Oseltamivir, inhaled zanamivir, and baloxavir all have indications for use as chemoprophylaxis in certain ages. Decisions regarding prophylaxis should weigh risk of complications for exposed patient, vaccination status, type and duration of contract, public health recommendations in local area, and clinical judgment, and should begin within 48 hours of exposure.[23]

Resistance to antivirals can emerge, though testing of the 2019-2020 circulating viruses showed almost no resistance to NAIs and none to baloxavir. Baloxavir resistance has been reported in Japan where it is more widely used. Amantadine and rimantadine resistance to influenza A continues to persist and they are not currently recommended for use.[23]

After review, no guidelines were excluded due to poor quality.

New Formulations or Indications:

- Peramivir (RAPIVAB)[6]:
    - Expanded indication for treatment of acute uncomplicated influenza in patients **6 months** of age and older who have been symptomatic for no more than two days. (January 2021)
- Baloxavir marboxil (XOFLUZA):[7]
    - Expanded indication for treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours who are otherwise healthy expanded to include pediatric patients **5 years of age** and older. (August 2022)
    - Expanded indication for post-exposure prophylaxis of influenza in patients **5 years of age** and older following contact with an individual who has influenza. (August 2022)
    - Expanded indication for **post-exposure prophylaxis** of influenza in patients 12 years of age and older following contact with an individual who has influenza. (November 2020)
    - **Suspension formulation** approved in for treatment of flu in ages 12 years and older and post-exposure prophylaxis in patients 12 years of age and older (November 2020)
    - Indication updated from “treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours” to “acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and **who are otherwise healthy, or at high risk of developing influenza-related complications**”. (October 2019)

New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Baloxavir marboxil[7]	XOFLUZA	October 2019	Warnings and Precautions	Hypersensitivity subsection added

Randomized Controlled Trials:

A total of 69 citations were manually reviewed from the initial literature search. After further review, 66 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Baker et al.[3] miniSTONE-2 MC, DB, DD, RCT	1. baloxavir -oral -Wt-based single dose ranging from 2mg/kg to 40 mg N=117 2. oseltamivir -oral -wt-based BID doses for 5 d ranging from 30 mg to 75 mg per dose -wt based N=59 -2:1 randomization -Stratification by age -1 to <5 years -5 to <12 years Followed x 29 d	-children 1 to 11 years -Clinical influenza diagnosis, but otherwise healthy -2018/2019 Northern Hemisphere influenza season -symptom onset </= 48 h -excluded if hospitalization required or other antiviral use	Safety	AE incidence 1. 46.1% 2. 53.4% AE related to study drug 1. 2.6% 2. 8.6% Most common AE Gastrointestinal 1. 10.4% 2. 17.2% Withdrawal d/t AE 1. 2 -accidental OD of oseltamivir placebo -grade 2 rash on day 4 2. 0 No deaths, serious AE, or hospitalizations	--sites in US, South America, and Europe -Predominant strains: -Influenza A H3N2 65.5% -Influenza A H1N1pdm09 24.1% -Influenza B 6%
Ison et al.[4] CAPSTONE-2	1. baloxavir wt-based x 1 dose	-outpatients 12 years and older -ILI	TTIIS in mITT Time from start of treatment to patient-	<u>Efficacy</u> Median mITT 1. 73.2 h	-551 sites in 17 countries and territories -Influenza A H3N2 48%

MC, DB, DD, RCT	2. oseltamivir 75 mg BID x 5 d 3. placebo N= 2184 mITT N=1163 1:1:1 randomization Stratified by: -baseline symptom score -pre-existing or worsening symptoms at onset of illness compared to pre-influenza -region -weight	-≥ one risk factor for influenza-associated complications -symptom onset ≤ 48 h	reported improvement in all 7 influenza associated symptoms 7 influenza symptoms: -cough -sore throat -headache -nasal congestion -feverishness or chills -muscle or joint pain -fatigue Frequency and severity of AEs	2. 81.0 h 3. 102.3 h 1 vs. 2 Median difference 7.7 h 95% CI -7.9 to 22.7 h <u>Safety</u> Any AE 1. 183 (25% 2. 202 (28%) 3. 216 (30%) TRAE leading to study withdrawal 1. 2 (<1%) 2. 3 (<1%) 3. 2 (<1%) Serious AE (excluding death) 1. 0 2. 2 (<1%) 3. 2 (<1%) Death 1. 0 2. 0 3. 0	-Influenza B 42% -Influenza A H1N1 7% -"high-risk" for complications adapted from CDC definition -mITT population included those with paired baseline and f/u samples confirmed influenza + by RT-PCR and received at least one dose of study drug -missing data not imputed -sponsor involved in study design, data collection, data analysis, and manuscript preparation. Data compiled by sponsor and analyzed by sponsor-employed statistician.
Kato et al.[5] MC, OL, RCT	1. IV peramivir 600 mg daily x 2 d 2. IV peramivir 300 mg x 1 dose 3. oseltamivir 75 mg BID x 5 d 1:1:1 randomization N = 214	-age 16 to 70 years -inpatient or outpatient -confirmed influenza A or B -preexisting chronic respiratory diseases (bronchial asthma, COPD, or pulmonary fibrosis) -symptom onset ≤ 48 h	CATVS in ITT Expressed as index value for AUC of total score of cough, sore throat, nasal congestion from start of study drug administration to 2 wk post-administration	<u>Efficacy</u> Mean (SD) 1. 782.78 (487.17) 2. 717.35 (347.55) 3. 856.34 (404.99) 1 vs 3 Est difference -78.36 95% CI -215.69 to 58.96 2 vs 3 Est difference -145.07 95% CI -284.57 to -5.56 P=0.0416	-50 sites, all in Japan -FDA approved peramivir dose 600 mg IV x 1 dose -inpatient status ranged from 2.8% (oseltamivir) to 10.4% (peramivir 300mg) - preexisting chronic respiratory disease was bronchial asthma in >90% of patients -non-standard endpoint metric

		-excluded if on mechanical ventilator		Safety TEAE 1. 25.7% 2. 13.4% 3. 13.9% Severe AE 1. 2 (vomiting, pneumonia) 2. 1 (pneumococcal pneumonia) 3. 0	

Abbreviations: AE = adverse events; AUC = area under the curve; BID = twice daily; d = days; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CATVS = cumulative area of time vs symptoms; COPD = chronic obstructive pulmonary disorder; DB = double-blind; DD = double-dummy; h= hours; f/u = follow-up; ILI = influenza-like illness; ITT = intent-to-treat; ITTi = intent-to-treat influenza-infected; IV =intravenous; MC = multicenter; mITT = modified intention-to-treat; OD = overdose; OL = open-label; RCT = randomized clinical trial, RT-PCR = reverse transcription-polymerase chain reaction molecular assay; TEAE = treatment-emergent adverse events; TRAE = treatment-related adverse event; TTIIS = time to improvement of influenza symptoms; US = United States; wk = week; wt = weight.

References:

1. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. *Clin Infect Dis.* 2019;68(6):e1-e47.
2. Fang Y-H, Hsu T-H, Lin T-Y, et al. Comparing intravenous peramivir with oral oseltamivir for patients with influenza: a meta-analysis of randomized controlled trials. *Expert Review of Anti-infective Therapy.* 2021;19(8):1039-1046.
3. Baker J, Block SL, Matharu B, et al. Baloxavir Marboxil Single-dose Treatment in Influenza-infected Children: A Randomized, Double-blind, Active Controlled Phase 3 Safety and Efficacy Trial (miniSTONE-2). *Pediatr Infect Dis J.* 2020;39(8):700-705.
4. Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis.* 2020;20(10):1204-1214.
5. Kato M, Saisho Y, Tanaka H, Bando T. Effect of peramivir on respiratory symptom improvement in patients with influenza virus infection and pre-existing chronic respiratory disease: Findings of a randomized, open-label study. *Influenza Other Respir Viruses.* 2021;15(1):132-141.
6. Peramivir (RAPIVAB) prescribing information. BioCryst Pharmaceuticals Inc. Durham, NC. Jan 2021.
7. Baloxavir marboxil (XOFLUZA) prescribing information. Genentech, Inc. South San Francisco, CA. August 2022.
8. Centers for Disease Control and Prevention. Disease Burden of Influenza. Last reviewed October 4, 2022. Available at: https://www.cdc.gov/flu/about/burden/index.html. Accessed October 11, 2022.
9. Merced-Morales A, Daly P, Abd Elal AI, et al. Influenza Activity and Composition of the 2022–23 Influenza Vaccine — United States, 2021–22 Season. MMWR Morb Mortal Wkly Rep 2022;71:913–919. DOI: http://dx.doi.org/10.15585/mmwr.mm7129a1.
10. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. Last reviewed Sept 9, 2022. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed October 11, 2022.
11. Beard KR, Brendish NJ, Clark TW. Treatment of influenza with neuraminidase inhibitors. *Curr Opin Infect Dis.* 2018;31(6):514-519.
12. Chen JY, Wei SK, Lai CC, Weng TS, Wang HH. A Meta-Analysis Comparing the Efficacy and Safety of Peramivir with Other Neuraminidase Inhibitors for Influenza Treatment. *Medicina.* 2020;56(2):05.
13. Choi M, Lee SH, Chang GT. Herbal Medicine Treatment for Influenza: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *American Journal of Chinese Medicine.* 2020;48(7):1553-1576.
14. Kuo YC, Lai CC, Wang YH, Chen CH, Wang CY. Clinical efficacy and safety of baloxavir marboxil in the treatment of influenza: A systematic review and meta-analysis of randomized controlled trials. *Journal of Microbiology, Immunology & Infection.* 2021;54(5):865-875.
15. Liu JW, Lin SH, Wang LC, Chiu HY, Lee JA. Comparison of Antiviral Agents for Seasonal Influenza Outcomes in Healthy Adults and Children: A Systematic Review and Network Meta-analysis. *JAMA netw.* 2021;4(8):e2119151.
16. Okoli GN, Rabbani R, Al-Juboori A, Copstein L, Askin N, Abou-Setta AM. Antiviral drugs for coronavirus disease 2019 (COVID-19): a systematic review with network meta-analysis. *Expert Rev Anti Infect Ther.* 2022;20(2):267-278.
17. Su HC, Feng IJ, Tang HJ, Shih MF, Hua YM. Comparative effectiveness of neuraminidase inhibitors in patients with influenza: A systematic review and network meta-analysis. *J Infect Chemother.* 2022;28(2):158-169.
18. Taieb V, Ikeoka H, Ma FF, et al. A network meta-analysis of the efficacy and safety of baloxavir marboxil versus neuraminidase inhibitors for the treatment of influenza in otherwise healthy patients. *Current Medical Research & Opinion.* 2019;35(8):1355-1364.
19. Taieb V, Ikeoka H, Wojciechowski P, et al. Efficacy and safety of baloxavir marboxil versus neuraminidase inhibitors in the treatment of influenza virus infection in high-risk and uncomplicated patients - a Bayesian network meta-analysis. *Current Medical Research & Opinion.* 2021;37(2):225-244.
20. Tejada S, Campogiani L, Sole-Lleonart C, Rello J. Alternative Regimens of Neuraminidase Inhibitors for Therapy of Hospitalized Adults with Influenza: A Systematic Review of Randomized Controlled Trials. *Advances in Therapy.* 2020;37(6):2646-2666.
21. Tejada S, Jansson M, Sole-Lleonart C, Rello J. Neuraminidase inhibitors are effective and safe in reducing influenza complications: meta-analysis of randomized controlled trials. *Eur J Intern Med.* 2021;86:54-65.

22. Zhao Y, Huang G, He W, et al. Efficacy and safety of single-dose antiviral drugs for influenza treatment: A systematic review and network meta-analysis. *J Med Virol.* 2022;94(7):3270-3302.
23. Committee On Infectious D. Recommendations for Prevention and Control of Influenza in Children, 2021-2022. *Pediatrics.* 2021;148(4).

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
zanamivir	RELENZA	INHALATION	BLST W/DEV	N
oseltamivir phosphate	OSELTAMIVIR PHOSPHATE	ORAL	CAPSULE	Y
oseltamivir phosphate	TAMIFLU	ORAL	CAPSULE	Y
oseltamivir phosphate	OSELTAMIVIR PHOSPHATE	ORAL	SUSP RECON	Y
oseltamivir phosphate	TAMIFLU	ORAL	SUSP RECON	Y
rimantadine HCl	FLUMADINE	ORAL	TABLET	N
rimantadine HCl	RIMANTADINE HCL	ORAL	TABLET	N
baloxavir marboxil	XOFLUZA	ORAL	TABLET	N
peramivir/PF	RAPIVAB	INTRAVEN	VIAL	

Appendix 2: Abstracts of Comparative Clinical Trials

Baker J, Block SL, Matharu B, et al. Baloxavir Marboxil Single-dose Treatment in Influenza-infected Children: A Randomized, Double-blind, Active Controlled Phase 3 Safety and Efficacy Trial (miniSTONE-2). *Pediatr Infect Dis J.* 2020;39(8):700-705.

BACKGROUND: Baloxavir marboxil (baloxavir) is a novel, cap-dependent endonuclease inhibitor that has previously demonstrated efficacy in the treatment of influenza in adults and adolescents. We assessed the safety and efficacy of baloxavir in otherwise healthy children with acute influenza.
METHODS: MiniSTONE-2 (Clinicaltrials.gov: NCT03629184) was a double-blind, randomized, active controlled trial enrolling children 1-<12 years old with a clinical diagnosis of influenza. Children were randomized 2:1 to receive either a single dose of oral baloxavir or oral oseltamivir twice daily for 5 days. The primary endpoint was incidence, severity and timing of adverse events (AEs); efficacy was a secondary endpoint.
RESULTS: In total, 173 children were randomized and dosed, 115 to the baloxavir group and 58 to the oseltamivir group. Characteristics of participants were similar between treatment groups. Overall, 122 AEs were reported in 84 (48.6%) children. Incidence of AEs was similar between baloxavir and oseltamivir groups (46.1% vs. 53.4%, respectively). The most common AEs were gastrointestinal (vomiting/diarrhea) in both groups [baloxavir: 12 children (10.4%); oseltamivir: 10 children (17.2%)]. No deaths, serious AEs or hospitalizations were reported. Median time (95% confidence interval) to alleviation of signs and symptoms of influenza was similar between groups: 138.1 (116.6-163.2) hours with baloxavir versus 150.0 (115.0-165.7) hours with oseltamivir.
CONCLUSIONS: Oral baloxavir is well tolerated and effective at alleviating symptoms in otherwise healthy children with acute influenza. Baloxavir provides a new therapeutic option with a simple oral dosing regimen.

Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis.* 2020;20(10):1204-1214.

Background Baloxavir marboxil (hereafter baloxavir), a selective inhibitor of influenza cap-dependent endonuclease, was approved in 2018 in the USA and Japan for the treatment of uncomplicated influenza in otherwise healthy individuals aged 12 years and older. We aimed to study the efficacy of baloxavir in outpatients at high risk of developing influenza-associated complications.
Methods We did a double-blind, placebo-controlled and oseltamivir-controlled trial in outpatients aged 12 years and older in 551 sites in 17 countries and territories. Eligible patients had clinically diagnosed influenza-like illness, at least one risk factor for influenza-associated complications (eg, age older than 65 years), and a symptom duration of less than 48 h. Patients were stratified by baseline symptom score (≤14 vs ≥15), pre-existing and worsened symptoms at onset of illness compared with pre-influenza (yes or no), region (Asia, North America and Europe, or southern hemisphere), and weight (<80 kg vs ≥80 kg), and randomly assigned (1:1:1) via an interactive web-response system to either a single weight-based dose of baloxavir (40 mg for patients weighing <80 kg and 80 mg for patients weighing ≥80 kg; baloxavir group), oseltamivir 75 mg twice daily for 5 days (oseltamivir group), or matching placebo (placebo group). All patients, investigators, study personnel, and data analysts were masked to treatment assignment until database lock. The primary endpoint was time to improvement of influenza symptoms (TTIIS) in the modified intention-to-treat population, which included all patients who received at least one dose of study drug and had RT-PCR-confirmed influenza virus infection. Safety was assessed in all patients who receved at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT02949011.
Findings 2184 patients were enrolled from Jan 11, 2017, to March 30, 2018, and randomly assigned to receive baloxavir (n=730), placebo (n=729), or oseltamivir (n=725). The modified intention-to-treat population included 1163 patients: 388 in the baloxavir group, 386 in the placebo group, and 389 in the oseltamivir group. 557 (48%) of 1163 patients had influenza A H3N2, 484 (42%) had influenza B, 80 (7%) had influenza A H1N1, 14 patients had a mixed infection, and 28 had infections with non-typable viruses. The median TTIIS was shorter in the baloxavir group (73·2 h [95% CI 67·2 to 85·1]) than in the placebo group (102·3 h [92·7

to 113·1]; difference 29·1 h [95% CI 14·6 to 42·8]; p<0·0001). The median TTIIS in the oseltamivir group was 81·0 h (95% CI 69·4 to 91·5), with a difference from the baloxavir group of 7·7 h (–7·9 to 22·7). Adverse events were reported in 183 (25%) of 730 patients in the baloxavir group, 216 (30%) of 727 in the placebo group, and 202 (28%) of 721 in the oseltamivir group. Serious adverse events were noted in five patients in the baloxavir group, nine patients in the placebo group, and eight patients in the oseltamivir group; one case each of hypertension and nausea in the placebo group and two cases of transaminase elevation in the oseltamivir group were considered to be treatment related. Polymerase acidic protein variants with Ile38Thr, Ile38Met, or Ile38Asn substitutions conferring reduced baloxavir susceptibility emerged in 15 (5%) of 290 baloxavir recipients assessed for amino acid substitutions in the virus.
Interpretation Single-dose baloxavir has superior efficacy to placebo and similar efficacy to oseltamivir for ameliorating influenza symptoms in high-risk outpatients. The safety of baloxavir was comparable to placebo. This study supports early therapy for patients at high risk of complications of influenza to speed clinical recovery and reduce complications.

Kato M, Saisho Y, Tanaka H, Bando T. Effect of peramivir on respiratory symptom improvement in patients with influenza virus infection and pre-existing chronic respiratory disease: Findings of a randomized, open-label study. *Influenza Other Respir Viruses.* 2021;15(1):132-141.

BACKGROUND: The efficacy of neuraminidase inhibitors on improvement of respiratory symptoms triggered by influenza in patients with pre-existing chronic respiratory diseases is unknown. METHODS: This 2-week, randomized, open-label study evaluated intravenous peramivir 600 mg on two consecutive days (peramivir-repeat), peramivir 300 mg single dose (peramivir-single), and oral oseltamivir 75 mg twice daily for 5 days in patients with confirmed influenza and chronic respiratory diseases. Patients recorded symptom scores daily. The primary endpoint of cumulative area of time vs symptoms (CATVS) was expressed as an index value of area under the curve vs time of the total score of cough, sore throat, and nasal congestion from baseline to 2 weeks. RESULTS: Of 214 randomized patients, 209 (56% female, 77% aged <65 years, 94% outpatients, 91% bronchial asthma, 62% influenza A) received >/=1 dose of study drug. Mean (standard deviation) CATVS was similar for peramivir-repeat (782.78 [487.17]) vs peramivir-single (717.35 [347.55]; P = .4371), and for peramivir-repeat vs oseltamivir (856.34 [404.99]; P = 1.00). However, CATVS was significantly shorter for peramivir-single vs oseltamivir, with an estimated treatment difference (TD) of -145.07 (95% confidence interval: -284.57, -5.56; P = .0416). In subgroup analyses, CATVS was significantly shorter for peramivir-single vs oseltamivir among patients with influenza A (TD: -206.31 [-383.86, -28.76]; P = .0231), bronchial asthma (TD: -156.57 [-300.22, -12.92]; P = .0328), baseline respiratory severity score <5 (TD: -265.32 [-470.42, -60.21]; P = .0120), and age <65 (TD: -184.30 [-345.08, -23.52]; P = .0249). CONCLUSIONS: In patients with chronic respiratory diseases, peramivir-single was not significantly different from peramivir-repeat and was more effective than oseltamivir at alleviating respiratory symptoms.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 1, 2018 to Oct 7th, 2022

1	Zanamivir/ae, tu [Adverse Effects, Therapeutic Use]	361	Advanced
2	Oseltamivir/ae, tu [Adverse Effects, Therapeutic Use]	1606	Advanced
3	Rimantadine/ae, tu [Adverse Effects, Therapeutic Use]	281	Advanced
4	baloxavir.mp.	268	Advanced
5	peramivir.mp.	506	Advanced
6	1 or 2 or 3 or 4 or 5	2565	Advanced
7	limit 6 to (english language and humans and yr="2018 -Current" and (clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	94	Advanced

Appendix 4: Key Inclusion Criteria

Population	**Patients with or at risk for influenza**
Intervention	Drugs in Appendix 1
Comparator	Drugs listed in Appendix 1
Outcomes	Symptom Improvement (fever, cough, sore throat, muscle pain, malaise, etc) Quality of Life, Morbidity, Mortality
Timing	Prevention Acute treatment within 48 hours of symptom onset
Setting	Outpatient

Antivirals - Influenza

Goal:

- Restrict use of extended prophylactic influenza antiviral therapy to high-risk populations recognized by the Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA).

Length of Authorization:

- Up to 30 days

Requires PA:

- Non-preferred drugs for point of sale (POS) or provider administered drugs (PAD).
- Oseltamivir therapy for greater than 7~~5~~ days

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is the antiviral agent to be used to treat a current influenza infection?	**Yes:** Go to #4	**No:** Go to #5

Approval Criteria		
4. 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 by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for length of therapy or 5 days, whichever is less.	**No:** Approve based on standard FDA or compendia-supported dosing for influenza treatment. Note: baloxavir and peramivir are FDA approved as a single dose for treatment of influenza.
5. Is the antiviral prescribed oseltamivir, zanamivir, or baloxavir?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the request for post-exposure chemoprophylaxis AND does the patient have any of the following CDC[1] and IDSA[2] criteria that may place them at increased risk for complications ~~requiring chemoprophylaxis~~? • Persons at high risk of influenza complications during the first 2 weeks following vaccination after exposure to an infectious person (6 weeks in children not previously vaccinated and require 2 doses of vaccine). • Persons with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to an infectious person. • Persons at high risk for complications from influenza who cannot receive influenza vaccine after exposure to an infectious person. • Residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution. • Pregnancy and ~~women~~ individuals up to 2 weeks postpartum (including after pregnancy loss) who have been in close contact with someone suspected or confirmed of having influenza.	**Yes:** Approve for duration of prophylaxis or 30 days, whichever is less. Current recommended duration of prophylaxis: 7 days (after last known exposure; minimum 2 weeks to control outbreaks in institutional settings and hospitals, and continue up to 1 week after last known exposure.	**No:** ~~Pass to RPh. Deny; medical appropriateness.~~ Go to #7

Approval Criteria		
7. Is the request for pre-exposure prophylaxis with oseltamivir or zanamivir AND does the patient meet IDSA[2] criteria that would qualify for prophylaxis for duration of season? • Adults and children aged ≥3 months who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (eg, persons who are severely immunocompromised). • Adults and children aged ≥3 months who have the highest risk of influenza-associated complications, such as recipients of hematopoietic stem cell transplant in the first 6–12 months posttransplant and lung transplant recipients.	**Yes:** Approve for duration of prophylaxis or 9 months, whichever is less.	**No:** Pass to RPh. Deny; medical appropriateness.

References:
1. ~~Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinician.pdf. Accessed June 2, 2015.~~ Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. Last reviewed Sept 9, 2022. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed October 11, 2022.
2. ~~Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2009; 48:1003-32.~~ Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. *Clin Infect Dis.* 2019;68(6):e1-e47.

P&T/DUR Review: *12/22 (SF); 1/19 (SS); 1/16; 1/12; 9/10*
Implementation: *TBD; 3/1/19; 4/1/18; 10/13/16; 2/12/16; 1/11*

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Drug Class Update with New Drug Evaluations: Topical Products for Inflammatory Skin Conditions

Date of Review: December 2022

Date of Last Review: June 2022 (Topical Products for Skin Inflammatory Skin Conditions)
September 2017 (Topical Anti-Psoriatics)

Dates of Literature Search: 01/01/2017 – 09/01/2022

Generic Name:
Roflumilast
Tapinarof

Brand Name (Manufacturer):
Zoryve™ (Arcutis Biotherapeutics)
Vtama® (Dermavant Sciences, Inc.)

Dossiers Received: yes

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

Plain Language Summary:

- Is there any new evidence for different topical medicines (treatments applied to the skin) for skin conditions including psoriasis, eczema (dry, itchy, red skin), and vitiligo (patchy loss of skin color) that would change the current policy of topical medicines for skin conditions?
- Psoriasis is a life-long condition that can cause red patches of thickened skin (plaques) and itching. The most commonly affected parts of the body are the elbows, knees, body, and scalp.
- One review looked to see if using topical pimecrolimus or tacrolimus caused cancer. People who apply pimecrolimus or tacrolimus may have a slightly increased risk of lymphoma. Lymphoma is a cancer of the lymphatic system, which is part of the body's germ-fighting defense system. This study did not find an overall increased risk cancer when these medicines are used
- The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) recommend several topical medicines to reduce irritation, redness, and itching in adults with psoriasis. These medicines include steroids like hydrocortisone, vitamin D products (calcipotriene, calcitriol), coal tar preparations, and vitamin A products (tazarotene).
- Topical medicines have not been studied very well in children and teenagers. The highest quality evidence is for a combination product containing calcipotriene and a steroid called betamethasone in people that are 12 years of age and older.
- This review also looked at the evidence for 2 new topical medicines, roflumilast and tapinarof, recently approved by the Food and Drug Administration (FDA) to treat psoriasis.
- Two 2-month studies showed that when roflumilast cream is applied to areas of the skin with psoriasis in people that were 2 years and older, the thickness of the skin improved and the redness decreased more than when people used a skin cream without medicine. People that used roflumilast cream did not experience very many side effects. The most common side effects were diarrhea and headache.

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- Two 3-month studies showed that tapinarof cream helped improved skin redness, itching and irritation from psoriasis in adults better than a skin cream without medicine. In these studies, some people developed itching and a rash where they put the tapinarof cream on their skin.
- Medicaid will pay for most generic topical steroid creams and ointments, calcipotriene, tazarotene, and an ointment that has both calcipotriene and a steroid called betamethasone.
- Providers must explain to the Oregon Health Authority why someone needs roflumilast or tapinarof cream before Medicaid will pay for it. This process is called prior authorization. Medicaid will pay for some older and less expensive topical medicines without prior authorization. Tapinarof and roflumilast have not been studied compared to older and less expensive agents to see if they work better.

Purpose for Class Update:
To review evidence for topical agents approved to treat inflammatory skin conditions published since the last literature scan and to evaluate place in therapy for 2 topical agents, roflumilast and tapinarof, recently FDA-approved for treatment of plaque psoriasis (PsO).

Research Questions:
1. Is there new evidence regarding the comparative safety and efficacy of topical agents to manage inflammatory skin conditions?
2. For adults and children with PsO, what is the safety and effectiveness of roflumilast 0.3% cream?
3. For adults with PsO, what is the safety and effectiveness of tapinarof 1% cream?
4. Are there patients based on demographics characteristics (i.e., age, race, ethnicity, gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one topical agent is more effective or associated with fewer adverse events in treating inflammatory skin diseases?

Conclusions:
- Since the last review of topical agents for inflammatory skin diseases, one systematic review[1] and 2 guidelines[2,3] were published.
- A 2021 systematic review and meta-analysis investigated the association between topical calcineurin inhibitor use and risk of cancer including lymphoma, keratinocyte carcinoma and melanoma.[1] Compared with non-active comparators, moderate quality evidence from observational studies suggests there is no association between topical calcineurin inhibitor use and overall cancer risk (relative risk [RR], 1.03; 95% confidence interval [CI], 0.92 to 1.16).[1] However, moderate quality evidence suggests lymphoma risk is elevated with topical calcineurin inhibitor use when compared with both nonactive comparators (RR, 1.86; 95% CI, 1.39 to 2.49) and topical corticosteroids (RR, 1.35; 95% CI, 1.13 to 1.61).[1] In summary, these findings suggest an association between topical calcineurin inhibitor use and risk of lymphoma but without an increased risk of other cancers.[1]
- In July 2020, the American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) published recommendations for the treatment of adult psoriasis with topical therapy.[2] Moderate-to-high quality of evidence (QoE) supports a strong recommendation for the use of the following medications in managing psoriasis in adults:
    - Topical corticosteroids for up to 4 weeks the treatment of mild-to-severe psoriasis not involving intertriginous areas (high QoE).[2]
    - Topical vitamin D analogues (i.e., calcipotriene, calcitriol) for up to 52 weeks for the treatment of mild-to-moderate psoriasis (moderate-to-high QoE).[2]
    - Mild-to-high-potency topical corticosteroids in combination with tazarotene for 8 to 16 weeks for mild-to-moderate psoriasis (high QoE).[2]
    - Topical salicylic acid for 8 to 16 weeks for mild-to-moderate psoriasis (moderate-to-high QoE).[2]
    - Coal tar preparations for treatment of mild-to-moderate psoriasis (moderate-to-high QoE).[2]

- In November 2019, the AAD-NPF published recommendations for the treatment of psoriasis in pediatric patients.[3] Most of the available evidence for administering topical medications in children and adolescents ranges from low-to-moderate quality, resulting in recommendations based on inconsistent or limited-quality evidence.[3] Combination products containing calcipotriene and betamethasone are FDA-approved for use in children ages 12 years and older with mild-to-moderate PsO for use on the body and scalp.[4] The evidence for use of this product in children and adolescents is considered moderate-to-high QoE by AAD-NPF.[3]
- There is insufficient evidence to base conclusions on the comparative safety and efficacy of topical agents for treatment of inflammatory skin conditions. specific to demographic characteristics, socioeconomic status, concomitant medications, severity of disease, or co-morbidities, for individuals with inflammatory skin disease.
- Roflumilast 0.3% cream, a selective inhibitor of phosphodiesterase type 4 (PDE-4), received FDA approval July 2022 for topical treatment of PsO, including intertriginous areas, in patients 12 years of age and older.[5] Two phase 3 multicenter, double-blind, vehicle-controlled RCTs, DERMIS-1 and DERMIS-2, supported the FDA-approval of topical roflumilast.[6] The primary endpoint was IGA success, defined as the percentage of patients who achieved IGA status of 0 or 1 and a 2 grade or greater improvement in IGA score from baseline at week 8.[6] In both studies, moderate-quality evidence showed a greater percentage of roflumilast-treated patients achieved IGA success at week 8 compared with vehicle-treated patients (DERMIS-1: 42.4% vs. 6.1%, respectively; difference, 39.6%; 95% CI 32.3 to 46.9; p<0.001 and DERMIS-2: 37.5% vs. 6.9%, respectively; difference, 28.9%; 95% CI 20.8% to 36.9%; p<0.001).[6] The number of pediatric patients assessed in these trials was small, making it difficult to draw firm conclusions regarding efficacy of roflumilast in this population.
- There were low rates of application-site adverse effects (AEs) with roflumilast 0.3% cream in phase 3 clinical trials.[5] The most frequently reported AEs included diarrhea, headache, insomnia, and nausea.[5]
- Tapinarof 1% cream, a novel aryl hydrocarbon receptor agonist, received FDA-approval for the topical treatment of PsO in adults May 2022.[7] Two identical, double-blind, multi-center, phase 3, vehicle-controlled, randomized clinical trials (PSOARING 1 and PSOARING 2) evaluated the safety and efficacy of tapinarof 1% cream in treating adults with mild-to-severe PsO.[8] The primary efficacy endpoint was Physician's Global Assessment (PGA) success, defined as a PGA score of 0 or 1 and a minimum 2-grade PGA score improvement from baseline at week 12.[8] Moderate-quality evidence showed the primary efficacy endpoint of a PGA success was achieved by a higher proportion of patients at week 12 in the tapinarof cream group versus the vehicle group in PSOARING 1 (35.4% versus 6.0%, respectively; difference 29.4%; RR 5.8; 95% CI 2.9 to 11.6; p<0.001) and PSOARING 2 (40.2% versus 6.3%, respectively; difference 33.9%; RR 6.1; 95% CI 3.3 to 11.4; p<0.001).[8]
- In clinical trials, folliculitis, contact dermatitis, and headache occurred more frequently in the tapinarof groups than in the vehicle groups.[7]
- Clinical trials of longer duration and with larger populations are needed to assess long-term safety and efficacy of roflumilast and tapinarof in patients with PsO. There is insufficient evidence to compare the safety and efficacy of roflumilast or tapinarof with other topical agents approved for treatment of PsO.
- The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents who are 20 years of age and younger enrolled in Medicaid.[9] The goal of this benefit is to ensure that children receive age-appropriate screening, preventive services, and treatment services that are medically necessary to correct or ameliorate any identified conditions.[9] Management of symptoms associated with inflammatory skin conditions when they impact the ability to grow, develop or participate in school falls under this benefit.
- In July 2022, ruxolitinib cream received an expanded FDA indication for topical treatment of nonsegmental vitiligo in patients aged 12 years and older.[10]

Recommendations:

- Revise clinical prior authorization (PA) criteria for "Topical Agents for Inflammatory Skin Conditions" 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 or those having hand, foot, face, or mucous membrane involvement.
- Designate roflumilast and tapinarof as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP). Revise clinical prior authorization (PA) criteria for "Topical Agents for Inflammatory Skin Conditions" to include roflumilast and tapinarof and limit 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 topical corticosteroids for at least 4 weeks
- Modify PA criteria for non-preferred topical products for inflammatory skin conditions in children and adolescents with inflammatory skin conditions to allow for an EPSDT request up to their 21st birthday to enhance the ability to grow, develop, or participate in school per the EPSDT Medicaid benefit.
- Add the medications listed in the "Topical Anti-Psoriatic" class to the "Topical Agents for Inflammatory Skin Conditions" class.
- Evaluate costs in the Executive Session to inform Preferred Drug List (PDL) status.

Summary of Prior Reviews and Current Policy

- A literature scan for topical anti-psoriatic medications was presented to the Pharmacy and Therapeutics (P & T) Committee at the September 2017 meeting. At that time, coal tar products were designated as non-preferred products on the PDL.
- Topical agents for inflammatory skin conditions were recently reviewed by the P & T Committee at the June 2022 meeting as part of the OHSU Drug Effectiveness Review Project (DERP) summary on treatment of atopic dermatitis. A literature scan on management of vitiligo was also presented at the June 2022 P & T Committee meeting. First line, off-label, topical treatments for vitiligo are topical corticosteroids and topical calcineurin inhibitors. Clinical PA criteria for all drugs used to manage inflammatory skin conditions were updated to reflect 2022 Health Evidence Review Commission (HERC) guidance from Guideline Note 21, which was revised to include facial involvement in the severity assessment of skin conditions and severe vitiligo as a funded inflammatory skin condition.[11] The title for clinical PA criteria for "Topical Therapies for Atopic Dermatitis and Psoriasis" was revised to "Topical Agents for Inflammatory Skin Conditions" (**Appendix 4**). Topical ruxolitinib was added to the clinical PA criteria for "Topical Agents for Inflammatory Skin Conditions" and designated as non-preferred on the PDL.
- Calcipotriene, calcipotriene/betamethasone, and tazarotene are designated as preferred topical agents on the PDL and do not require PA authorization. Both of the drugs used to treat atopic dermatitis (pimecrolimus and tacrolimus) are preferred, but require PA to ensure appropriate utilization in FDA-approved populations. Non-preferred agents include anthralin, calcitriol, coal tar, crisaborole and ruxolitinib, which require PA to ensure appropriate utilization in inflammatory skin conditions funded by HERC.

Background:

Plaque psoriasis is a chronic, immune-mediated inflammatory disorder of the skin which affects about 3% of the United States (U.S.) adult population.[12] The onset generally occurs between 20 and 30 years of age.[12] Approximately 1% of children are affected by psoriasis, typically with onset during adolescence.[3] 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%.[12]

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), the duration of antipsoriatic treatments, endocrine factors, sunlight, alcohol, smoking, and stress.[13] Psoriasis is driven by multiple pathways of immune mediators, including tumor necrosis factor (TNF), interleukin (IL)-17 and IL-23 cytokines.[14] Plaque psoriasis is characterized by itchy, red, scaly, raised lesions on the skin, especially on the elbows, knees, scalp, and trunk, hands and feet.[15] Typically, PsO is classified as mild, moderate or severe. An estimated 20% of patients with PsO have moderate-to-severe disease, defined as greater than 10% of body surface area (BSA).[12] Mild disease involves less than 5% of BSA and has little to no impact on quality of life or function.[15] Mild PsO is not a funded condition per the HERC Guideline Note 21.[16] Per 2020 AAD-NPF guidance, first-line topical agents to treat mild-to-moderate PsO include: corticosteroids, vitamin D analogues (e.g., calcipotriene), retinoids (e.g., tazarotene) or salicylic acid.[2] The potency of topical corticosteroids varies depending on the drug and formulation. Formulation considerations are presented in **Table 1**. **Table 2** summarizes the 7 different potency classifications (ranging from low to super-high potency) according to United States (U.S.) nomenclature.

Table 1. Topical Corticosteroid Formulation Considerations[17]

Ointment	Generally, most potent due to occlusive nature
	Most lubricating and greasy; limited use in intertriginous areas
	Least aesthetically appealing
Cream	Contain preservatives that can cause irritation or allergic reaction
	Can be used in intertriginous areas; may have a drying effect
	Most aesthetically appealing; quick absorption
Lotion	Contain alcohol which can cause irritation
	Can be used on scalp or hairy areas
	Typically cause a drying effect
Gel, Solution, Spray, Foam	Dry and absorb quickly
	Useful for exudative inflammation, scalp, or hairy areas
	Often contain alcohol or propylene glycol, which may cause irritation
	Most drying formulations

Table 2. Potency of topical corticosteroid preparations[17,18]

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
	Betamethasone dipropionate	0.05%	lotion

Medium-Low Potency (Group 5)	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

Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy.[19] Systemic non-biologic treatments are recommended for patients with moderate-to-severe PsO unresponsive to topical treatment or phototherapy and include methotrexate, cyclosporine, mycophenolate or azathioprine.[20] Targeted immune modulators including TNF-inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab), IL-12/23 antagonists (ustekinumab), IL-23 antagonists (guselkumab, risankizumab, tildrakizumab), or IL-17 antagonists (secukinumab, ixekizumab, brodalumab), may be added for patients with moderate-to-severe PsO not controlled by other therapies.[21]

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.[22,23] 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.[22] 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.[23] This tool is rarely used in clinical practice to assess psoriasis severity due to the substantial amount of time required to complete the scoring.[2] The PGA is a scoring system that assesses degree of erythema, induration, and scaling.[2] There are several different versions of the PGA, with most severity scores ranging from 0 to 4 or 0 to 5.[2] Higher scores indicate more severe disease. The PGA is also used in research, but not frequently used in clinical practice.[2] The IGA has also been used to measure the severity of PsO based on skin thickening and hyperpigmentation in clinical trials.[24] 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).[24] Response to therapy is indicated by a score of 0 or 1.[24]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and CADTH resources were manually searched for high quality and relevant systematic reviews. When necessary,

systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:

Topical Calcineurin Inhibitor Use and Risk of Cancer

A 2021 systematic review and meta-analysis investigated the association between topical calcineurin inhibitor use and the risk of cancer including lymphoma, keratinocyte carcinoma and melanoma.[1] The review was based a 2006 box FDA warning indicating a potentially elevated risk of cancer with topical calcineurin inhibitors based on the findings of case reports (primarily of lymphomas and skin cancers), animal carcinogenicity studies, and studies on systemic tacrolimus use in organ transplant recipients.[25] The box warning was based on approximately 25 case reports, without systematic analysis supporting causation between topical calcineurin inhibitor use and malignant neoplasms.[1]

Literature was searched through August 21, 2020.[1] Observational studies investigating the association between treatment with tacrolimus and pimecrolimus and the development of cancer with nonactive or active comparators were included in the review.[1] Eight cohort studies and 3 case-control studies met inclusion criteria.[1] Six studies were conducted in the U.S., 3 studies were based in Europe (Denmark and United Kingdom), one study was conducted in Singapore, and one study included individuals from centers across North America and Europe.[1] Five studies included a nonactive comparator or untreated control group.[1] Two studies used expected or standardized incidence rates from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute as a comparator.[1] Four studies included an active comparator group treated with topical corticosteroids.[1]

A total of 408,366 participants were treated with topical calcineurin inhibitors in cohort studies, with a mean age of 17.1 years and a mean percentage of female participants of 55.1% and male participants of 44.9%.[1] Of these participants, 151,772 were treated with tacrolimus and 214,640 with pimecrolimus.[1] In the 5 studies with a nonactive comparator group, a total of 1,764,313 untreated controls were reported.[1] Of the 4 studies using a topical corticosteroid comparator, a total of 1,067,280 topical corticosteroid-treated participants were reported.[1] Mean follow-up time ranged from 1.5 to 10 years. [1] Duration of treatment with topical calcineurin inhibitors was not reported. Four cohort studies included a children-only group (n=93,120).[1] Quality of studies was assessed using the Newcastle-Ottawa scale for cohort and case-control studies.[26] One study was assigned 3 stars, indicating a high or unclear risk of bias, owing to insufficient description of study cohorts and self-report of malignant neoplasm; 6 studies were assigned 4 to 6 stars, indicating a moderate risk of bias; and 4 studies were assigned 7 to 9 stars, indicating a low risk of bias.[1]

Compared with nonactive comparators, there was no association between topical calcineurin inhibitor use and any cancer overall (RR, 1.03; 95% CI, 0.92 to 1.16).[1] Lymphoma risk was elevated with topical calcineurin inhibitor use with both nonactive (RR, 1.86; 95% CI, 1.39 to 2.49) and topical corticosteroid comparators (RR, 1.35; 95% CI, 1.13 to 1.61).[1] No significant association was found between topical calcineurin inhibitor use and increased skin cancer (melanoma and keratinocyte carcinoma).[1] The association with lymphoma was stronger in studies with a nonactive comparator, as opposed to those that compared topical calcineurin inhibitor and topical corticosteroid use, indicating that some of the association is likely a result of confounding by indication.[1] Overall, these findings suggest an association between topical calcineurin inhibitor use and risk of lymphoma but with no increased risk of other cancers, including skin cancers.[1] Lymphoma is rare, with an annual worldwide incidence of 1.35 per 100,000 in children and 9.88 per 100,000 in adults.[27] The 35%

increased relative risk found in this study for topical calcineurin inhibitor use compared with topical corticosteroids would, therefore, result in estimated numbers needed to harm for lymphoma of more than 200,000 in children and almost 30,000 in adults.[1]

There were several limitations of this systemic review. Some of the included studies were small with relatively short follow-up periods, which limits the ability to determine the risk of malignant neoplasm induction with long latency periods.[1] Lymphoma represents a heterogeneous group of diseases, which could bias the results toward the null if a true association exists for only one or some lymphoma subtypes.[1] Atopic dermatitis itself may be associated with increased risk of lymphoma and keratinocyte carcinoma.[1] In addition, there may be a severity gradient with worse skin disease (and associated increased systemic inflammation) associated with further increased risk of cancer.[1] Finally, given the observational design of the included studies, unmeasured confounding limits interpretation of association and causation.[1]

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),[28] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[29-31]

New Guidelines:

High Quality Guidelines:

American Academy of Dermatology–National Psoriasis Foundation Guidelines for Treatment of Psoriasis with Topical Therapy

In July 2020, the AAD and NPF published recommendations for the treatment of adult psoriasis with topical therapy.[2] Topical medications are frequently used as adjunctive therapies for patients with psoriasis receiving phototherapy, systemic non-biologic, or targeted immune modulator (TIM) therapy.[2] This guideline evaluates the efficacy, effectiveness, and adverse effects of topical corticosteroids, vitamin D analogues, tazarotene, salicylic acid, anthralin, and coal tar. Clinical recommendations were developed by the guideline development committee after reviewing available evidence and ranked as "A" (based on consistent and good quality evidence), or "B" (based on inconsistent or limited-quality evidence) or "C" (based on consensus, opinion, or case studies).[2] For the purposes of this review, only recommendations warranting an "A" or "B" ranking are included in the summary.

Corticosteroids

Evidence on the efficacy of topical corticosteroids from RCTs varies due to the differences in study designs, patient populations, and end points, making it difficult to do an accurate statistical comparison of the majority of published studies.[2] In numerous RCTs, different potency topical corticosteroids were safe and effective at 2 to 4 weeks in the treatment of mild-to-severe PsO.[2] Choosing a corticosteroid with appropriate potency plus the appropriate vehicle should be based on the disease severity, disease location, patient preference, and the age of the patient.[2] Lower potency corticosteroids should be used on the face, intertriginous areas, and areas that are susceptible to steroid atrophy (e.g., forearms) and other adverse effects.[2] In adults, moderate- to high-potency corticosteroids are generally recommended as initial therapy.[2] Areas with thick, chronic plaques often require treatment with super-high potency corticosteroids.[2]

The most common local skin adverse effects of topical corticosteroid use include skin atrophy, striae, folliculitis, telangiectasia, and purpura.[2] The face and intertriginous areas, as well as chronically treated areas, are at greatest risk to develop these adverse effects.[2] Topical corticosteroids may exacerbate acne, rosacea, perioral dermatitis, and tinea infections and may occasionally cause contact dermatitis.[2] Risk of hypothalamic pituitary adrenal (HPA) axis suppression from the use of topical corticosteroids for extensive plaque or scalp psoriasis has been reported to be low.[2] Despite the safety data, caution is advised, because the greatest risk for systemic adverse effects occurs when super-high- or high-potency corticosteroids are used over a large surface (i.e., BSA greater than 20%)

or under occlusion for a prolonged period (i.e., more than 4 weeks).[2] Clinicians should consider limiting the use of super-high-potency corticosteroids to no more than twice daily for up to 4 weeks, when possible.[2]

In rare cases, low fetal birth weight has been reported with prolonged potent topical corticosteroid use during pregnancy.[2] In addition, there is a single case report of a nursing mother who applied a potent topical corticosteroid on the nipple and the breastfeeding infant developed hypertension.[32] Therefore, the use of a high- or super-high potency corticosteroids in the nipple and the areola area should be avoided in nursing mothers.[2]

Recommendations:

- The use of moderate to super-high potency topical corticosteroids for up to 4 weeks is recommended for the treatment plaque psoriasis not involving intertriginous areas (strength of recommendation A; high QoE).[2]
- The use of mild to super-high potency topical corticosteroids for a minimum of 4 weeks is recommended as initial and maintenance treatment of scalp psoriasis (strength of recommendation A; high QoE).[2]

Vitamin D Analogues

The vitamin D analogues, calcitriol and calcipotriene, exert their effect in psoriasis by binding to vitamin D receptors, which inhibit keratinocyte proliferation and enhance keratinocyte differentiation.[2] Several studies have shown that 4-to-8 week treatment of calcipotriene and calcitriol is safe and efficacious for treating mild-to-moderate psoriasis.[2] The use of combination treatment with a vitamin D analogue and a potent topical corticosteroid from 3 to 52 weeks is more effective than either agent alone for the treatment of psoriasis.[2] Local adverse effects with vitamin D analogues can affect up to 35% of patients and include burning, pruritus, edema, peeling, dryness, and erythema.[2] With continued treatment, these adverse effects usually subside or disappear.[2] Systemic adverse effects due to topical vitamin D analogues include hypercalcemia and parathyroid hormone suppression.[2] These effects are quite rare unless more than 30% of BSA is treated, the recommended dose is exceeded, or the patient has an underlying renal disease or impaired calcium metabolism.[2]

Recommendations:

- The long-term use of topical vitamin D analogues (i.e., up to 52 weeks), is recommended for the treatment of mild-to-moderate psoriasis (strength of recommendation A; moderate-to-high QoE).[2]
- Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel is recommended for 4-12 weeks for the treatment of mild to moderate scalp psoriasis (strength of recommendation A; high QoE).[2]
- Topical calcipotriene combined with hydrocortisone for 8 weeks can be used for the treatment of facial psoriasis (strength of recommendation B; moderate-to-high QoE).[2]
- Use of combination treatments with vitamin D analogues and potent class topical corticosteroids up to 52 weeks is recommended for the treatment of psoriasis (strength of recommendation A; moderate-to-high QoE).[2]

Tazarotene

Tazarotene is a topical retinoid that exerts its therapeutic effects by acting on keratinocyte differentiation and proliferation and by downregulating the expression of proinflammatory genes.[2] The use of topical tazarotene for 8 to 12 weeks is recommended for the treatment of mild-to-moderate psoriasis.[2] Adverse effects with tazarotene include erythema, burning, and pruritus and are more prominent at higher concentrations.[2] Adverse effects can be reduced by using a cream formulation or lower concentration formulation, combining tazarotene with moisturizers, applying it on alternate days, or short-contact (i.e., 30 to 60 minutes) treatment, and combining it with topical corticosteroids.[2] The use of a medium- or high-potency topical corticosteroid in combination with

tazarotene for 8 to 16 weeks is recommended for the treatment of mild-to-moderate psoriasis.[2] Tazarotene should not be used in pregnant women.[33] No human data are available on excretion in human milk.[33]

Recommendations:

- Topical tazarotene can be used for the treatment of mild-to-moderate psoriasis (strength of recommendation B; low-to-high QoE).[2]
- The use of mid- or high-potency topical corticosteroid in combination with tazarotene for 8-16 weeks is more effective than monotherapy with tazarotene and is recommended for the treatment of mild-to-moderate psoriasis (strength of recommendation A; high QoE).[2]
- The use of topical corticosteroids along with tazarotene is recommended to decrease the duration of treatment as well as increase the length of remission (strength of recommendation A; high QoE).[2]

Salicylic Acid

Salicylic acid is used as a topical keratolytic agent in the treatment of psoriasis.[2] Its mechanism of action is believed to involve the reduction of the binding between keratinocytes; it minimizes scaling and softens psoriatic plaques.[2] Topical salicylic acid for 8 to 16 weeks is recommended for the treatment of mild- to-moderate psoriasis.[2] Salicylic acid is effective for the treatment of psoriasis, alone or combined with other topical therapies, including corticosteroids and topical immunomodulators.[2] Systemic absorption and increased risk for salicylate toxicity are higher in patients with renal disease and patients with hepatic disease when treating large body surface areas (i.e., greater than 20%); therefore, its use should be avoided or used with caution in these groups.[2] Topical salicylic acid should not be applied before ultraviolet B (UVB) phototherapy because it reduces the efficacy of phototherapy.[2] There are inadequate human data available for the use of salicylic acid during pregnancy or lactation.[2]

Recommendations:

- Topical salicylic acid can be used for 8 to 16 weeks for the treatment of mild-to-moderate psoriasis (strength of recommendation B; moderate-to-high QoE).[2]
- The combination of salicylic acid with topical corticosteroids can be used for the treatment of moderate-to-severe psoriasis with BSA less than or equal to 20% (strength of recommendation B; high QoE).[2]

Anthralin

Anthralin is a polycyclic aromatic hydrocarbon derivative.[2] The exact mechanism of action of anthralin is not fully understood, although it is thought to be mediated by preventing T-lymphocyte activation and promoting keratinocyte differentiation.[2] Topical anthralin is effective in the treatment of psoriasis.[2] The recommended treatment for mild-to-moderate psoriasis is 8 to 12 weeks of topical anthralin starting at 0.1% concentration, with increasing concentration over time as tolerated.[2] Short contact (i.e., up to 2 hours per once-daily application) anthralin therapy is recommended to limit adverse effects.[2] Adverse effects include perilesional erythema, burning, and mild-to-severe staining of the skin.[2] These are improved by using the short-contact application method (i.e., up to 2 hours). Application to the face or other highly visible areas should be avoided.[2] There is no evidence of any topical or systemic toxicities related to prolonged anthralin use.[2] No data are available on human milk excretion.[2]

Recommendation:

- Topical anthralin for 8-12 weeks can be used for the treatment of mild-to-moderate psoriasis. Short contact (up to 2 hours per day) anthralin is recommended to limit adverse side effects (strength of recommendation B; low-to-high QoE).[2]

Coal Tar

Coal tar has been used for the treatment of psoriasis for more than a century.[2] The polyaromatic hydrocarbons bind to the aryl hydrocarbon receptor, and tar is known to decrease keratinocyte proliferation by suppressing DNA synthesis.[2] It also suppresses inflammation and may affect immunologic function.[2] Coal tar preparations are recommended for the treatment of mild-to-moderate psoriasis.[2] Coal tar products can stain clothes, and tar odor is present in most preparations, thus reducing patient adherence.[2] The risks of coal tar application include local irritation, folliculitis, contact dermatitis, and phototoxicity.[2] Therapy is associated with possible carcinogenicity, but risk remains unproven.[2] Dermatologic studies on topical preparations have not revealed an increased risk, but animal and occupational studies document carcinogenicity with prolonged exposures over many years.[2] A retrospective analysis of human use of coal tar preparations during pregnancy has not shown any adverse effects on the fetus, although in animal studies, large doses have been observed to increase the risk of cleft palates, small lungs, and perinatal mortality.[34] Thus, it may be advisable to avoid the use of coal tar preparations during pregnancy and lactation.[2]
Recommendation:

- Coal tar preparations are recommended for the treatment of mild-to-moderate psoriasis (strength of recommendation A; moderate-to-high QoE).[2]

American Academy of Dermatology–National Psoriasis Foundation Guidelines for Treatment of Psoriasis in Pediatric Patients
In November 2019, the AAD and NPF published recommendations for the treatment of psoriasis in pediatric patients.[3] The guidance addresses the use of topical agents, systemic nonbiologic agents, and TIMs in children and adolescents. For the purposes of this class update, recommendations and strength of evidence for just the topical treatments are summarized.

Corticosteroids
Topical steroid use for psoriasis in children is technically an off-label treatment (due to lack of clinical trials in this population) but is frequently practiced and widely considered for localized disease.[3] The adverse effect profile for topical corticosteroids in children is analogous to that in adults, particularly relating to burning and stinging at the application site.[3] Younger patients 0 through 6 years of age, especially infants are vulnerable to HPA axis suppression given their high BSA-to-volume ratio compared with older children and adults.[3] High-potency or super-high-potency topical corticosteroids should be used with caution, and patients should be followed closely by a dermatologist to ensure proper use and to monitor for overuse and adverse effects.[3]
Recommendation:

- Topical corticosteroids are recommended for the treatment of pediatric psoriasis as an off-label therapy (strength of recommendation B; moderate QoE).

Vitamin D Analogues
An important advantage of the vitamin D analogues, especially for pediatric use, is their corticosteroid-sparing function.[3] Treatment with vitamin D analogues is safe, effective, and relatively well tolerated in children of all ages.[3] Several small case series and clinical trials of low to good quality have been performed in children.[3] Vitamin D analogue preparations can cause local irritation and are often avoided on the face, genitals, and intertriginous skin.[3] Irritation is often improved or ameliorated with the concomitant application of an emollient.[3] Caution must be taken regarding quantities used, given the theoretical risk of hypercalcemia and vitamin D deficiency associated with systemic absorption, although no specific data or recommendations exist on maximum use in children.[3]
Recommendations:

- Calcipotriene is recommended as a treatment option for childhood PsO (strength of recommendation B; moderate QoE).[3]
- Because of the theoretical risk of increased calcium absorption and systemic effects of hypercalcemia, calcipotriene applied to large body surface areas is not recommended (strength of recommendation B; low QoE).[3]
- Monitoring of vitamin D metabolites may be considered during calcipotriene therapy when applied to a large body surface area (strength of recommendation B; moderate-to-high QoE).[3]

Combination Topical Therapy

Combination products containing calcipotriene and betamethasone are FDA-approved for use in children ages 12 years and older with mild-to-moderate PsO for use on the body and scalp.[4] Transitioning from combination therapy to topical vitamin D monotherapy upon disease improvement may be beneficial to decrease topical steroid use.[3] Combination calcipotriene and betamethasone may result in adverse effects (such as striae and HPA axis suppression) due largely to the steroid component.[3]

Recommendations:

- The combination of calcipotriene/betamethasone dipropionate ointment applied once daily for up to 4 weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild-to-moderate PsO (strength of recommendation B; moderate-to-high QoE).[3]
- The combination of calcipotriene/betamethasone dipropionate suspension applied once daily for up to 8 weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild-to-moderate plaque psoriasis of the scalp (strength of recommendation B; moderate QoE).[3]

Anthralin

Anthralin is FDA-approved for use in children and adolescents aged 12 years and older with scalp psoriasis.[35] Anthralin has many adverse effects, including burning, stinging, pruritus, and perilesional erythema.[3] Staining often results upon application and removal, affecting the skin, clothing, and tub/shower.[3] As such, anthralin application is usually limited by poor tolerability and cosmetic concerns and is rarely used on the face and intertriginous areas.[3]

Recommendation:

- Long-term use (12 weeks or longer) of topical anthralin is recommended for the treatment of mild-to-moderate psoriasis. Short-contact anthralin protocols are recommended to limit adverse effects (strength of recommendation B; moderate QoE).[3]

Tazarotene and Coal Tar

Tazarotene cream is only FDA-approved for the treatment of stable PsO of less than 20% BSA in adults.[35] The safety and efficacy of tazarotene gel have not been established in pediatric patients with psoriasis under the age of 12 years.[33] Coal tar is commonly used in combination with phototherapy (Goeckerman treatment) for psoriasis.[3] There is no current literature studying coal tar in pediatric psoriasis as monotherapy.[3]

New Formulations or Indications:

December 2018: The combination product of calcipotriene and betamethasone dipropionate (ENSTILAR, TACLONEX) received expanded FDA-approval for topical treatment of PsO in patients aged 12 years and older.[4] The combination product is available as an ointment, foam, and topical suspension which can be applied to the scalp or body. Prior to this approval, these products were approved for topical treatment of psoriasis vulgaris in adults aged 18 years and older.

November 2019: Calcipotriene (SORILUX) topical foam received expanded FDA-approval for use in patients aged 4 years and older.[36] Prior to this approval, calcipotriene was approved for topical treatment of PsO of the scalp and body in patients 12 years and older.

July 2020: Calcitriol (VECTICAL) topical ointment received expanded FDA-approval for use in patients 2 years and older.[37] Prior to this approval, calcitriol was approved for topical treatment of mild-to-moderate PsO in adults 18 years and older.

August 2020: Halobetasol (ULTRAVATE) topical lotion received expanded FDA-approval for use in patients aged 12 years and older.[38] Prior to this approval, halobetasol was approved for topical treatment of PsO in adults 18 years and older.

May 2021: Halobetasol (LEXETTE) topical foam received expanded FDA-approval for use in patients aged 12 years and older.[39] Prior to this approval, halobetasol was approved for topical treatment of PsO in adults 18 years and older.

July 2022: Ruxolitinib (OPZELURA) cream received an expanded FDA indication for topical treatment of nonsegmental vitiligo in patients aged 12 years and older.[10] The initial approval of ruxolitinib cream in 2021 was for the short-term and non-continuous treatment of mild-to-moderate atopic dermatitis in non-immunocompromised patients aged 12 years and older.[10] The expanded approval was based on 2 RCTs, TRuE-V1 and TRuE-V2, conducted in 674 adults and pediatric patients 12 years of age and older with nonsegmental vitiligo.[10] Ruxolitinib was administered twice daily for 24 weeks and compared with an inert vehicle.[10] Lesions were assessed using the total body Vitiligo Area Scoring Index (T-VASI) or the facial Vitiligo Area Scoring Index (F-VASI).[10] The primary efficacy endpoint was the proportion of subjects achieving at 75% improvement in the F-VASI at week 24.[10] In TRuE-V1, 30% of patients receiving ruxolitinib achieved F-VASI-75 compared with 7.5% of placebo-treated patients (difference = 22.5%; 95% CI 14.2% to 30.8%).[10] Similar results in 75% achievement of F-VASI-75 were observed in TRuE-V2 with ruxolitinib versus vehicle (30% vs. 12.9%, respectively; difference=16.9%; 95% CI 7.8% to 26.0%).[10]

New FDA Safety Alerts: No new safety alerts were identified.

Randomized Controlled Trials:
A total of 67 citations were manually reviewed from the initial literature search. After further review, 67 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: Roflumilast Topical Cream
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Roflumilast (ZORYVE) 0.3% cream received FDA approval July 2022 for topical treatment of PsO, including intertriginous areas, in patients 12 years of age and older.[5] Roflumilast is a selective inhibitor PDE-4.[5] Overexpression of PDE-4 appears to contribute to the pathogenesis of psoriasis.[40] The inhibition of PDE-4 increases cyclic adenosine monophosphate (cAMP) levels, leading to a downregulation of immune modulators involved in psoriasis pathophysiology such as TNF, interferon, IL-17 and IL-23.[40]

Two phase 3 multicenter, double-blind, vehicle-controlled RCTs, DERMIS-1 and DERMIS-2, supported the FDA-approval of topical roflumilast.[6] The 2 studies were conducted in patients aged 2 years and older with an affected BSA of 2 to 20% (excluding scalp, palms or soles) with mild-to-severe PsO.[6] The median age was 47 years, the majority of subjects were male (64%) and White (82%).[6] At baseline, 16% of subjects had an IGA score of 2 (mild), 76% had an IGA score of 3 (moderate), and 8% had an IGA score of 4 (severe).[6] Patients were randomized 2:1 to roflumilast 0.3% cream or vehicle applied to skin once a day for 8 weeks.[6] The primary efficacy outcome was Investigator's Global Assessment (IGA) success at week 8.[6] This was defined as an IGA status of clear or almost clear (assessed on a 5-point scale of plaque thickening, scaling, and erythema; a score of 0 indicates clear, 1 almost clear, and 4 severe) and a 2-grade or greater improvement from baseline.[6] Secondary outcomes, included IGA score of clear, 75% reduction in Psoriasis Area and Severity Index (PASI) score, and Worst Itch Numeric Rating Scale score of 4 or higher at baseline and with a 4-point reduction (WI-NRS success) at week 8 (scale: 0 [no itch] to 10 [worst imaginable itch]; minimum clinically important difference, 4 points).[6]

In both studies, a greater percentage of roflumilast-treated patients achieved IGA success at week 8 compared with vehicle-treated patients (DERMIS-1: 42.4% vs. 6.1%, respectively; difference = 39.6%; 95% CI 32.3 to 46.9; p<0.001 and DERMIS-2: 37.5% vs. 6.9%, respectively; difference = 28.9%; 95% CI 20.8% to 36.9%; p<0.001).[6] At 8-week follow-up, compared with vehicle, roflumilast improved IGA clear status (DERMIS-1: 63.5% vs. 10.3%; difference, 58.1%; 95% CI, 39.3 to 76.9; p<0.001 and DERMIS-2: 57.4% vs. 7.4%; difference, 52.2%; 95% CI, 32.1 to 72.2; p<0.001).[6] At 8-week follow-up, compared with vehicle, roflumilast increased the proportion of patients who achieved a 75% reduction from baseline in PASI score (DERMIS-1: 41.6% vs. 7.6%; difference, 36.1% ; 95% CI, 28.5 to 43.8; p<0.001 and DERMIS-2: 39.0% vs. 5.3%; difference, 32.4%; 95% CI, 24.9 to 39.8; p<0.001).[6] Among patients with WI-NRS scores of 4 or higher at baseline, compared with vehicle, roflumilast improved the proportion of patients achieving at least a 4-point WI-NRS reduction.[6] At week 8, percentages of patients with at least a 4-point WI-NRS reduction were 67.5% versus 26.8% for DERMIS-1 (difference, 42.6%; 95% CI, 31.3 to 53.8; p<0.001) and 69.4% versus 35.6% for DERMIS-2 (difference, 30.2%; 95% CI, 18.2 to 42.2; p<0.001).[6] Of the 4 patients 2 to 11 years of age who participated in either trial, 1 (33.3%) of the 3 roflumilast-treated patients achieved IGA success at week 8; the 1 vehicle-treated patient did not achieve IGA success at week 8.[6] Of the 14 patients 12 to 17 years of age who participated in either trial, 2 (25.0%) of the 8 roflumilast-treated and 1 (16.7%) of the 6 vehicle-treated patients achieved IGA success at week 8.[6] Additional phase 3 study details are presented in **Table 3.**

This study has several limitations. First, the lack of an active comparator treatment group makes the comparative efficacy of topical roflumilast with other active treatments uncertain.[6] Second, the trials did not assess the efficacy of roflumilast beyond 8-week follow-up.[6] Third, the proportion of children and adolescents enrolled in the studies was very small. Further research is needed to assess efficacy compared with other active treatments and to assess longer-term efficacy and safety.[6]

Clinical Safety:
In clinical trials, low rates of application-site AEs were observed with roflumilast.[5] The most frequently reported AEs were diarrhea, headache, insomnia, and nausea.[5] Rates of AEs with roflumilast compared with vehicle are described in **Table 1**. Because metabolism of roflumilast is primarily via hepatic enzymes, it is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C).[5] Medications that inhibit CYP3A4 or CYP1A2 (e.g., erythromycin, ketoconazole, fluvoxamine, cimetidine) should be cautiously co-administered with roflumilast, as they may increase systemic exposure of roflumilast and result in increased AEs.[5] There are no RCTS of topical roflumilast in pregnant or lactating women.[5]

Table 1. Adverse Effects Reported in Clinical Trials with Roflumilast Cream 0.3% Versus Vehicle Cream[5]

Adverse Effect	Roflumilast Cream (n=576) n (%)	Vehicle Cream (n=305) n (%)
Diarrhea	18 (3.1)	0 (0.0)
Headache	14 (2.4)	3 (1.0)
Insomnia	8 (1.4)	2 (0.7)
Nausea	7 (1.2)	1 (0.3)
Application Site Pain	6 (1.0)	1 (0.3)
Upper Respiratory Tract Infection	6 (1.0)	1 (0.3)
Urinary Tract Infection	6 (1.0)	2 (0.7)

Look-alike / Sound-alike Error Risk Potential: No issues identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Symptom improvement
2) Quality of life
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percentage of patients with achievement of IGA score of clear (0) or almost clear (1) at 8 weeks

Table 2. Pharmacology and Pharmacokinetic Properties.[5,17]

Parameter	
Mechanism of Action	Phosphodiesterase-4 inhibitor
Oral Bioavailability	Not Applicable
Distribution and Protein Binding	Volume of distribution: 2.9 Liters/kilogram; 99% protein bound
Elimination	Total body clearance:9.6 Liters/hour
Half-Life	4.6 days
Metabolism	Extensively metabolized via CYP1A2 and CYP3A4 hepatic enzymes

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. Lebwohl MG, et al[6] DERMIS-1 Phase 3, DB, PG, MC, RCT	1. Roflumilast 0.3% cream applied once a day 2. Vehicle cream applied once a day Duration: 8 wks	Demographics: 1. Mean age: 47 yo 2. Male: 64% 3. Race - White: 81% Black: 3% Asian: 7% Other: 3% 4. Median psoriasis-affected BSA: 4.6% (range 2 to 20%) 5. Mean PASI score: 3.5 6. Mild PsO: 15% Moderate PsO: 75% Severe PsO: 9% Key Inclusion Criteria: -2 yo and older -PsO for > 6 mos in adults and 3 mos in children -IGA ≥ 2 -PASI ≥ 2 -PsO BSA of 2 to 20% Key Exclusion Criteria: -Above normal exposure to sun or tanning beds - Diagnosis of guttate psoriasis or pustular psoriasis - Currently taking cytochrome P450 inducers or inhibitors or oral roflumilast or other PDE-4 inhibitors	ITT: 1. 286 2. 153 Attrition: 1. 31 (11%) 2. 20 (13%)	Primary Endpoint: Proportion of patients with IGA success at week 8 (IGA score of 0 or 1 and ≥ 2-grade improvement in IGA from baseline). 1. 42.4% (n=108) 2. 6.1% (n=8) Difference: 39.6%, 95% CI 32.3 to 46.9; p<0.001 Secondary Endpoints: 1. Proportion of patients achieving IGA clear status (score = 0) at week 8 1. 63.5% 2. 10.3% Difference: 58.1% 95% CI 39.3 to 76.9; p<0.001 2. Proportion of patients achieving PASI-75 at week 8 1. 41.6% 2. 7.6% Difference: 36.1% 95% CI 28.5 to 43.8; p<0.001 3. Proportion of patients with a ≥ 4 point reduction in WI-NRS at week 8 1. 67.5% 2. 26.8% Difference: 42.6% 95% CI 31.3 to 53.8; p<0.001	39.6%/ 3 58.1%/ 2 36.1%/ 3 42.6%/ 3	AEs: 1. 25.2% (n=72) 2. 23.5% (n=36) SAEs: 1. 0.7% (n=2) 2. 0.7% (n=1) AE leading to withdrawal: 1. 3.5% (n=10) 2. 0 p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:1 via computer-generated list. Patients stratified by study site, baseline IGA (IGA=2 vs. IGA≥3) and intertriginous area involvement. Baseline characteristics balanced among groups. Performance Bias: Low. Active drug similar in appearance to inert vehicle cream. Detection Bias: Unclear. Patients and investigators blinded to treatment allocation. Method of blinding not described. Unblinding may have occurred with local reactions to active drug or non-response to inert vehicle. Attrition Bias: High. More attrition in placebo arm due to withdrawal, loss to follow-up, or an AE. Missing data imputed, but method not described. Reporting Bias: Low. Protocol available on-line and all pre-specified outcomes were reported. Other Bias: Unclear. Manufacturer compiled and analyzed data, funded the study. **Applicability**: Patient: Study population was mostly adult, white males with moderate PsO which limits applicability to other races and patients with severe PsO. Small percentage of children and adolescents also enrolled in the trial. Intervention: Dosing used in this trial was proven efficacious in phase 2 trials. Comparator: Placebo comparator appropriate for safety and efficacy comparison. Outcomes: IGA is a validated measure to assess efficacy of new drugs used to treat PsO. Setting: 40 sites in the US and Canada

2. Lebwohl MG, et al[6] DERMIS-2 Phase 3, DB, PG, MC, RCT	1. Roflumilast 0.3% cream applied once a day 2. Vehicle cream applied once a day Duration: 8 wks	Demographics: 1. Mean age: 47 yo 2. Male: 63% 3. Race - White: 82% Black: 5% Asian: 6% Other: 3% 4. Median psoriasis-affected BSA: 4.9% (range 2 to 20%) 5. Mean baseline PASI score: 3.3 6. Mild PsO: 16% Moderate PsO: 76% Severe PsO: 6.7% Key Inclusion Criteria: see DERMIS-1 Key Exclusion Criteria: see DERMIS-1	ITT: 1. 290 2. 152 Attrition: 1. 26 (9%) 2. 21 (14%)	Primary Endpoint: Proportion of patients with IGA success at week 8 (IGA score of 0 or 1 and ≥ 2-grade improvement in IGA from baseline). 1. 37.5% (n=99) 2. 6.9% (n=9) Difference: 28.8%, 95% CI 20.8 to 36.9 p<0.001 Secondary Endpoints: 1.Proportion of patients achieving IGA clear status (score = 0) at week 8 1. 57.4% 2. 7.4% Difference: 52.2% 95% CI 32.1 to 72.2 P<0.001 2.Proportion of patients achieving PASI-75 at week 8 1. 39.0% 2. 5.3% Difference: 32.4% 95% CI 24.9 to 39.8 P<0.001 3. Proportion of patients with a WI-NRS score reduction of at least 4 points at week 8 1. 69.4% 2. 26.8% Difference: 30.2% 95% CI 18.2 to 42.2 P<0.001	28.8/4 52.2%/2 32.4%/4 30.2%/4	AEs: 1. 25.9% (n=75) 2. 18.4% (n=28) SAEs: 1. 0 2. 0.7% (n=1) AE leading to withdrawal: 1. 0.3% (n=1) 2. 1.3% (n=2) p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see DERMIS-1 Performance Bias: see DERMIS-1 Detection Bias: see DERMIS-1 Attrition Bias: see DERMIS-1 Reporting Bias: see DERMIS-1 Other Bias: see DERMIS-1 **Applicability**: Patient: see DERMIS-1 Intervention: see DERMIS-1 Comparator: see DERMIS-1 Outcomes: see DERMIS-1 Setting: 39 sites in the US and Canada

Abbreviations: AE = adverse event: RR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; IGA = Investigator's Global Assessment; ITT = intention to treat; MC = multi-center; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PDE = phosphodiesterase; PG = parallel group; PSAI = Psoriasis Area and Severity Index; PsO = plaque psoriasis; SAE = serious adverse event; US = United States; WI-NRS = Worst Itch Numeric Rating Scale; wks = weeks; yo = years old

NEW DRUG EVALUATION: Tapinarof Topical Cream

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

Clinical Efficacy:

Tapinarof 1% cream, an aryl hydrocarbon receptor agonist, received FDA-approval for the topical treatment of PsO in adults May 2022.[7] The aryl hydrocarbon receptor is a ligand-dependent transcription factor expressed in keratinocytes, which is increased in patients with psoriasis.[40] Aryl hydrocarbon receptor signaling regulates the terminal differentiation of T helper (Th) type-17 and Th-22 lymphocytes, which ultimately decreases pro-inflammatory interleukin cytokines.[40] In summary, tapinarof is a novel anti-inflammatory agent. Tapinarof cream is currently being studied for use in atopic dermatitis and in pediatric patients with psoriasis.

Two identical, double-blind, multi-center, phase 3, RCTs, PSOARING 1 and PSOARING 2, evaluated the safety and efficacy of tapinarof 1% cream in treating adults with psoriasis.[8] These RCTs were conducted over 12 weeks in 1,025 adults with mild-to-severe PsO and an affected BSA of 3% to 20%. Patients were randomized 2:1 to once-daily application of tapinarof 1% cream or inert vehicle cream to any lesions.[8] Study participants ranged in age from 18 to 75 years, with an overall median age of 51 years.[7] The majority of participants were White (85%) and male (57%); and 85% were non-Hispanic or Latino.[7] Most of the adults enrolled in the RCTs (82%) had moderate PsO (baseline PGA score of 3).[7] The primary efficacy endpoint was PGA response, defined as a PGA score of clear (0) or almost clear (1) with at least a two-grade reduction from baseline in PGA at week 12.[8] Secondary endpoints included proportion of subjects achieving PASI-75, PASI-90, PGA score of 0 or 1, and change in percent of BSA affected at week 12.[8]

The primary efficacy endpoint of a PGA response was achieved by a higher proportion of patients in the tapinarof cream group versus the vehicle group in PSOARING 1 (35.4% vs. 6.0%, respectively; difference 29.4%; RR 5.8; 95% CI 2.9 to 11.6; p<0.001) and PSOARING 2 (40.2% vs. 6.3%, respectively; difference 33.9%; RR 6.1; 95% CI 3.3 to 11.4; p<0.001).[8] Secondary endpoints also improved in more patients treated with tapinarof cream compared with vehicle cream. PASI-75 response at Week 12 was achieved by a higher proportion of patients in the tapinarof cream group than the vehicle group in PSOARING 1 (36.1% vs. 10.2%, difference 25.9%; RR 2.8; 95% CI 1.7 to 4.5; p<0.001) and PSOARING 2 (47.6% vs. 6.9%, difference 40.7%; RR 6.5; 95% CI 3.7 to 11.5; p<0.001).[8] A PGA score of 0 (clear) or 1 (almost clear) at Week 12 was achieved by a higher proportion of patients in the tapinarof cream group than the vehicle group in PSOARING 1 (37.8% vs. 9.9%; difference 27.9%; RR 2.7; 95% CI 1.6 to 4.4; p<0.001) and PSOARING 2 (43.6% vs. 8.1%, difference 35.5%; RR 4.6; 95% CI 2.7 to 7.6; p<0.001).[8] A PASI-90 response at Week 12 was achieved by a higher proportion of patients in the tapinarof group than the vehicle group in PSOARING 1 (18.8% vs. 1.6%, difference 17.2%; RR 8.5; 95% CI 26 to 28.4; p<0.001) and PSOARING 2 (20.9% vs. 2.5%, difference 18.4, RR 7.2; 95% CI 2.9 to 18.4; p<0.001).[8] Finally, a greater mean improvement in percent BSA affected at Week 12 was observed in the tapinarof cream group compared with the vehicle group in PSOARING 1 (-3.5% vs. -0.2%, difference -3.3; 95% CI -4.4 to -2.1; p<0.001) and PSOARING 2 (-4.2% vs. 0.1%, difference -4.3; 95% CI -5.2 to -3.5; p<0.001).[8] Additional study details are presented in **Table 5**.

Approximately 15 to 20% of end-point data were missing, and multiple imputation was used to adjust for missing data as prespecified in the statistical analysis plan in providing estimates of many of the trial end points.[8] Larger and longer trials are needed to evaluate the efficacy and safety of tapinarof cream as compared with existing treatments for psoriasis.[8]

Results from an open-label, extension trial (PSOARING 3) from patients who completed PSOARING 1 or PSOARING 2 (n=763) are available.[41] This trial assessed the safety, efficacy, durability of response, and tolerability of tapinarof 1% cream applied once daily after 40 weeks of treatment.[41] The treatment phase was followed by 4 weeks of off-treatment assessment.[41] The primary efficacy endpoint was the proportion of patients who achieved complete disease clearance (PGA = 0).[41] Of the eligible enrolled patients, 40.9% of them achieved complete disease clearance (PGA = 0).[41] Mean duration of off-therapy remittive effect for patients achieving PGA = 0 was 130.1 days.[41] No new safety signals were observed.[41] Most frequent adverse events were folliculitis (22.7%), contact dermatitis (5.5%), and upper respiratory tract infection (4.7%).[41] Trial discontinuation rates due to folliculitis or contact dermatitis were low (1.2% and 1.4%), respectively.[41] Of the 763 patients enrolled, 69.6% (n=531) completed the trial.[41] Attrition was approximately 30% and primarily due to withdrawal of consent (10%), loss to follow-up (8%), and adverse events (6%).[41] Trial limitations include the open-label design, high attrition rate, and lack of a control group.[41] As is possible with all extension trials, patients who opted to enroll might represent a self-selected, enriched population, with improved response and tolerability to treatment.[41]

Clinical Safety:

In clinical trials, folliculitis, contact dermatitis, and headache occurred more frequently in the tapinarof groups than in the vehicle groups.[7] No SAEs were observed with tapinarof administration.[8] AEs that occurred in at least 1% of individuals treated with tapinarof cream compared to the inert vehicle are presented in **Table 4**. There is insufficient data regarding the safety of tapinarof administration in pregnancy and lacatation.[7] Although tapinarof is extensively metabolized by the liver, no significant drug interactions were observed during clinical trials.[7]

Table 4. Adverse Reactions Observed in Clinical Trials With Tapinarof Cream Versus Vehicle Cream[7]

Adverse Effect	Tapinarof 1% Cream n = 683 n (%)	Vehicle Cream n= 342 n (%)
Folliculitis	140 (20)	3 (1)
Nasopharyngitis	73 (11)	31 (9)
Contact Dermatitis	45 (7)	2 (1)
Headache	26 (4)	5 (1)
Pruritus	20 (3)	2 (1)
Influenza	14 (2)	2 (1)

Look-alike / Sound-alike Error Risk Potential: No issues identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement
2) Quality of life
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

2) PGA response (score of 0 or 1 with $\geq$2 point decrease from baseline) at week 12

Table 5. Pharmacology and Pharmacokinetic Properties.[7]

Parameter	
Mechanism of Action	Aryl hydrocarbon receptor agonist
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Volume of distribution not reported due to limited systemic absorption after topical administration; plasma protein binding: approximately 99%
Elimination	Not reported
Half-Life	Not reported
Metabolism	Extensive hepatic metabolism

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Lebwohl M, et al.[8] PSOARING-1 Phase 3, DB, MC, PC, RCT	1. Tapinarof 1% applied cream once a day 2. Vehicle cream applied once a day Duration: 12 wks	Demographics: 1. Mean age: 49 yo 2. Male: 56% 3. Race White: 84% Black: 5% Asian: 4% Other: 4% 4. Mild PsO: 11% Moderate PsO: 79% Severe PsO: 8% 5. Mean baseline PASI: 8.9 Key Inclusion Criteria: -Adults aged 18-75 yo with chronic PsO and stable disease for 6 mos prior to study enrollment -BSA between 3 and 20%, excluding scalp, palms, nails, and soles -PGA score of 2, 3, or 4 (mild, moderate, severe PsO) Key Exclusion Criteria: -Psoriasis other than the plaque variant	ITT: 1.340 2.170 Attrition: 1. 71 (20.9%) 2. 40 (23.5%)	Primary Endpoint: Proportion with PGA response (score of 0-1 & 2-point change from baseline) at week 12 1. 35.4% 2. 6% Difference: 29.4% RR 5.8; 95% CI 2.9 to 11.5; p<0.001 Secondary Endpoints: 1. Proportion with PASI-75 at week 12 1. 36.1% 2. 10.2% Difference: 25.9% RR 2.8; 95% CI 1.7 to 4.5; p<0.001 2. Proportion with PASI-90 at week 12 1. 18.8% 2. 1.6% Difference: 17.2% RR 8.5; 95% CI 2.6 to 28.4; p<0.001 3. Percentage of subjects with a PGA score of 0 or 1 at week 12 1. 37.8% 2. 9.9% Difference: 27.9% RR 2.7; 95% CI 1.6 to 4.4; p<0.001	29.4%/4 25.9%/4 17.2%/6 27.9%/4	AEs 1. 171 (50.3%) 2. 38 (22.4%) SAEs: 1. 0 2. 0 AE leading to withdrawal: 1. 19 (5.6%) 2. 0 p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to tapinarof: vehicle. Subjects randomized using a pseudo-random number generator and stratified according to PsO severity. Baseline characteristics balanced between groups. Performance Bias: Low. Vehicle cream and tapinarof cream were identical in excipients, amount (30 gm) and color. Detection Bias: Unclear. Investigator, study center staff, and subjects blinded to treatment assignment. Method of blinding not described. Non-response to inert vehicle or local AEs with active drug may have resulted in unblinding. Attrition Bias: High. High attrition rates in both arms. Missing data imputed using multiple imputation. Reporting Bias: Low. Protocol available online and all prespecified outcomes were reported. Other Bias: Unclear. Manufacturer designed the trials, provided medication and placebo, analyzed the data and funded writing assistance. **Applicability**: Patient: Small study population, mostly white males with stable, moderate PsO limits applicability to other races and patients with severe PsO or those experiencing flares.

		-Prolonged exposure to ultraviolet light within 4 wks of study enrollment -Hepatic disease -Use of biologic agents, systemic immunomodulators or glucocorticoids		4. Mean change from baseline to week 12 in percent of BSA affected 1. -3.5% 2. -0.2% Difference: -3.3% 95% CI -4.4 to -2.1; p<0.001	NA			Intervention: Phase 2b dose finding trials indicated efficacy with tapinarof 1% daily. Comparator: Placebo comparator appropriate for safety and efficacy comparison. Comparison with a topical corticosteroid would provide more meaningful evaluation. Outcomes: PGA and PASI-75 are validated measures to assess efficacy of new drugs used to treat PsO. Setting: 48 centers in the US (n=40) and Canada (n=8)
2. Lebwohl M, et al.[8] PSOARING-2 Phase 3, DB, MC, PC, RCT	1. Tapinarof 1% applied cream once a day 2. Vehicle cream applied once a day Duration: 12 wks	Demographics: 1. Mean age: 50 yo 2. Male: 57% 3. Race White: 84% Black: 3.5% Asian: 9% Other: 2% 4. Mild PsO: 8% Moderate PsO: 84% Severe PsO: 7% 5. Mean baseline PASI: 9.1 Key Inclusion Criteria: see PSOARING-1 Key Exclusion Criteria: see PSOARING-1	ITT: 1.343 2.172 Attrition: 1.61 (17.8%) 2.30 (17.4%)	Primary Endpoint: Proportion of subjects with PGA response (score of 0 or 1- and 2-point improvement from baseline) at week 12 1. 40.2% 2. 6.3% Difference: 33.9% RR: 6.1; 95% CI 3.3 to 11.4; p<0.001 Secondary Endpoints: 1. Proportion of subjects achieving PASI-75 at week 12 1. 47.6% 2. 6.9% Difference: 40.7% RR 6.5; 95% CI 3.7 to 11.5; p<0.001 2. Proportion of subjects achieving PASI-90 at week 12 1. 20.9% 2. 2.5% Difference: 18.4% RR 7.2; 95% CI 2.9 to 18.4; p<0.001 3. Percentage of subjects with a PGA score of 0 or 1 at week 12 1. 43.6% 2. 8.1% Difference: 35.5% RR 4.6; 95% CI 2.7 to 7.6; p<0.001 4. Mean change from baseline to week 12 in percentage of BSA affected 1. -4.2% 2. 0.1% Difference: -4.3% 95% CI -5.2 to -3.5; p<0.001	33.9%/3 40.7%/3 18.4%/5 35.5%/3 NA	AEs 1. 187 (54.5%) 2. 45 (26.2%) SAEs: 1. 0 2. 0 AE leading to withdrawal: 1. 20 (5.8%) 2. 1 (0.6) p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see PSOARING-1 Performance Bias: see PSOARING-1 Detection Bias: see PSOARING-1 Attrition Bias: see PSOARING-1 Reporting Bias: see PSOARING-1 Other Bias: see PSOARING-1 **Applicability**: Patient: see PSOARING-1 Intervention: see PSOARING-1 Comparator: see PSOARING-1 Outcomes: see PSOARING-1 Setting: 49 centers in the US (n=41) and Canada (n=80)

Abbreviations: AE = adverse event: RR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; IGA = Investigator's Global Assessment; ITT = intention to treat; MC = multi-center; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PDE = phosphodiesterase; PG = parallel group; PP = per protocol; PSAI = Psoriasis Area and Severity Index; PsO = plaque psoriasis; RR = relative rate; SAE = serious adverse event; US = United States; wks = weeks; yo = years old

References:

1. Lam M, Zhu JW, Tadrous M, Drucker AM. Association Between Topical Calcineurin Inhibitor Use and Risk of Cancer, Including Lymphoma, Keratinocyte Carcinoma, and Melanoma: A Systematic Review and Meta-analysis. *JAMA dermatology.* 2021;157(5):549-558.
2. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol.* 2021;84(2):432-470.
3. Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol.* 2020;82(1):161-201.
4. TACLONEX (calcipotriene and bethamethasone dipropionate) topical ointment. Prescribing Information. Madison, NJ; LEO Phama, Inc. December 2018.
5. ZORYVE (roflumilast) topical cream. Prescribing Information. Westlake Village, CA; Arcutis Biotherapeutics, Inc. July 2022.
6. Lebwohl MG, Kircik LH, Moore AY, et al. Effect of Roflumilast Cream vs Vehicle Cream on Chronic Plaque Psoriasis: The DERMIS-1 and DERMIS-2 Randomized Clinical Trials. *Jama.* 2022;328(11):1073-1084.
7. VTAMA (tapinarof) topical cream. Prescribing Information. Long Beach, CA; Dermavant Sciences, Inc. May 2022.
8. Lebwohl MG, Stein Gold L, Strober B, et al. Phase 3 Trials of Tapinarof Cream for Plaque Psoriasis. *N Engl J Med.* 2021;385(24):2219-2229.
9. Medicaid Early Periodic Screening, Diagnostic, and Treatment www.medicaid.gov/medicaid/benefits/early-and-periodic-screening-diagnostic-and-treatment/index.html. Accessed August 18, 2022.
10. OPZELURA (ruxolitinib) topical cream. Prescribing Information. Wilmington, DE; Incyte Corporation. July 2022.
11. Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx. Accessed March 1, 2022.
12. Armstrong AW, Mehta MD, Schupp CW, Gondo GC, Bell SJ, Griffiths CEM. Psoriasis Prevalence in Adults in the United States. *JAMA dermatology.* 2021;157(8):940-946.
13. Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. *Cochrane Database Syst Rev.* 2013(3).
14. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker J. Psoriasis. *Lancet (London, England).* 2021;397(10281):1301-1315.
15. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *Jama.* 2020;323(19):1945-1960.
16. Oregon Health Authory: Health Evidence Review Commission. Prioritized List of Health Services. January 2022. https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List.aspx Accessed July 12, 2022.
17. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed November 1, 2021.
18. Cornell RC, Stoughton RB. Correlation of the vasoconstriction assay and clinical activity in psoriasis. *Arch Dermatol.* 1985;121(1):63-67.
19. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol.* 2020;82(6):1445-1486.
20. Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Recommendation. Abrocitinib (Cibinqo). September 2022. https://www.cadth.ca/abrocitinib. Accessed September 12, 2022.

21. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2019;80(4):1029-1072.
22. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol.* 2012;66(3):369-375.
23. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *The British journal of dermatology.* 1999;141(2):185-191.
24. Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *The Journal of dermatological treatment.* 2015;26(1):23-31.
25. Food and Drug Administration. FDA Approved Updated Labeling with Boxed Warning and Medication Guide for Two Excema Drugs, Elidel and Protopic. January 19, 2006 https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-approves-updated-labeling-boxed-warning-and-medication-guide-two-eczema-drugs Accessed August 31, 2022.
26. Wells GS., O'Connell D, Peterson J, Welch V, Losos L, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa Health Research Institute. Published 2019. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 7, 2022.
27. Institute for Health Metrics and Evaluation. Global Health Data Exchange. http://ghdx.healthdata.org/. Accessed January 14, 2021.
28. Bark C, Brown C, Svangren P. Systematic literature review of long-term efficacy data for topical psoriasis treatments. *Journal of Dermatological Treatment.* 2022;33(4):2118-2128.
29. Young TK, Glick AF, Yin HS, et al. Management of Pediatric Atopic Dermatitis by Primary Care Providers: A Systematic Review. *Acad Pediatr.* 2021;21(8):1318-1327.
30. Svendsen MT, Feldman SR, Tiedemann SN, Sorensen ASS, Rivas CMR, Andersen KE. Psoriasis patient preferences for topical drugs: a systematic review. *Journal of Dermatological Treatment.* 2021;32(5):478-483.
31. Svendsen MT, Jeyabalan J, Andersen KE, Andersen F, Johannessen H. Worldwide utilization of topical remedies in treatment of psoriasis: a systematic review. *Journal of Dermatological Treatment.* 2017;28(5):374-383.
32. Chi CC, Wang SH, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. *Cochrane Database Syst Rev.* 2015(10).
33. TAZORAC (tazarotene) gel. Prescribing Information. Madison, NJ; Allergan. April 2018.
34. Franssen ME, van der Wilt GJ, de Jong PC, Bos RP, Arnold WP. A retrospective study of the teratogenicity of dermatological coal tar products. *Acta Derm Venereol.* 1999;79(5):390-391.
35. Lexicomp Online. Wolters Kluwer Health, Hudson, Ohio, USA. Available at http://online.lexi.com. Accessed November 1, 2021.
36. SORILUX (calcipotriene) topical foam. Prescribing Information. Greenville, NC; Mayne Pharma. November 2019.
37. VECTICAL (calcitriol) topical ointment. Prescribing Information. Fort Worth, TX; Galderma Laboratories. July 2020.
38. ULTRAVATE (halobetasol) topical lotion. Prescribing Information. Cranbury, NJ; Sun Pharmaceutical Industries. August 2020.
39. LEXETTE (halobetasol) topical foam. Prescribing Information. Greenville, NC; Mayne Pharma. May 2021.
40. Le AM, Torres T. New Topical Therapies for Psoriasis. *Am J Clin Dermatol.* 2022;23(1):13-24.
41. Strober B, Stein Gold L, Bissonnette R, et al. One-year safety and efficacy of tapinarof cream for the treatment of plaque psoriasis: Results from the PSOARING 3 trial. *J Am Acad Dermatol.* 2022;87(4):800-806.

Generic	Brand	Route	Form	PDL
pimecrolimus	ELIDEL	TOPICAL	CREAM (G)	Y
pimecrolimus	PIMECROLIMUS	TOPICAL	CREAM (G)	Y
tacrolimus	PROTOPIC	TOPICAL	OINT. (G)	Y
tacrolimus	TACROLIMUS	TOPICAL	OINT. (G)	Y
crisaborole	EUCRISA	TOPICAL	OINT. (G)	N
ruxolitinib phosphate	OPZELURA	TOPICAL	CREAM (G)	N

Generic	Brand	Route	Form	PDL
calcipotriene	CALCIPOTRIENE	TOPICAL	CREAM (G)	Y
calcipotriene	DOVONEX	TOPICAL	CREAM (G)	Y
tazarotene	TAZAROTENE	TOPICAL	CREAM (G)	Y
tazarotene	TAZORAC	TOPICAL	CREAM (G)	Y
tazarotene	TAZORAC	TOPICAL	GEL (GRAM)	Y
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE DP	TOPICAL	OINT. (G)	Y
calcipotriene/betamethasone	TACLONEX	TOPICAL	OINT. (G)	Y
calcipotriene	CALCIPOTRIENE	TOPICAL	SOLUTION	Y
anthralin	ANTHRALIN	TOPICAL	CREAM (G)	N
tapinarof	VTAMA	TOPICAL	CREAM (G)	N
calcipotriene	CALCIPOTRIENE	TOPICAL	FOAM	N
calcipotriene/betamethasone	ENSTILAR	TOPICAL	FOAM	N
coal tar	PSORIATAR	TOPICAL	FOAM	N
calcipotriene	SORILUX	TOPICAL	FOAM	N
halobetasol propion/tazarotene	DUOBRII	TOPICAL	LOTION	N
calcipotriene	CALCIPOTRIENE	TOPICAL	OINT. (G)	N
calcitriol	CALCITRIOL	TOPICAL	OINT. (G)	N
calcitriol	VECTICAL	TOPICAL	OINT. (G)	N
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE	TOPICAL	SUSPENSION	N
calcipotriene/betamethasone	TACLONEX	TOPICAL	SUSPENSION	N
coal tar	ANTI-DANDRUFF	TOPICAL	SHAMPOO	N
coal tar	DHS TAR	TOPICAL	SHAMPOO	N
coal tar	DHS TAR GEL	TOPICAL	SHAMPOO	N
coal tar	IONIL T	TOPICAL	SHAMPOO	N
coal tar	POLYTAR	TOPICAL	SHAMPOO	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 4 2022; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 01, 2022

1	exp Psoriasis/	31016
2	exp Dermatitis, Atopic/	17675
3	tapinarof.mp.	59
4	exp Tacrolimus/	15377
5	pimecrolimus.mp.	904
6	Administration, Topical/	27072
7	Anti-Inflammatory Agents, Non-Steroidal/	60734
8	crisaborole.mp.	135
9	ruxolitinib.mp.	1913
10	roflumilast.mp.	664
11	Calcitriol/	8617
12	tazarotene.mp.	598
13	Betamethasone/ or Calcitriol/	11382
14	Anthralin/	287
15	Coal Tar/	486
16	3 or 4 or 5 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	91232
17	6 and 16	2911
18	exp Skin Diseases/	734309
19	1 or 2 or 18	734309
20	17 and 19	1615
21	limit 20 to (English language and humans and yr="2017 -Current")	231
22	limit 21 to (clinical trial, all or comparative study or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	67

Appendix 3: Prescribing Information Highlights

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

ZORYVE™ (roflumilast) cream, for topical use
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------
ZORYVE is a phosphodiesterase 4 inhibitor indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Apply once daily to affected areas. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Cream, 0.3%: 3 mg of roflumilast per gram in 60-gram tubes. (3)

----------CONTRAINDICATIONS----------
- Moderate to severe liver impairment (Child-Pugh B or C). (4)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (reported in ≥1% of patients) are diarrhea, headache, insomnia, application site pain, upper respiratory tract infections, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Arcutis Biotherapeutics, Inc. at 1-844-692-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. (7.1)
- Coadministration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit. (7.2)

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

Revised: 7/2022

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VTAMA (tapinarof) cream, for topical use
Initial U.S. Approval: 2022

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

VTAMA cream, 1% is an aryl hydrocarbon receptor agonist indicated for the topical treatment of plaque psoriasis in adults. (1)

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

- Apply a thin layer of VTAMA cream to affected areas once daily. (2)
- VTAMA cream is not for oral, ophthalmic, or intravaginal use. (2)

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

Cream, 1% (3)

Each gram of VTAMA cream contains 10 mg of tapinarof. (3)

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

None. (4)

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

Most common adverse reactions (incidence ≥ 1%) in subjects treated with VTAMA cream were folliculitis, nasopharyngitis, contact dermatitis, headache, pruritus, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dermavant Sciences, Inc. at 1-8DERMAVANT or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 05/2022

Topical Agents for Inflammatory Skin Disease

Goal(s):

- Restrict dermatological drugs only for funded OHP diagnoses for adults. Treatments are funded on the OHP for severe 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 atopic dermatitis and vitiligo 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

Generic Drug Name	Brand Name	Minimum Age	Indication (severity)
Crisaborole 2% ointment	EUCRISA	3 months	Atopic Dermatitis (Mild-to-Moderate)
Pimecrolimus 1% cream	ELIDEL	2 years	Atopic Dermatitis (Mild-to-Moderate)
Ruxolitinib 1.5% cream	OPZELURA	12 years	Atopic Dermatitis (Mild-to-Moderate) Nonsegmental Vitiligo
Tacrolimus 0.03% ointment	PROTOPIC	2 years	Atopic Dermatitis (Moderate-to-Severe)
Tacrolimus 0.1% ointment	PROTOPIC	16 years	Atopic Dermatitis (Moderate-to-Severe)

Roflumilast 0.3% cream	ZORYVE	12 years	Plaque Psoriasis
Tapinarof 1% cream	VTAMA	18 years	Plaque Psoriasis
Calcipotriene cream, solution, and ointment Calcipotriene foam	DOVONEX SORILUX	18 years 4 years	Plaque Psoriasis
Tazarotene cream and gel	TAZORAC	12 years	Plaque Psoriasis
Calcipotriene/Betamethasone ointment, suspension, and foam Calcipotriene/Betamethasone cream	TACLONEX ENSTILAR WYNZORA	12 years 18 years	Plaque Psoriasis
Anthralin Shampoo Anthralin Cream	ZITHRANOL	12 years 18 years	Plaque Psoriasis
Halobetasol propionate/Tazarotene Lotion	DUOBRII	18 years	Plaque Psoriasis
Calcitriol ointment	VECTICAL	2 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
	Betamethasone dipropionate	0.05%	lotion

Medium-Low Potency (Group 5)	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 treatment of severe inflammatory skin disease ~~OR is the patient 20 years of age or younger~~? 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 #3	**No:** **For age ≥ 21 years:** Pass to RPh; deny, not funded by the OHP For age < 21 years: Go to #3

Approval Criteria		
~~2.~~3. Is the diagnosis plaque psoriasis, atopic dermatitis or nonsegmental vitiligo?	**Yes:** Go to #4	**No:** Go to #8
4. 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 #5	**No:** Pass to RPh. Deny; medical appropriateness
~~3.~~5. Is the requested product preferred?	**Yes**: Go to #6	**No**: Go to #7
~~4.~~6. For patients 20 years of age or younger, is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?~~is there documentation or provider attestation that the therapy is expected to improve the patient's ability to grow, develop or participate in school~~?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical ~~appropriateness~~necessity

Approval Criteria		
~~5.~~7. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 preferred first line agents (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
~~6.~~8. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP. *	**If funded, and clinic provides supporting literature:** Approve for 1 year.	**If not funded:** Go to # **9**
~~7.~~9. Is the request for an FDA approved indication?	**Yes**: Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *12/22 (DM); 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: *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*

**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:

1. *Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. J Am Acad Dermatol. 2021;84(2):432-470.*
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*
3. *Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed October 6, 2022.*
~~3.~~*Oregon*4. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx. Accessed March 1, 2022.*