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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, June 2nd, 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. Approval of Agenda	R. Citron (OSU)
	C. Conflict of Interest Declaration	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. Tetracycline Quantity Limit	
	C. Oncology Prior Authorization Updates	
	D. 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. Pre- and Post-Exposure Prophylaxis of HIV	
	2. Anti-SARS-CoV-2 Therapeutics can Effectively Treat, Prevent COVID-19 Infection	
	IV. DUR NEW BUSINESS	
2:00 PM	A. Sublingual Buprenorphine Policy Evaluation	S. Servid (OSU)
	1. Policy Evaluation	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
2:15 PM	B. ADHD Drug Utilization Evaluation and DERP Summary	
	1. Drug Utilization Evaluation	G. Karagodsky (OSU)
	2. DERP Summary/Safety Edit	M. Herink (OSU)

	3. Public Comment	D. Engen (OSU)
	4. Discussion and Clinical Recommendations to OHA	
	V. PREFERRED DRUG LIST NEW BUSINESS	
2:55 PM	A. Diuretics Literature Scan and New Drug Evaluation	M. Herink (OSU)
	1. Literature Scan	
	2. Kerendia®(Finerenone) New Drug Evaluation	
	3. Public Comment	
	4. Discussion and Clinical Recommendations to OHA	
3:10 PM	BREAK	
3:25 PM	B. Targeted Immune Modulators for Asthma and Drugs for Inflammatory Skin Conditions	D. Moretz (OSU)
	1. Atopic Dermatitis DERP Summary	
	2. Asthma Biologics Class Update	
	3. Tezspire™ (tezepelumab) New Drug Evaluation	
	4. Vitiligo Literature Scan	
	5. Prior Authorization Criteria	
	6. Public Comment	
	7. Discussion and Clinical Recommendations to OHA	
4:05 PM	C. Mycobacterium Agents Class Review	S. Fletcher (OSU)
	1. Class Review	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
4:20 PM	D. Estrogens Class Update	K. Sentena (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
4:35 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
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, April 7th, 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: Cat Livingston, MD; Tim Langford, PharmD; Robin Moody, MPH; Bill Origer, MD; Russ Huffman, PMHNP; Patrick DeMartino, MD; Eddie Saito, PharmD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Lan Starkweather, PharmD; Deanna Moretz, PharmD; Amanda Parish, LCSW; Sarah Servid, PharmD; Megan Herink, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH; Kathy Sentena, PharmD; Deborah Weston, JD

Audience: Stuart O'Brochta* - Gilead, **Charlie Lovan* - Abbvie**, **Amy Burns* - Allcare**, **Andy Seaman* - OHSU, Ann Thomas* - OHA Center for Public Health Practice**, Baltazar Chavez-Diaz – PacificSource Health Plan, Beth Englander – Oregon Law Center, Brandie Feger – Advanced Health, Casey Eastman, Claudette Banks - OHSU, Dennis Schaffner – Sanofi Specialty Care, **Douglas Carr* – CMO Umpqua Health Alliance**, Ed Eldridge, Emma Anderson – Sick Cells, Jason Kniffin, Jeff Mussack - Immunocore, Jeremy Strand - Alexion, Jim Slater - CareOregon, **Kate Jelline* - Ardon Health Specialty Pharmacy**, Katie Scheelar – EOCCO/Moda Health, Kelly Wright – Gilead, Kenneth Orr – Global Blood Therapeutics, Laura Jeffcoat - Abbvie, **Lorren Sandt* – Caring Ambassadors Program**, Mark Kantor – AllCare Health, Matt Worthy - OHSU, Melissa Bailey-Hall, Melissa Snider - Gilead, Michael Foster - BMS, Michele Sabados, Mike Donabedian – Sarepta Therapeutics, Mit Patel - Calliditas, Nana Ama Kuffour - IHN, Olaf Reinwald – Global Blood Therapeutics, **Robin Traver* – Umpqua Health Alliance,** Roy Lindfield - Sunovion, Saghi, **Santries Booze* – Global Blood Therapeutics**, Shannon Lee - Trillium, Shauna Wick - Trillium, Steve Angelcyk – BD Diabetes, Terence Lee - Gilead, Tiffany Jones – Pacific Source, Tina Andrews – Umpqua Health Alliance, Brandon Yip – Sanofi, YJ Shukla – EOCCO/Moda Health

(*) 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. Conflict of Interest Declaration – no new conflicts of interest were declared

C. Approval of Agenda and February 2022 Minutes presented by Roger Citron
ACTION: Motion to approve, 2nd, all in favor

D. Department Update provided by Andrew Gibler, PharmD

E. Legislative Update provided by Dee Weston, JD

II. CONSENT AGENDA TOPICS

A. **Oncology Prior Authorization (PA) Updates**
Recommendation:
- Add: Kimmtrak® (tebentafusp) to Table 1 in the Oncology Agents prior authorization (PA) criteria

B. **Orphan Drug Policy Updates**
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Enjaymo™ (sutimlimab-jome) based on FDA-approved labeling
ACTION: Motion to Approve, 2nd, all in favor

III. DUR NEW BUSINESS

A. **Citizenship Waived Medical (CWM) Coverage Update:** Sarah Servid, PharmD
Recommendation:
Implement PA criteria for drugs prescribed for patients with the CWM benefit, and update PA criteria with relevant diagnoses if emergency drug coverage is expanded to other conditions in the future
ACTION: Motion to approve, 2nd, all in favor with one abstention

B. **Prior Authorization Updates: Sarah Servid, PharmD**
   a. **Botulinum Toxins PA Update**
   Recommendation:
   -Update PA criteria as proposed
   ACTION: Motion to approve, 2nd , all in favor
   b. **Drugs for Non-Funded Conditions PA Update**
   Recommendation:

- Update PA criteria as proposed to align with final version of Statement of Intent 4 (SOI4)

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

c. **Non-Preferred Drugs in Select PDL classes PA Update**

Recommendation:

- Update PA criteria as proposed to align with final version of Statement of Intent 4 (SOI4)

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

IV. DUR OLD BUSINESS

A. **Hepatitis C Direct-Acting Antivirals Policy Discussion**

Policy Discussion: Andrew Gibler, PharmD; Dee Weston, JD

Prior Authorization Update: Megan Herink, PharmD

Public Comment:

Charlie Lovan, AbbVie; Stuart O'Brochta, Gilead; Amy Burns, AllCare CCO; Robin Traver, Umpqua Health CCO; Douglas Carr, Umpqua Health CCO; Kate Jelline, Ardon Health Specialty Pharmacy; Lorren Sandt, Caring Ambassadors Program; Andy Seaman, Central City Concern; Ann Thomas, OHA Public Health

Recommendations:

-Remove PA criteria and required case management for preferred DAA regimens for treatment-naïve patients with hepatitis C virus

ACTION: Motion to Approve, 2nd, all in favor with one abstention

-Continue to require PA for: retreatment of HCV; non-preferred DAAs; and for uses not FDA approve

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

- Make sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) non-preferred and continue to reserve it for treatment-experienced individuals

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

V. PREFERRED DRUG LIST NEW BUSINESS

A. **Sickle Cell Disease Literature Scan**: Kathy Sentena, PharmD

Recommendations:

- No Preferred Drug List (PDL) changes recommended based on the clinical evidence
- Update PA criteria to include the expanded age indication for voxelotor
- Evaluate costs in executive session

Public Comment: Santries Booze, Global Blood Therapeutics

ACTION: The Committee recommended: removing baseline pain crisis from approval criteria #8 for voxelotor approval; reword question #6 in approval criteria to change "failure" of hydroxyurea to "has the patient received (or have contraindications to) a 3 month trial of hydroxyurea at stable doses and will treatment of hydroxyurea be maintained"; reword question #7 in renewal criteria to simply require documented improvement from baseline (similar to question #5); and add "in pain symptoms" to #5 of renewal criteria
Motion to approve, 2nd, all in favor

B. **Fabry Disease Literature Scan**: Deanna Moretz, PharmD
Recommendation:
- Revise PA criteria to reflect expanded indication for agalsidase beta
ACTION: Motion to approve, 2nd, all in favor

C. **Voxzogo™ (vosoritide) New Drug Evaluation:** David Engen, PharmD
Recommendation:
- Implement proposed PA criteria for vosoritide to ensure appropriate use
ACTION: Motion to approve, 2nd, all in favor

D. **Vyvgart™ (efgartigimod alfa-fcab) New Drug Evaluation**: Kathy Sentena, PharmD
Recommendations:
- Designate efgartigimod as non-preferred on the PDL and subject to PA criteria
- Implement proposed PA criteria to ensure appropriate use
ACTION: Motion to approve, 2nd, all in favor

E. **Fluoroquinolone Drug Class Update**: Deanna Moretz, PharmD
Recommendations:
- Designate moxifloxacin as a preferred on the PDL
- Review drug costs in Executive Session
ACTION: Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Members Present: Cat Livingston, MD; Tim Langford, PharmD; Bill Origer, MD; Russ Huffman, PMHNP; Patrick DeMartino, MD; Eddie Saito, PharmD; Robin Moody, MPH

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Lan Starkweather, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Megan

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Herink, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH; Kathy Sentena, PharmD; Deborah Weston, JD

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Sickle Cell Disease Literature Scan**
Recommendation: No PDL changes recommended
ACTION: Motion to approve, 2nd, all in favor

B. **Fluoroquinolone Drug Class Update**
Recommendations: No PDL changes recommended
ACTION: Motion to approve, 2nd, all in favor

VIII. ADJOURN

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Pharmacy Utilization Summary Report: October 2020 - September 2021

Eligibility	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
Total Members (FFS & Encounter)	1,105,304	1,124,250	1,142,287	1,155,608	1,165,327	1,176,534	1,186,439	1,195,359	1,203,243	1,212,729	1,222,901	1,230,474	1,176,705
FFS Members	99,759	110,699	110,136	110,971	104,212	106,887	108,646	109,364	105,833	109,457	112,375	108,825	108,097
OHP Basic with Medicare	7,395	8,031	7,925	7,781	7,599	7,743	7,998	8,048	7,967	8,110	8,273	8,141	7,918
OHP Basic without Medicare	11,546	11,692	11,422	11,524	11,224	11,074	11,063	11,039	10,911	10,947	11,003	10,811	11,188
ACA	80,818	90,976	90,789	91,666	85,389	88,070	89,585	90,277	86,955	90,400	93,099	89,873	88,991
Encounter Members	1,005,545	1,013,551	1,032,151	1,044,637	1,061,115	1,069,647	1,077,793	1,085,995	1,097,410	1,103,272	1,110,526	1,121,649	1,068,608
OHP Basic with Medicare	74,103	74,533	75,527	76,328	77,441	78,598	79,521	80,356	81,391	82,240	83,030	83,993	78,922
OHP Basic without Medicare	65,428	65,582	66,083	67,172	67,155	66,975	67,232	67,380	67,600	67,639	67,674	68,041	66,997
ACA	866,014	873,436	890,541	901,137	916,519	924,074	931,040	938,259	948,419	953,393	959,822	969,615	922,689

Gross Cost Figures for Drugs	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	YTD Sum
Total Amount Paid (FFS & Encounter)	$89,981,179	$86,379,474	$97,937,751	$93,371,393	$89,727,807	$105,261,398	$100,546,385	$97,764,720	$104,283,869	$100,490,996	$103,492,931	$104,831,425	$1,174,069,329
Mental Health Carve-Out Drugs	$9,450,992	$9,149,232	$10,068,420	$10,188,372	$10,196,300	$12,111,185	$11,752,441	$11,397,638	$12,053,846	$11,641,751	$11,841,727	$11,298,671	$131,150,576
OHP Basic with Medicare	$25,916	$26,636	$43,711	$26,605	$27,401	$8,529	$7,638	$5,904	$5,729	$2,855	$5,699	$4,725	$191,347
OHP Basic without Medicare	$3,691,659	$3,621,907	$3,904,114	$4,007,981	$4,074,811	$4,679,151	$4,597,507	$4,351,758	$4,649,849	$4,471,529	$4,508,744	$4,329,328	$50,888,338
ACA	$5,686,192	$5,445,824	$6,066,550	$6,100,012	$6,035,622	$7,354,762	$7,066,833	$6,959,911	$7,312,632	$7,078,920	$7,238,733	$6,887,158	$79,233,149
FFS Physical Health Drugs	$2,574,537	$2,299,707	$2,595,333	$4,476,647	$4,155,163	$5,053,244	$4,754,753	$4,393,918	$4,834,685	$4,614,741	$4,677,562	$4,541,598	$48,971,889
OHP Basic with Medicare	$47,671	$43,752	$48,453	$160,402	$142,248	$158,533	$162,141	$168,313	$178,788	$167,400	$169,133	$164,822	$1,611,655
OHP Basic without Medicare	$922,623	$775,671	$942,688	$1,356,464	$1,131,622	$1,270,918	$1,225,033	$1,016,510	$1,183,172	$1,156,021	$1,203,339	$1,138,726	$13,322,787
ACA	$1,491,377	$1,366,636	$1,474,166	$2,840,636	$2,764,862	$3,504,330	$3,213,989	$3,090,845	$3,332,260	$3,157,399	$3,142,438	$3,046,541	$32,425,477
FFS Physician Administered Drugs	$1,714,989	$1,266,654	$1,278,585	$1,491,742	$1,874,653	$1,555,847	$1,383,983	$1,157,559	$1,690,190	$1,349,003	$1,260,437	$1,118,772	$17,142,414
OHP Basic with Medicare	$83,897	$106,382	$99,269	$163,563	$227,684	$107,630	$93,742	$146,554	$120,921	$115,075	$130,463	$140,885	$1,536,064
OHP Basic without Medicare	$693,639	$392,520	$308,372	$333,496	$781,443	$455,386	$328,642	$266,582	$739,306	$346,913	$203,066	$223,700	$5,073,065
ACA	$462,017	$355,686	$473,659	$514,641	$482,771	$473,168	$520,595	$368,312	$389,928	$507,838	$467,644	$424,948	$5,441,207
Encounter Physical Health Drugs	$59,976,082	$58,139,873	$63,072,889	$60,784,231	$58,132,984	$68,339,856	$64,932,942	$63,403,821	$66,947,228	$64,703,958	$65,512,820	$64,155,544	$758,102,228
OHP Basic with Medicare	$758,829	$718,275	$761,522	$622,868	$587,798	$381,081	$411,644	$391,978	$456,358	$424,389	$397,532	$415,486	$6,327,760
OHP Basic without Medicare	$14,226,252	$14,407,178	$15,840,694	$14,931,190	$14,191,872	$16,781,963	$15,974,835	$15,499,296	$16,275,568	$15,564,371	$16,279,275	$15,394,912	$185,367,405
ACA	$44,253,819	$42,329,777	$45,799,895	$44,567,933	$42,664,531	$50,312,076	$47,700,780	$46,708,796	$49,177,293	$47,561,420	$47,805,457	$47,494,382	$556,376,160
Encounter Physician Administered Drugs	$16,264,580	$15,524,009	$20,922,525	$16,430,401	$15,368,707	$18,201,265	$17,722,265	$17,411,784	$18,757,918	$18,181,542	$20,200,386	$23,716,841	$218,702,223
OHP Basic with Medicare	$657,207	$638,131	$631,945	$783,377	$676,724	$988,336	$911,413	$902,596	$951,935	$795,359	$877,654	$847,720	$9,662,399
OHP Basic without Medicare	$3,726,081	$3,478,353	$7,198,922	$3,699,057	$3,122,586	$3,817,080	$3,724,628	$4,095,120	$4,007,199	$3,971,530	$3,781,153	$10,442,618	$55,064,327
ACA	$11,444,468	$10,878,942	$12,756,725	$11,508,129	$11,113,233	$13,047,738	$12,753,420	$12,123,056	$13,603,032	$12,836,044	$15,178,029	$12,097,166	$149,339,981

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

Last Updated: April 21, 2022

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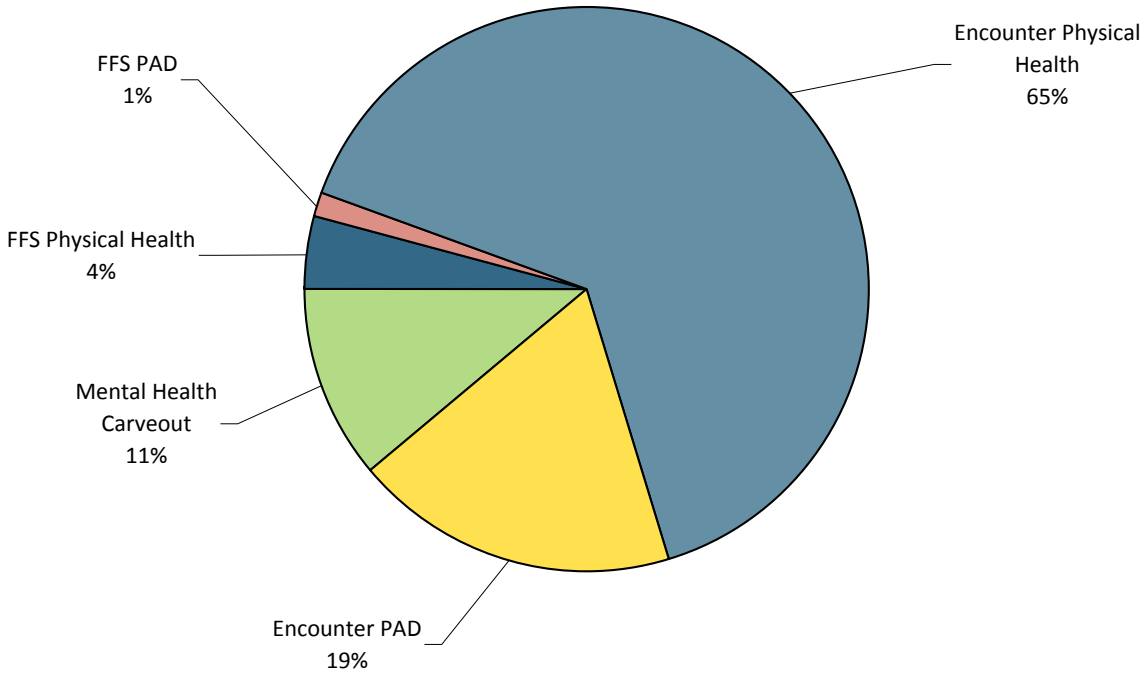
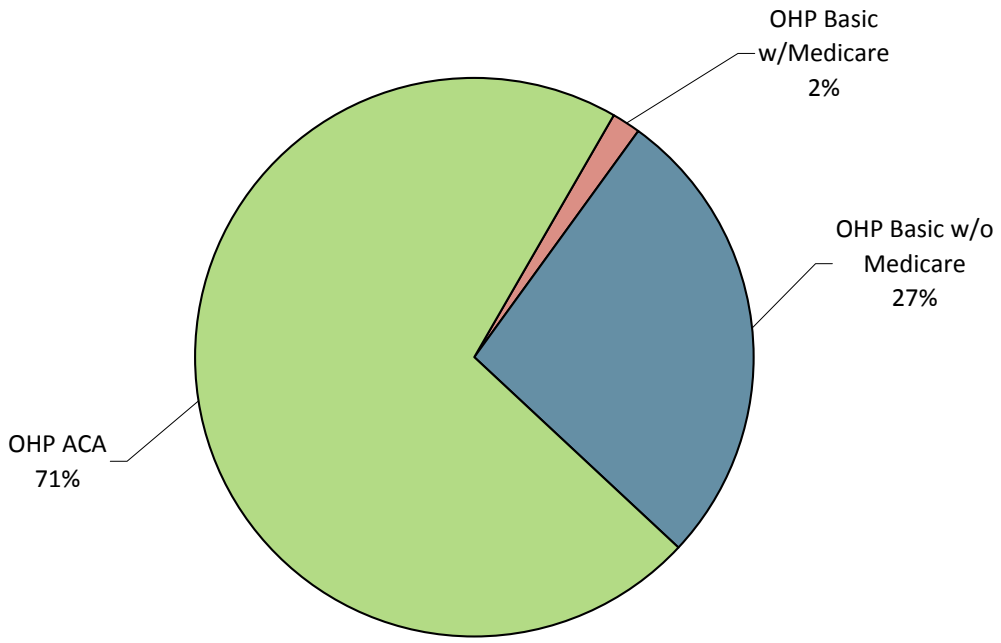
Pharmacy Utilization Summary Report: October 2020 - September 2021

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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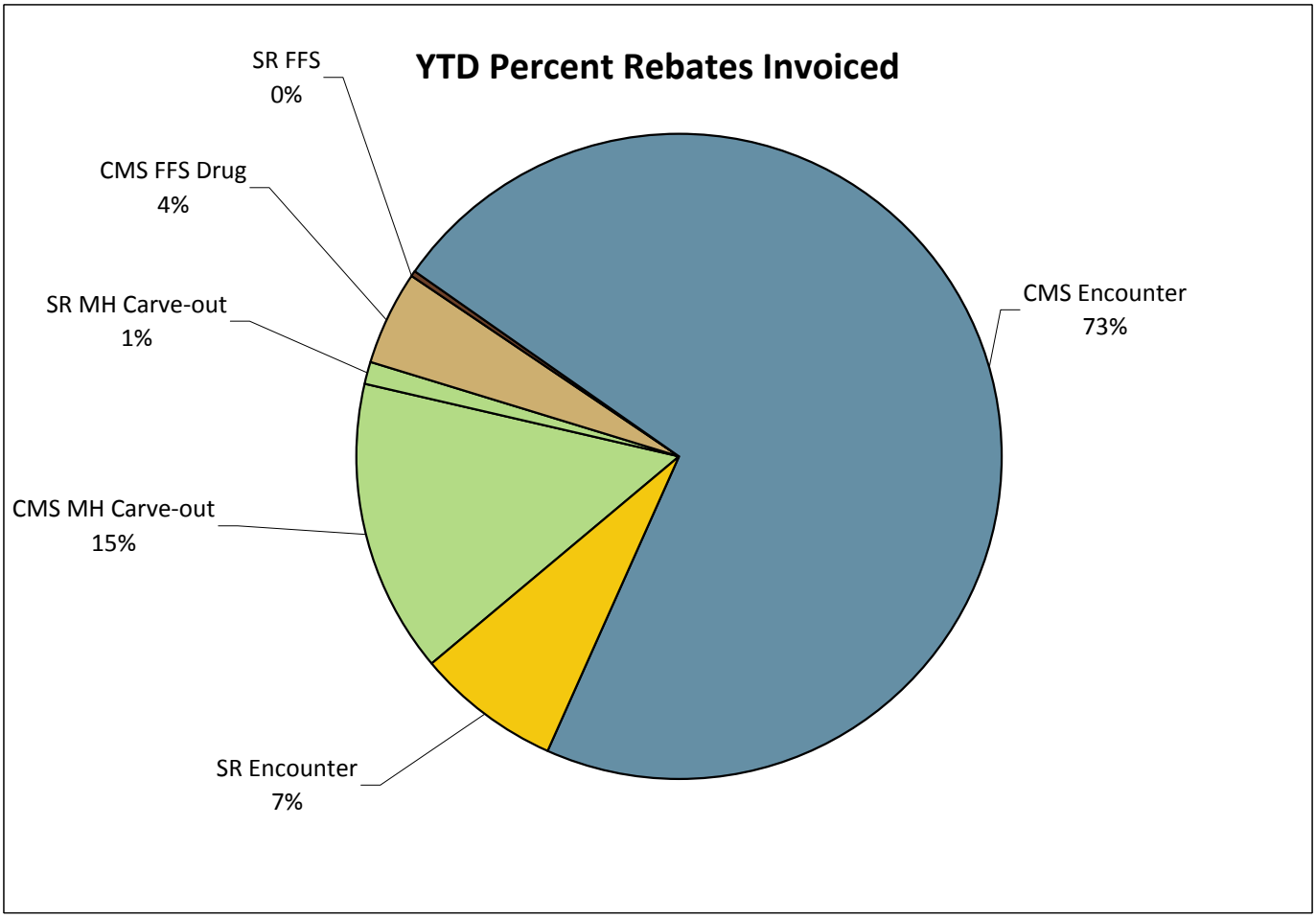
Pharmacy Utilization Summary Report: October 2020 - September 2021

Quarterly Rebates Invoiced	2020-Q4	2021-Q1	2021-Q2	2021-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$108,780,996	$117,817,621	$120,281,873	$115,016,574	$461,897,065
CMS MH Carve-out	$13,100,806	$16,644,196	$19,346,510	$18,545,927	$67,637,438
SR MH Carve-out	$1,460,752	$1,484,299	$1,416,550	$1,618,306	$5,979,906
CMS FFS Drug	$4,666,648	$6,047,824	$5,355,790	$4,657,652	$20,727,914
SR FFS	$512,651	$540,442	$512,939	$452,218	$2,018,250
CMS Encounter	$81,483,103	$84,648,942	$84,813,377	$80,670,554	$331,615,977
SR Encounter	$7,557,036	$8,451,920	$8,836,708	$9,071,916	$33,917,580

Quaterly Net Drug Costs	2020-Q4	2021-Q1	2021-Q2	2021-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$165,517,409	$170,542,976	$182,313,101	$193,798,779	$712,172,265
Mental Health Carve-Out Drugs	$14,107,087	$14,367,362	$14,440,866	$14,617,916	$57,533,232
FFS Phys Health + PAD	$6,550,504	$12,019,031	$12,346,361	$12,452,242	$43,368,139
Encounter Phys Health + PAD	$144,859,817	$144,156,583	$155,525,874	$166,728,621	$611,270,895



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

Last Updated: April 21, 2022

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Pharmacy Utilization Summary Report: October 2020 - September 2021

Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$81.41	$76.83	$85.74	$80.80	$77.00	$89.47	$84.75	$81.79	$86.67	$82.86	$84.63	$85.20	$83.09
Mental Health Carve-Out Drugs	$8.55	$8.14	$8.81	$8.82	$8.75	$10.29	$9.91	$9.53	$10.02	$9.60	$9.68	$9.18	$9.27
FFS Physical Health Drugs	$25.81	$20.77	$23.56	$40.34	$39.87	$47.28	$43.76	$40.18	$45.68	$42.16	$41.62	$41.73	$37.73
FFS Physician Administered Drugs	$17.19	$11.44	$11.61	$13.44	$17.99	$14.56	$12.74	$10.58	$15.97	$12.32	$11.22	$10.28	$13.28
Encounter Physical Health Drugs	$59.65	$57.36	$61.11	$58.19	$54.78	$63.89	$60.25	$58.38	$61.00	$58.65	$58.99	$57.20	$59.12
Encounter Physician Administered Drugs	$16.17	$15.32	$20.27	$15.73	$14.48	$17.02	$16.44	$16.03	$17.09	$16.48	$18.19	$21.14	$17.03

Claim Counts	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
Total Claim Count (FFS & Encounter)	1,089,202	1,033,334	1,091,121	1,071,426	1,010,661	1,162,906	1,133,763	1,123,319	1,160,382	1,127,416	1,125,239	1,080,241	1,100,751
Mental Health Carve-Out Drugs	177,441	174,286	186,760	182,949	172,693	197,110	186,973	184,209	191,541	188,149	191,024	185,313	184,871
FFS Physical Health Drugs	37,802	33,999	36,602	37,988	35,897	42,164	41,557	41,077	41,594	38,322	38,645	36,720	38,531
FFS Physician Administered Drugs	10,463	9,905	10,250	11,219	10,114	11,178	10,444	9,987	9,802	9,855	9,195	8,909	10,110
Encounter Physical Health Drugs	743,125	704,799	743,869	722,896	682,022	787,684	773,211	768,024	796,095	770,632	772,576	742,834	750,647
Encounter Physician Administered Drugs	120,371	110,345	113,640	116,374	109,935	124,770	121,578	120,022	121,350	120,458	113,799	106,465	116,592

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$82.61	$83.59	$89.76	$87.15	$88.78	$90.52	$88.68	$87.03	$89.87	$89.13	$91.97	$97.04	$88.85
Mental Health Carve-Out Drugs	$53.26	$52.50	$53.91	$55.69	$59.04	$61.44	$62.86	$61.87	$62.93	$61.88	$61.99	$60.97	$59.03
FFS Physical Health Drugs	$68.11	$67.64	$70.91	$117.84	$115.75	$119.85	$114.42	$106.97	$116.24	$120.42	$121.04	$123.68	$105.24
FFS Physician Administered Drugs	$163.91	$127.88	$124.74	$132.97	$185.35	$139.19	$132.51	$115.91	$172.43	$136.89	$137.08	$125.58	$141.20
Encounter Physical Health Drugs	$80.71	$82.49	$84.79	$84.08	$85.24	$86.76	$83.98	$82.55	$84.09	$83.96	$84.80	$86.37	$84.15
Encounter Physician Administered Drugs	$135.12	$140.69	$184.11	$141.19	$139.80	$145.88	$145.77	$145.07	$154.58	$150.94	$177.51	$222.77	$156.95

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$20.10	$20.76	$21.35	$23.41	$23.47	$23.02	$22.31	$21.87	$22.92	$22.24	$22.44	$22.01	$22.16
Mental Health Carve-Out Drugs	$16.35	$16.38	$16.55	$17.97	$17.97	$17.58	$17.26	$17.01	$17.05	$17.01	$16.68	$16.14	$16.99
FFS Physical Health Drugs	$21.14	$21.28	$22.62	$70.09	$70.63	$74.19	$73.45	$72.93	$78.71	$78.35	$78.53	$77.98	$61.66
Encounter Physical Health Drugs	$21.05	$21.95	$22.62	$22.65	$22.72	$22.04	$21.28	$20.88	$21.95	$21.16	$21.53	$21.18	$21.75

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$476.98	$507.89	$548.82	$552.09	$556.62	$549.80	$472.98	$427.02	$463.45	$519.26	$504.88	$498.45	$506.52
Mental Health Carve-Out Drugs	$1,104.96	$1,083.85	$1,098.66	$1,124.67	$1,108.91	$1,052.53	$1,030.67	$1,018.03	$1,013.80	$1,012.86	$1,019.49	$1,006.46	$1,056.24
FFS Physical Health Drugs	$261.67	$264.25	$281.87	$332.60	$304.14	$289.49	$232.94	$191.77	$226.53	$265.20	$257.84	$269.58	$264.82
Encounter Physical Health Drugs	$455.52	$488.06	$529.89	$528.69	$534.54	$531.11	$453.97	$409.69	$443.42	$499.57	$484.25	$477.19	$486.33

Generic Drug Use Percentage	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
Generic Drug Use Percentage	88.0%	88.6%	89.2%	89.3%	89.1%	88.6%	86.9%	85.7%	86.7%	88.1%	87.7%	87.2%	87.9%
Mental Health Carve-Out Drugs	96.6%	96.6%	96.5%	96.6%	96.2%	95.8%	95.5%	95.5%	95.4%	95.5%	95.5%	95.5%	95.9%
FFS Physical Health Drugs	80.5%	80.9%	81.4%	81.8%	80.7%	78.8%	74.3%	71.4%	74.6%	77.5%	76.3%	76.1%	77.9%
Encounter Physical Health Drugs	86.3%	87.0%	87.7%	87.9%	87.8%	87.3%	85.5%	84.1%	85.3%	86.9%	86.3%	85.7%	86.5%

Preferred Drug Use Percentage	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Avg Monthly
Preferred Drug Use Percentage	86.68%	86.67%	86.65%	86.70%	86.60%	86.56%	89.71%	89.80%	89.70%	89.98%	89.92%	89.82%	88.2%
Mental Health Carve-Out Drugs	77.28%	77.16%	77.37%	77.24%	76.90%	76.91%	93.02%	93.06%	93.04%	93.11%	93.08%	93.01%	85.1%
FFS Physical Health Drugs	94.36%	94.28%	94.78%	94.41%	94.16%	94.20%	94.35%	94.39%	94.36%	94.68%	94.90%	94.71%	94.5%
Encounter Physical Health Drugs	88.57%	88.67%	88.58%	88.69%	88.66%	88.59%	88.68%	88.79%	88.67%	89.00%	88.91%	88.80%	88.7%

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

Last Updated: April 21, 2022

Drug Use Research & Management Program
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Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2022

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,831,984	15.8%	5,472	$1,249	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,458,378	8.0%	1,578	$2,192	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,896,558	6.7%	2,478	$1,169	Y
4	STRATTERA*	ADHD Drugs	$2,824,664	6.5%	6,186	$457	Y
5	REXULTI	Antipsychotics, 2nd Gen	$2,045,965	4.7%	1,746	$1,172	V
6	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,922,837	4.5%	889	$2,163	Y
7	INVEGA TRINZA	Antipsychotics, Parenteral	$946,447	2.2%	141	$6,712	Y
8	TRINTELLIX	Antidepressants	$785,356	1.8%	1,839	$427	V
9	ARISTADA	Antipsychotics, Parenteral	$723,354	1.7%	317	$2,282	Y
10	INVEGA	Antipsychotics, 2nd Gen	$687,565	1.6%	1,772	$388	V
11	SERTRALINE HCL	Antidepressants	$576,109	1.3%	58,091	$10	Y
12	VIIBRYD	Antidepressants	$542,421	1.3%	1,739	$312	V
13	BUPROPION XL	Antidepressants	$522,434	1.2%	39,048	$13	Y
14	DULOXETINE HCL	Antidepressants	$508,374	1.2%	35,855	$14	Y
15	FLUOXETINE HCL	Antidepressants	$466,966	1.1%	42,304	$11	Y
16	TRAZODONE HCL	Antidepressants	$461,314	1.1%	45,930	$10	
17	ESCITALOPRAM OXALATE	Antidepressants	$385,014	0.9%	38,872	$10	Y
18	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$307,871	0.7%	25,020	$12	
19	LAMOTRIGINE	Antiepileptics (non-injectable)	$303,655	0.7%	27,996	$11	Y
20	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$259,260	0.6%	272	$953	Y
21	CAPLYTA	Antipsychotics, 2nd Gen	$247,428	0.6%	176	$1,406	V
22	TRIKAFTA*	Cystic Fibrosis	$246,756	0.6%	33	$7,477	N
23	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$233,638	0.5%	18,654	$13	Y
24	VENLAFAXINE HCL ER	Antidepressants	$232,155	0.5%	18,335	$13	Y
25	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$215,509	0.5%	2,880	$75	V
26	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$212,818	0.5%	19,185	$11	Y
27	BIKTARVY	HIV	$208,298	0.5%	95	$2,193	Y
28	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$208,210	0.5%	1	$208,210	
29	CHOLBAM*	Bile Therapy	$207,504	0.5%	3	$69,168	N
30	BUPROPION XL	Antidepressants	$206,294	0.5%	1,103	$187	V
31	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$179,520	0.4%	17	$10,560	Y
32	VENLAFAXINE HCL ER	Antidepressants	$178,592	0.4%	2,211	$81	V
33	Inj Pembrolizumab	Physican Administered Drug	$178,372	0.4%	48	$3,716	
34	CITALOPRAM HBR	Antidepressants	$178,324	0.4%	20,522	$9	Y
35	AMITRIPTYLINE HCL*	Antidepressants	$175,895	0.4%	13,825	$13	Y
36	Epoetin Beta Esrd Use	Physican Administered Drug	$170,879	0.4%	17	$10,052	
37	Elosulfase Alfa, Injection	Physican Administered Drug	$167,721	0.4%	13	$12,902	
38	MIRTAZAPINE	Antidepressants	$162,501	0.4%	11,262	$14	Y
39	LANTUS SOLOSTAR*	Diabetes, Insulins	$159,524	0.4%	450	$354	Y
40	CONCERTA*	ADHD Drugs	$159,283	0.4%	419	$380	N
		Top 40 Aggregate:	**$31,385,748**		**446,794**	**$8,660**	
		All FFS Drugs Totals:	**$43,176,265**		**691,147**	**$633**	

*** Drug requires Prior Authorization**

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

Last updated: April 21, 2022

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	TRIKAFTA*	Cystic Fibrosis	$246,756	2.5%	33	$7,477	N
2	BIKTARVY	HIV	$208,298	2.2%	95	$2,193	Y
3	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$208,210	2.1%	1	$208,210	
4	CHOLBAM*	Bile Therapy	$207,504	2.1%	3	$69,168	N
5	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$179,520	1.9%	17	$10,560	Y
6	Inj Pembrolizumab	Physican Administered Drug	$178,372	1.8%	48	$3,716	
7	Epoetin Beta Esrd Use	Physican Administered Drug	$170,879	1.8%	17	$10,052	
8	Elosulfase Alfa, Injection	Physican Administered Drug	$167,721	1.7%	13	$12,902	
9	LANTUS SOLOSTAR*	Diabetes, Insulins	$159,524	1.6%	450	$354	Y
10	CONCERTA*	ADHD Drugs	$159,283	1.6%	419	$380	N
11	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$137,204	1.4%	241	$569	Y
12	STELARA*	Targeted Immune Modulators	$135,293	1.4%	18	$7,516	N
13	VYVANSE*	ADHD Drugs	$132,993	1.4%	688	$193	Y
14	Aflibercept Injection	Physican Administered Drug	$126,079	1.3%	218	$578	
15	IBRANCE*	Antineoplastics, Newer	$125,866	1.3%	9	$13,985	
16	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$122,945	1.3%	5	$24,589	
17	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$119,135	1.2%	500	$238	
18	VIMPAT	Antiepileptics (non-injectable)	$114,469	1.2%	223	$513	Y
19	HUMIRA(CF) PEN*	Targeted Immune Modulators	$114,442	1.2%	48	$2,384	Y
20	SABRIL	Antiepileptics (non-injectable)	$109,383	1.1%	6	$18,230	N
21	Etonogestrel Implant System	Physican Administered Drug	$104,020	1.1%	149	$698	
22	ELIQUIS	Anticoagulants, Oral and SQ	$99,171	1.0%	274	$362	Y
23	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$87,180	0.9%	2,626	$33	Y
24	REVLIMID	STC 30 - Antineoplastic	$86,789	0.9%	6	$14,465	
25	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$76,426	0.8%	6	$12,738	
26	Mirena, 52 Mg	Physican Administered Drug	$72,034	0.7%	113	$637	
27	FLOVENT HFA	Corticosteroids, Inhaled	$71,435	0.7%	490	$146	Y
28	Injection, Vedolizumab	Physican Administered Drug	$67,840	0.7%	23	$2,950	
29	EPIDIOLEX*	Antiepileptics (non-injectable)	$66,666	0.7%	104	$641	N
30	AFINITOR DISPERZ*	Antineoplastics, Newer	$66,501	0.7%	6	$11,084	
31	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$64,572	0.7%	1,156	$56	Y
32	TREMFYA*	Targeted Immune Modulators	$61,675	0.6%	5	$12,335	N
33	ENBREL SURECLICK*	Targeted Immune Modulators	$58,526	0.6%	15	$3,902	Y
34	PROMACTA	Thrombocytopenia Drugs	$56,758	0.6%	9	$6,306	Y
35	Pertuzu, Trastuzu, 10 Mg	Physican Administered Drug	$55,510	0.6%	4	$13,877	
36	NORDITROPIN FLEXPRO*	Growth Hormones	$55,136	0.6%	23	$2,397	Y
37	Mifepristone, Oral, 200 Mg	Physican Administered Drug	$53,043	0.5%	591	$90	
38	PULMOZYME	Cystic Fibrosis	$52,529	0.5%	38	$1,382	Y
39	JYNARQUE	STC 79 - Diuretics	$50,478	0.5%	3	$16,826	
40	CREON	Pancreatic Enzymes	$50,461	0.5%	60	$841	Y
		Top 40 Aggregate:	**$4,480,622**		**8,753**	**$12,389**	
		All FFS Drugs Totals:	**$9,685,558**		**115,939**	**$647**	

*** Drug requires Prior Authorization**

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

Last updated: April 21, 2022

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Prior Authorization Criteria Update: Tetracyclines, Oral

Purpose of Update:

To clarify implementation of previously approved quantity limit (QL) policy. In May 2017, a quantity limit was enacted to allow two 14 day supplies within a 3 month time frame, as there was insufficient evidence to support use beyond 14 days for indications beyond acne and rosacea.[1] This QL was not changed when the class was reviewed more recently in March 2019.[2] At the time of approval, acne and rosacea were Oregon Health Plan (OHP) unfunded conditions, though forms of severe acne are now funded.[3]

The QL was implemented at point of sale and defaulted prescriptions beyond the limit to the standard "Preferred Drug List (PDL)- Non-Preferred Drugs in Select PDL Classes" to ensure prescribed medication was being used for a medically appropriate and OHP funded condition. As this QL applies to both preferred and non-preferred medications in this drug class, a class-specific QL document is proposed to improve clarity.

Recommendation:

- No change to current policy
- Incorporate specific criteria for oral tetracyclines

References:

1. Drug Use Research and Management. Oregon State University. Class Update: Tetracyclines. Available at: https://www.orpdl.org/durm/meetings/meetingdocs/2017_05_25/archives/2017_05_25_TetracyclinesClassUpdate.pdf. Accessed: April 28, 2022.
2. Drug Use Research and Management. Oregon State University. Class Update: Tetracyclines. Available at: https://www.orpdl.org/durm/meetings/meetingdocs/2019_03_21/archives/2019_03_21_Tetracyclines_ClassUpdateNDE.pdf. Accessed: April 28, 2022.
3. Oregon Health Authority. Prioritized List of Health Services version Jan 1, 2022. Available at: https://www.oregon.gov/oha/HPA/DSI-HERC/PrioritizedList/1-1-2022%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed: April 28, 2022.

Tetracyclines (Oral)-Quantity Limit

Goal(s):
- Restrict use of oral tetracyclines to OHP-funded diagnoses.
- 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:** Go to #6
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4	**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

Approval Criteria		
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. 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: Deny; not funded by the OHP. • If not funded and patient is 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

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

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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
Ciltacabtagene autoleucel	CARVYKTI
Lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
Nivolumab; Relatlimab-rmbw	OPDUALAG
Pacritinib	VONJO

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 4/28/2022)
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
gilteritinib	XOSPATA
glasdegib	DAURISMO

Generic Name	Brand Name
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
olaratumab	LARTRUVO

Generic Name	Brand Name
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
siltuximab	SYLVANT

Generic Name	Brand Name
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
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
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK

Generic Name	Brand Name
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA

Generic Name	Brand Name
ziv-aflibercept	ZALTRAP

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

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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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
Alpelisib	VIJOICE
Mitapivat	PYRUKYND

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)
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.
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.

Approval Criteria		
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
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	**Yes:** Approve for up to 6 months Document benefit	**No:** Pass to RPh. Deny; medical appropriateness

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

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

ProDUR Report for January through March 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	3	1	0	2	0.00%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,059	481	0	1,577	1.39%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	7,490	1,889	0	5,593	5.06%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	96,562	17,686	75	78,795	65.23%	**18.3%**
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	30,515	7,499	6	22,990	20.62%	**N/A**
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	778	127	0	650	0.53%	**N/A**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	2	2	0	0	0.00%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	747	207	0	540	0.50%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	468	177	1	289	0.32%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	19	14	0	5	0.01%	**73.7%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	9,380	2,523	0	6,850	6.34%	**N/A**
		Totals	**148,023**				**100.00%**	**0.0%**

ProDUR Report for January through March 2022

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,992	349	1,643	15,454	12.9%	10.6%
ER	Lorazepam	332	97	235	12,784	2.5%	1.8%
ER	Alprazolam	200	47	153	7,821	2.5%	1.9%
ER	Diazepam	128	33	95	4,462	2.9%	2.1%
ER	Buspar (Buspirone)	3,670	590	3,080	34,672	10.6%	8.9%
ER	Lamictal (Lamotrigine)	6,145	1,106	5,039	44,963	13.6%	11.2%
ER	Seroquel (Quetiapine)	4,814	1,005	3,808	32,669	14.7%	11.6%
ER	Zyprexa (Olanzapine)	2,760	624	2,136	20,158	13.7%	10.6%
ER	Risperdal (Risperidone)	2,025	367	1,658	14,117	14.3%	11.7%
ER	Abilify (Aripiprazole)	3,761	642	3,119	28,342	13.3%	11.0%
ER	Wellbutrin (Bupropion)	7,394	1,192	6,201	74,472	9.9%	8.3%
ER	Suboxone (Buprenorphine/Naloxone)	103	35	68	1,897	5.3%	3.5%
ER	Zoloft (Sertraline)	8,200	1,462	6,737	81,509	10.0%	8.2%
ER	Prozac (Fluoxetine)	5,745	940	4,805	56,928	10.0%	8.4%
ER	Lexapro (Escitalopram)	5,147	810	4,336	53,008	9.6%	8.1%
ER	Celexa (Citalopram)	2,239	338	1,901	26,400	8.4%	7.2%
ER	Trazodone	6,659	1,153	5,506	60,893	10.9%	9.0%
ER	Cymbalta (Duloxetine)	5,263	941	4,322	48,804	10.7%	8.8%
ER	Intuniv (Guanfacine)	1,792	230	1,562	12,885	13.9%	12.1%

ProDUR Report for January through March 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	January	4,326	82	252	805	7	2,898	124	0	158
ER	February	3,785	118	248	648	3	2,541	77	0	150
ER	March	4,344	139	236	855	9	2,837	113	0	155
	Total =	**12,455**	**339**	**736**	**2,308**	**19**	**8,276**	**314**	**0**	**463**
	Percentage of Total Overrides =		**2.7%**	**5.9%**	**18.5%**	**0.2%**	**66.4%**	**2.5%**	**0.0%**	**3.7%**

ProDUR Report for January through March 2022			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
Jan-22	DD	24	$2,096.18
Jan-22	ER	34	$14,372.53
Jan-22	HD	22	$2,062.85
Jan-22	ID	8	$2,139.92
Jan-22	LD	14	$637.03
Jan-22	MX	4	$523.30
Jan-22	TD	25	$3,879.29
		January Savings =	**$25,711.10**
Feb-22	DC	2	$238.40
Feb-22	DD	3	$686.67
Feb-22	ER	30	$7,887.25
Feb-22	ID	16	$3,577.96
Feb-22	TD	2	$1,666.23
		February Savings =	**$14,056.51**
Mar-22	DC	1	$94.99
Mar-22	DD	44	$3,648.77
Mar-22	ER	58	$17,755.39
Mar-22	HD	6	$713.88
Mar-22	ID	19	$2,073.31
Mar-22	LD	8	$458.64
Mar-22	LR	11	$1,187.58
Mar-22	MC	1	$502.91
Mar-22	TD	10	$1,610.24
		March Savings =	**$28,045.71**
		Total 1Q2022 Savings =	**$67,813.32**

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

Retro-DUR Intervention History by Quarter FFY 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		
		Unique Patients Identified		13		
		Total Faxes Successfully Sent		8		
		Prescriptions Changed to Recommended Within 6 Months of Intervention		4		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$5,443		
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	61	103	4	
		Unique Patients Identified	62	105	4	
		Total Faxes Successfully Sent	45	73	1	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	32	36		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$26,507	$13,467		
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	191	262	11	
		Unique Patients Identified	193	271	11	
		Total Faxes Successfully Sent	133	186	8	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	90	85		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$23,743	$13,888		

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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	1	
		Total Faxes Successfully Sent	9	17	1	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	4	5		
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	2		
		Prescriptions Unchanged after 3 Months of Fax Sent	19			
		Safety Monitoring Profiles Identified	1	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$2,121	$2,938		

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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
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	801	796		
		High risk patients identified	9	4		
		Prescribers successfully notified	9	2		
		Patients with change in antipsychotic drug in following 90 days	1			
		Patients with continued antipsychotic therapy in the following 90 days	7	2		
		Patients with discontinuation of antipsychotic therapy in the following 90 days	1			

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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
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	81	45	3	
		Total prescribers identified	80	45	3	
		Prescribers successfully notified	80	44		
		Patients with claims for the same antipsychotic within the next 90 days	35	21		
		Patients with claims for a different antipsychotic within the next 90 days	5	1		

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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		
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	2	55		
	Children in foster care under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	19	604		
	Children in foster care under age 6 on any psychotropic	RetroDUR_Profiles Reviewed		109		
	High Risk Patients - Bipolar	RetroDUR_Profiles Reviewed	13	18		
		RetroDUR_Letters Sent To Providers	9	9		
	High Risk Patients - Mental Health	RetroDUR_Profiles Reviewed	50	40		
		RetroDUR_Letters Sent To Providers	64	45		
	High Risk Patients - Opioids	RetroDUR_Profiles Reviewed	16	13	4	
		RetroDUR_Letters Sent To Providers	11	11	2	
	Lock-In	RetroDUR_Profiles Reviewed	20	4		
		RetroDUR_Letters Sent To Providers	4			
		Locked In	3	0		
	Polypharmacy	RetroDUR_Profiles Reviewed	1			

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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
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	90	85	11	
		Total prescribers identified	90	85	11	
		Prescribers successfully notified	90	85		
		Patients with discontinuation of therapy within next 90 days	25	27	11	
		Patients with new prescription for naloxone within next 90 days	3	2		
		Average number of sedative drugs dispensed within next 90 days	22	18	0	
		Average number of sedative prescribers writing prescriptions in next 90 days	22	18	0	
	Denied Claims due to Antipsychotic Dose Consolidation	Total patients identified	79	56	9	
		Patients with a paid claim for the drug (based on HSN) within 14 days	53	27		
		Patients without a paid claim within 14 days	26	18		
	ICS/LABA	ICS/LABA Denials	15	20	2	
		Disqualified	4	6		
		Faxes Sent	1	1		
		No Subsequent Pulmonary Claims	1	1		
	Oncology Denials	Total patients identified	1	2		
		Total prescribers identified	1	2		
		Prescribers successfully notified	1	2		
		Patients with claims for the same drug within the next 90 days	1	1		
		Patients with claims for any oncology agent within the next 90 days	1	1		

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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
	TCAs in Children	TCA Denials in Children	27	29	4	
		Total patients identified	6	13	1	
		Total prescribers identified	6	13	1	
		Prescribers successfully notified	3	11		
		Patients with claims for a TCA within the next 90 days		1		
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days	2			

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December 2021 Volume 11 Issue 9

A PEP Talk on PrEP-ing for HIV Prevention

Gary Karagodsky, Pharm.D. and Megan Herink, Pharm.D., Oregon State University Drug Use Research and Management Group

The human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS) if not managed with antiretroviral (ARV) therapy.[1] HIV is predominantly transmitted through sexual intercourse, sharing needles for injectable drugs, and other routes of bloodborne exposure.[1] In 2019, roughly 1.2 million people within the United States (U.S.) were living with a diagnosis of HIV, including 7,731people in Oregon.[2,3] Although the rate of new HIV infections in the US has been declining, there were approximately 36,801 new HIV diagnoses nationwide in 2019.[2] In the U.S. certain communities have been disproportionally affected by HIV, including men who have sex with men and transgender individuals. However, globally women have consistently accounted for approximately half of those who are living with HIV.[1,2] In addition to comprehensive harm reduction strategies, including treatment as prevention initiatives, preventive therapy should include preexposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) with ARV therapy when indicated (**Table 1**). This newsletter will review the pharmacological therapies and management considerations that comprise PEP/PrEP therapy for the prevention of HIV infection.

Table 1: Indications for PEP and PrEP[4,5,6,7]

Postexposure Prophylaxis	Preexposure prophylaxis
To be started as soon as possible and no more than 72 hours after possible exposure to HIV, via: ➢ Sex ➢ Shared needles or other items used to inject drugs ➢ Sexual assault ➢ Occupational exposure	People without HIV who: ➢ Injects non-prescribed drugs ➢ Has condomless sex ➢ Has sex with a partner living with HIV with a detectable or unknown HIV viral load, or who is not on ARV treatment, or whose ARV treatment status is not known ➢ Those with a HIV positive sexual partner ➢ Has had a recent STI ➢ Expresses interest PrEP

Abbreviations: ARV – antiretroviral therapy; HIV – human immunodeficiency virus ; IV – intravenous; STI – sexually transmitted infection

Screening and Testing for HIV

Screening for PEP treatment includes identification of possible HIV exposures, which can be categorized as occupational and non-occupational exposures. Types of exposures that warrant initiation of PEP include the following: 1) exposure to potentially infectious bodily fluids (e.g., blood, breast milk, genital secretions, or blood stained saliva), 2) exposure to mucous membranes (e.g., sexual exposure, splashes to eyes, nose or oral cavity), or 3) exposure to HIV via parenteral routes (e.g., shared needles or syringes for injection drug use or accidental needlesticks).[6] The initiation of PEP should be started as soon as possible and no more than 72 hours after exposure. The exposed individual should be offered PEP as soon as possible even if the HIV tests results are not yet available.[6] While all generations of HIV testing methods are acceptable, the utilization of a 4th generation HIV testing method allows for earlier detection of HIV infection.[6]

Screening for PrEP includes an assessment of potential exposures and risks of HIV acquisition. All adult and adolescent patients should be offered PrEP if they are interested or feel that they would benefit from PrEP. HIV screening should be discussed and completed. Patients with a negative HIV screening test should be considered for PrEP. Patients who have had a potential high risk exposure event and/or have had symptoms of acute retroviral syndrome in the previous 4 weeks should be considered for an HIV viral load RNA test as well before starting PrEP.[7] Patients should also be screened for other sexually transmitted infections (STIs), hepatitis, and pregnancy status. Patients with a positive HIV test at any time should be referred to an HIV specialist for starting a complete ARV treatment regimen as soon as possible.

Pharmacological Therapies

There are no randomized controlled trials evaluating ARV for PEP. Rather, the efficacy for PEP therapy has been established based upon extrapolated data from animal models, perinatal clinical trials, and observational studies.[6] Selection of an appropriate regimen is based on additional patient factors, such as age, renal function, and any known or suspected ARV resistance in the source person, if that information is available.Recommendations from the Center for Disease Control (CDC) specify that treatment for PEP should consist of a 3-drug antiretroviral regimen with a duration of 28 days (**Table 2**).[6]

Table 2. FDA Approved PEP Regimens[8,10,11]

Agents	Dosing	Dosing Considerations
Tenofovir disoproxil fumarate + emtricitabine (TRUVADA)	300mg/200 mg daily	➢ Avoid with CrCl < 60 ml/min ➢ Insufficient data to recommend tenofovir alafenamide-containing products (Descovy) for PEP
PLUS EITHER		
Raltegrevir (ISENTRESS)	400 mg twice daily	
OR		
Dolutegravir (TIVICAY)	50mg daily	➢ Avoid or separate from antacids and laxatives containing cations

Abbreviations: CrCl= creatinine clearance; INSTI= integrase strand transfer inhibitor

Randomized, placebo controlled trials have demonstrated that daily administration of PrEP reduces the incidence of HIV among men who have sex with men by 42% to 86%.[12] The efficacy of PrEP in heterosexual men and women and persons who inject drugs has also been demonstrated.[7] FDA approved agents for PrEP consist of 2-drug ARV regimens, that are available in combination products (**Table 3**). Selection of the appropriate agent is based on renal function, cost and HIV exposure risk (e.g. Tenofovir alafenamide + emtricitabine has not been studied in individuals who inject drugs or in cis-gender females). PrEP should be taken continuously as long as continued HIV prevention is warranted.[7] There is limited data on the safety of the developing fetus when PrEP is used in pregnant patients,however, data available from the Antiretoviral Pregnancy Registry on pregnancy outcomes provide no evidence of adverse effects among fetuses exposed to PrEP therapies.[7] With the increased risk of HIV acquisition with exposure being present during pregnancy, pregnant people who are at risk for HIV exposure or ask to be on PrEP should be started on PrEP.[7]

Table 3. FDA Approved PrEP Regimens[8,9]

Agents	Dosing	Dosing Considerations
Tenofovir disoproxil fumarate + emtricitabine (FTC/TDF; TRUVADA)	300mg/200 mg daily	➢ Avoid with CrCl < 60 ml/min ➢ Avoid if decreased bone mineral density ➢ Avoid with daily or high-dose NSAIDs
Tenofovir alafenamide + emtricitabine* (FTC/TAF; DESCOVY)	25mg/200 mg daily	➢ Avoid with CrCl < 30 ml/min ➢ Prefered if decreased bone mineral density

Abbreviations: CrCL = creatinine clearance
*= Approval does not include those at risk from IV drug use or sexual acquisition from receptive vaginal sex.

Medication adherence is necessary to ensure successful therapy with both PEP and PrEP. Clinical trials have shown a clear association between observed efficacy and adherence to therapy, with little to no efficacy seen in participants with the lowest adherence rates.[12,13] Thus, identifying potential adherence barriers, providing education regarding common medication side effects, and reviewing patient's current medications are critical components of treatment. Recently, cabotegravir,the first injectable treatment was FDA approved for PrEP.[14] It is a long acting injectable given every 2 months after an initial oral lead-in period. It was studied in men, transgender women and cisgender women at risk of acquiring HIV.[14]

PEP and PrEP regimens are both generally well tolerated. Side effects associated with both PEP and PrEP therapy are typically mild, but may include nausea, fatigue, malaise, diarrhea, headache, and rash.[6,7] Contrainidications to PEP and PrEP therapies can be found in **Table 4**. Concurrent medications should be screened to identify potential drug interactions that may affect the efficacy, safety, or monitoring requirements of PEP and PrEP treatment.

Table 4: Contraindications to PEP and PrEP Regimens[6,7,8,9,10,11]

Contraindications and Precautions
• Hypersensitivity to any single PEP or PrEP agent • Severe renal dysfunction (CrCl < 30ml/min) • Individuals with unknown (do not start PrEP) or positive HIV-1 status (Do not start PrEP or PEP) • Coadministration with dofetilide (dolutegravir only) • Certain medications (carbamazepine, phenobarbital, phenytoin, rifampin)

Follow Up and Monitoring

For patients requiring either PEP or PrEP, ensuring that the patient has an established healthcare provider is imperative to ensure proper follow up and increase the likeliness of successful and sustainable HIV prevention. After the initiation of PEP, providers should monitor the patient's renal function, liver function tests, and complete blood count to assess for any developing toxicities starting at 2 weeks.[6] Patients should undergo repeat testing for HIV at 4 weeks and 3 months after therapy initiation. Repeat testing for hepatitis C and sexually transmitted infections (STIs) should also occur.[6] For patients on PrEP, monitoring includes HIV and pregnancy (for those who can become pregnant) screening every 3 months, STI screening at least every 6 months (or every 3 months if indicated), and renal function.[7]

Any person who is at continued risk for HIV exposure should continue to take PrEP. Harm reduction and sexual health and safety topics may be reviewed and/or the person may be offered referral to additional services for assistance. Patients on PrEP should also be evaluated for adherence and drug interactions at each visit.

Policy Needs and Impacts

An individual's lack of awareness of risk for HIV transmission is a major barrier to appropriate prevention strategies.[15,16] Even with current government public health programs focused on increasing the awareness of risk and testing, those unaware of their HIV status account for 45% of new HIV transmissions.[17] The major barriers to awareness include: social stigma, cost of HIV testing, unawareness of risk factors and where to receive care for HIV.[16] There is a need for increased testing efforts and access to HIV treatment.

To enhance community education and access to resources, Oregon has empowered pharmacists to play a more active role in the screening and prevention of HIV. On June 23rd, 2021, the Oregon state legislature passed HB 2958, which

clarified that Oregon licensed pharmacists have the legal authority prescribe and dispense PEP or PrEP to patients after completion of a patient assessment.[18] This bill also requires insurers to reimburse pharmacists for consultation with patients, while also prohibiting the requirement of a prior authorization for PEP or PrEP therapies for the first 60 days of treatment. With Oregon pharmacists already having the legal authority to prescribe PEP and PrEP before the passing of this bill, HB 2958 provides additional incentives to pharmacists while also removing barriers to providing access to these HIV preventative therapies.

Resources

- University of Liverpool online HIV drug interaction checker
- Oregon Board of Pharmacy PrEP and PEP protocols
- HIV Alliance
- Cascade AIDS Project
- Oregon PrEP Provider List
- The Oregon AIDS Education & Training Center

Conclusion

HIV prevention is an important public health issue that impacts the Oregon community at large. With the multitude of preexisting barriers to HIV testing, prevention opportunities, and treatment, it is imperative that healthcare providers discuss PrEP with all adult and adolescent patients and identify those who may more specifically benefit from PrEP. Likewise, knowledge of available resources can help address additional health and social issues and minimize gaps in adequate HIV care and prevention. Knoweldge of appropriate screening and testing for HIV in combination with a foundational knowledge of the available pharmacological agents for HIV prevention are two of the three essential initiatives of the End HIV Oregon campaign to prevent new HIV transmissions.

Peer reviewed by: Devon Flynn, Pharm.D., HIV Clinical Pharmacist, Oregon Health and Science University

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December 2021 Volume 11 Issue 8

Anti-SARS-CoV-2 Therapeutics can Effectively Treat, Prevent COVID-19 Infection (*Evidence updated through 11/30/21*)

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

Introduction

Coronavirus disease 2019 (COVID-19) Treatment Guidelines recommend anti-SARS-CoV-2 monoclonal antibodies (mAb) for treatment of mild to moderate COVID-19 infection and for post-exposure prophylaxis (PEP) of COVID-19 infection.[1]

Individuals 12 years of age or older and weighing at least 40 kg who are at high risk of progression to severe COVID-19 are eligible for mAb treatment in outpatient settings. Some of the risk factors for severe COVID-19 infection are outlined in Table 1.[2]

Table 1. Some Risk Factors for Severe COVID-19 Illness.[2]

• Older age
• Obesity
Underlying comorbidities such as: • Cardiovascular disease • Hypertension • Chronic lung disease • Chronic kidney disease • Immunosuppressive conditions • Neurodevelopmental disorders
• People from racial or ethnic minority groups
• People with disabilities
• Pregnancy

The mAbs outlined in Table 2 are available for use by Emergency Use Authorization (EUA) for non-hospitalized individuals.[3-5]

Table 2. Monoclonal Antibodies with EUA for Outpatients.

	Indication	
	Treatment	PEP
Bamlanivimab and Etesevimab	✓	✓
Casirivimab and Imdevimab	✓	✓
Sotrovimab	✓	

Abbreviation: PEP = post-exposure prophylaxis

The EUAs allow for a one-time dose for treatment of COVID-19 infection. The casirivimab and imdevimab mAb combination and the bamlanivimab and etesevimab mAb combination also have EUAs for PEP for individuals who are not fully vaccinated or not expected to mount an adequate immune response to vaccination.[3-5]

Emergency use authorization requests have recently been submitted to the FDA for 3 new products: oral antiviral agents molnupiravir and Paxlovid™ (PF-07321332/ritonavir), and a long-acting mAb, a tixagevimab and cilgavimab.[6-9] A brief summary of these products will be provided at the end of the newsletter.

Monoclonal Antibodies Demonstrate Efficacy, Safety.

Authorization of mAbs for treatment of COVID-19 was based on analysis of phase 3 data from a randomized, double-blind, placebo-controlled trials (Table 3), which demonstrated safety and efficacy in patients at high risk for developing severe COVID-19 infection. *(Note: there is a potential risk of treatment failure from viral variants resistant to bamlanivimab and/or etesevimab. A list of states and territories in which bamlanivimab and etesevimab are not currently authorized based on current prevalence of specific variants is available online from the FDA.)*[3-5]

Table 3. Efficacy of mAbs for Treatment of COVID-19.[3-5]

Primary Endpoint *Day 29*	Casirivimab 600 mg and Imdevimab 600 mg (IV) (n=736)	Placebo (n=748)
COVID-19-related hospitalization or all-cause death	7 (1.0%) RRR 70% (95% CI NR, p=0.0024) NNT 46	24 (3.2%)

Primary Endpoint *Day 29*	Bamlanivimab 700 mg and etesevimab 1400 mg (IV) (n=511)	Placebo (n=258)
COVID-19-related hospitalization or all-cause death	4 (0.8%) RRR 87% (95% CI NR, p<0.0001) NNT 20	15 (5.8%)

Primary Endpoint *Day 29*	Sotrovimab 500 mg (IV) (n=528)	Placebo (n=529)
All-cause hospitalization or death	6 (1.1%) RRR 79% (95% CI, 50 to 91%) NNT 22	30 (5.7%)

Abbreviations: CI = confidence interval; IV = intravenous; NNT = number needed-to-treat; NR = not reported; RRR = relative risk reduction.

The casirivimab and imdevimab combination and bamlanivimab have also demonstrated efficacy in PEP trials.[3,4] Subcutaneous casirivimab 600 mg and imdevimab 600 mg reduced the odds of a positive COVID-19 test after exposure relative to placebo by 81% over 29 days (adjusted OR 0.17; p<0.001).[4] Bamlanivimab was studied without etesevimab for PEP which found that it reduced symptomatic COVID-19 infection relative to placebo over 57 days (adjusted OR 0.43; p<0.001) in exposed individuals.[3] The FDA concluded that it is reasonable to expect that bamlanivimab

and etesevimab together may also be safe and effective for PEP based on the totality of evidence.[3]

All 3 mAbs were well tolerated in clinical trials, with an incidence of infusion-related reactions similar to placebo at about 1%. Few cases of anaphylaxis were reported, and all resolved with treatment.[3-5]

The U.S. Department of Health and Human Services (HHS) currently distributes these treatments to the states and they are available at no charge to the patient. Weekly distribution amounts for each state are determined by HHS based on weekly reports of new COVID-19 cases, hospitalization rates, and current mAb utilization. The COVID-19 Community Vulnerability Index is also considered by the Oregon Health Authority.[10]

More information can be found on the OHA mAb webpage. The OHA can also be contacted with questions at: ORESF8.LogisticsChiefs@dhsoha.state.or.us

Pharmacists Prescribe, Administer REGEN-COV

On August 31, 2021, the Public Health and Pharmacy Formulary Advisory Committee (PHPFAC) for the Oregon Board of Pharmacy approved a protocol for pharmacist prescribing and subcutaneous administration of REGEN-COV. On September 13, the 9th amendment of the Public Readiness and Emergency Preparedness (PREP) Act was declared which also allows licensed pharmacists, qualified pharmacy technicians, and licensed or registered pharmacy interns to administer COVID-19 therapeutics subcutaneously, intramuscularly, or orally in accordance with FDA authorization.[11] The 9th amendment specifically outlines criteria in which these licensed pharmacy personnel may practice.[11] Such licensees are bound to practice within the scope of the PREP Act just as they would be if practicing under the PHPFAC statewide protocol.

New Therapeutic Options Expected Soon

On November 30, the FDA Antimicrobial Drugs Advisory Committee reviewed the EUA submission for molnupiravir oral capsules.[12] The FDA is soon expected to review EUA submissions for Paxlovid™ (PF-07321332/ritonavir) oral combination therapy, and AZD7442, a long-acting mAb combination of tixagevimab and cilgavimab.

Molnupiravir is an oral prodrug of the antiviral ribonucleoside analog N-hydroxycytidine which inhibits coronavirus replication. Evidence for efficacy comes from a 5-day course of molnupiravir studied in non-hospitalized, unvaccinated, non-pregnant, COVID-19-positive adults with 5 days or less of mild or moderate symptoms.[12-15] All participants had at least one risk factor for development of severe infection. Study results found molnupiravir decreases the risk of hospitalization (≥24 hours) or all-cause death through 28 days by 3% versus placebo in this population (6.8% vs. 9.7%, respectively; 95% CI, 0.1 to 5.9%; number needed-to-treat [NNT] = 35).[12-15] Only about 6% of trial participants were located in the United States.[12]

Interim analysis of a 5-day course of Paxlovid™ (PF-07321332/ritonavir), with the same primary endpoint and similar eligibility criteria as the molnupiravir trial, found the drug combination reduced hospitalizations or death through 28 days by 5.7% versus placebo (1.0% vs. 6.7%, respectively; p<0.0001; NNT = 18).[16] Efficacy increased if Paxlovid™ was initiated within 3 days of symptom onset.[16] No deaths were reported in patients who received Paxlovid™ as compared to 1.6% in patients who received placebo. About 45% of trial participants were located in the United States.[16]

Little information is available at this time to make conclusions about the potential real-world safety of these two oral antiviral products. When molnupiravir was reviewed, the Antimicrobial Drug Advisory Committee voiced concerns about potential teratogenicity, genotoxicity, and mutagenesis of molnupiravir, and the effectiveness of the drug in patients with diabetes, in patients with positive baseline antibodies against COVID-19, and in patients with new COVID-19 variants, such as Omicron (B.1.1.529).[12]

AZD7442 (tixagevimab and cilgavimab) is the first mAb cocktail to be studied intramuscularly for both pre-exposure prophylaxis (PrEP) and treatment of COVID-19. In the PrEP trial, more than 75% of participants had co-morbidities that put them at high risk for severe COVID-19 if they were to become infected, including people who are immunocompromised and may have a reduced immune response to vaccination.[17] Participants at the time of screening were unvaccinated adults and had a negative point-of-care SARS-CoV-2 serology test. A one-time injection of AZD7442 reduced the incidence of symptomatic COVID-19 by 83% relative to placebo over 6 months with no cases of hospitalization from COVID-19 or death.[17] In the placebo arm, there were 5 cases of severe COVID-19 and 2 COVID-19-related deaths at 6 months.[17] In an exploratory analysis of the treatment trial in mostly high-risk non-hospitalized adult participants with 3 days or less of mild or moderate symptoms of COVID-19, a one-time injection of AZD7442 reduced the incidence of hospitalization from COVID-19 or all-cause death by 88% relative to placebo through Day 29.[17]

Conclusion

These therapies under EUA provide more tools to potentially prevent the development of severe COVID-19 infection. Both REGEN-COV and AZD7442 provide convenient alternative routes of administration for mAb therapy that do not require intravenous line placement. The new oral antivirals may also provide convenient options for patients who present early with

symptoms from COVID-19 infection. Adequate and accessible supply of COVID-19 tests are critical to the success and utilization of these new therapies. More information on the safety of all of these therapies and their real-world effectiveness against evolving SARS-CoV-2 viral variants will determine their ultimate impact on this pandemic.

The FDA Adverse Event Reporting System (FAERS) Public Dashboard was launched for COVID-19 EUA products. The COVID-19 EUA FAERS Public Dashboard provides weekly updates of adverse event reports submitted to FAERS for drugs and therapeutic biological products used under EUA in COVID-19.[18] Providers using these therapies are encouraged to routinely review this dashboard and are required to submit adverse events potentially related to these therapeutic agents to MedWatch.[19]

Peer Reviewed By: Shimi Sharief, MD, MPH, Senior Health Advisor, Oregon Health Authority

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Drug Use Evaluation: Indications for Sublingual Buprenorphine

Research Question 1:

1. Since removal of the prior authorization (PA) criteria for medication assisted treatment (MAT), has there been a change in off-label prescribing and use for sublingual buprenorphine?

Conclusions:

- The number of patients prescribed sublingual buprenorphine over the 6-month study period increased by over 20% (from 364 patients to 472 patients after removal of the PA) indicating increased prescribing for sublingual buprenorphine. During this same timeframe the average monthly fee-for-service enrollment increased by about 5% from 2019 to 2020.
- Since removal of the PA for sublingual buprenorphine, the proportion of patients with a diagnosis of opioid use disorder (OUD) were similar before and after the PA removal (89% vs. 87%, respectively). Similar rates were observed for the subgroup of patients prescribed combination buprenorphine/naloxone.
- In a subgroup of patients with paid claims for sublingual buprenorphine monotherapy, the proportion of patients without a diagnosis of OUD increased after removal of the PA from 6.5% to 20.6%. However, this group still represents a small proportion of the overall population with claims for sublingual buprenorphine (4.4%).

Recommendations:

- No policy changes recommended.

Background

Numerous studies have demonstrated that use of MAT improved outcomes in patients with OUD. Recent guidelines updated in 2021 from the VA/DOD recommend use of combination buprenorphine/naloxone or methadone for treatment in patients with opioid use disorder (strong recommendation; high quality evidence).[1] Buprenorphine/naloxone is recommended in most situations because it discourages intravenous use and decreases risk of diversion.[1] However, any buprenorphine formulation has benefit over no treatment in patients with OUD, and there is insufficient evidence to recommend any specific buprenorphine formulation or route of administration over another based on available evidence for efficacy or safety.[1] These guidelines recommend that clinicians consider multiple factors in selecting the appropriate therapy including a patient's values and preferences, clinical history, and pharmacoeconomics.[1]

Currently available formulations of buprenorphine for treatment of OUD include subcutaneous injections, sublingual tablets, and sublingual films. Buprenorphine formulations which are indicated for treatment of severe pain include buccal film, transdermal patches, and intramuscular or intravenous injections. In FFS, various buprenorphine formulations are categorized by their FDA-approved indication. Therefore, transdermal patches and buccal films are

categorized as long-acting opioids and subject to clinical criteria for opioids. Subcutaneous injections and sublingual formulations are categorized as MAT for OUD and are available without PA. The focus of this policy evaluation is on sublingual formulations of buprenorphine and buprenorphine/naloxone.

In 2020, to reduce administrative barriers and improve access to MAT, Oregon legislation prohibited use of PA during the first 30 days of medication-assisted treatment for both opioid- and alcohol-related substance use disorders.[2] In accordance, the Fee-for-Service (FFS) policy was updated to remove PA for all MAT for treatment of OUD.[2] Since then, other Nationwide regulatory changes have been implemented in an effort to increase access to MAT for OUD. For example, in April 2021, the United States Department of Health and Human Services (HHS) and Substance Abuse and Mental Health Services Administration (SAMHSA) released updated practice guidelines which removed training requirements for providers treating up to 30 patients with buprenorphine for OUD.[3,4] Previously, providers had to complete this training before they were able to obtain a waiver to prescribe buprenorphine for OUD.[3] Training is still required for practitioners prescribing buprenorphine for more than 30 patients.[4]

While use of buprenorphine products for OUD is supported by high quality evidence, long-term use of opioids for pain is not without risk. Quantity limits of 24mg/day were maintained for sublingual buprenorphine to limit use of high doses for off-label conditions. While buprenorphine is a partial opioid agonist, it is associated with many of the same effects and risk factors as a full opioid agonist. Warnings and precautions for sublingual buprenorphine/naloxone and sublingual buprenorphine include withdrawal symptoms upon abrupt discontinuation, risk of hepatic injury, and risk of overdose in opioid naïve patients, and respiratory depression especially in conjunction with other respiratory depressants or in patients with underlying respiratory insufficiency.[5] Similar to other opioids, buprenorphine also has a warnings for addiction, abuse and misuse.[5] In January 2022, the FDA also released a safety warning regarding dental problems associated with use of sublingual and buccal formulations of buprenorphine.[6] Dental problems have included tooth decay, cavities, abscesses and infections, and loss of teeth. This warning was based on case reports from medical literature and data from the FDA Adverse Event Reporting System (FAERS) database which identified 305 cases of dental adverse events through December 31, 2018. In many cases, more than one tooth was involved (n=113) and dental problems were observed in individuals with and without a prior history of dental problems.[6] The most common treatment for these dental problems was removal of the affected tooth (n=71).[6] Labeling for these products was updated to recommend that providers screen patients for oral disease prior to initiation of therapy, refer patients for a baseline dental screening as soon as possible after initiation of therapy, recommend routine dental visits, and educate the patient regarding appropriate medication administration and oral health to minimize risk of these adverse events.[6]

The goal of this policy evaluation is to evaluate changes in access for MAT since removal of the PA criteria and to evaluate the proportion of patients who may be prescribed off-label use of MAT for non-OUD diagnoses such as chronic pain.

Methods:
Patients were identified for inclusion in the study based on paid FFS claims for sublingual buprenorphine (First Databank HICL sequence numbers [HSNs] 001762 or 024846; route: sublingual). The evaluation window for buprenorphine claims was from 1/1/2019 to 6/30/2019 for the control group and from 1/1/2020 to 6/30/2020 for the intervention group. Cohorts were assigned to the control or intervention groups based on the first paid FFS claim (the index event [IE]). For each patient, the baseline period was defined based as the 6 months prior to the IE (exclusive of the IE).

Inclusion Criteria:

1. At least one FFS paid claim for sublingual buprenorphine during the evaluation window for buprenorphine claims

Exclusion Criteria:

1. Patients not assigned to either the control or intervention groups

2. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline period
3. Patients with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods. Claims data for these patients may be incomplete. Patients were identified based on the following benefit packages:

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

4. Non-continuous Medicaid eligibility during the baseline period
5. Patients included in both the control and intervention groups.

Outcomes evaluated in this analysis included diagnosis of OUD defined based on ICD-10 codes on medical claims during the baseline period or on the index date.

Results:

Demographics of patients with paid claims for sublingual buprenorphine are shown in **Table 1.** The number of patients prescribed sublingual buprenorphine over the 6-month study period increased by over 20% (from 364 patients to 472 patients after removal of the PA). Total enrollment in fee-for-service has increased over time which may account for some changes in prescribing. In the study period before removal of the PA, the average monthly fee-for-service enrollment was 86,368 patients. This had increased to an average of 90,817 patients in the study period after removal of the PA (5.2% increase).

Almost 50% of patients were female and almost 60% were young adults (≤35 years of age). The largest racial groups identified in the study were patients identifying as White (36-38%) and patients identifying as American Indian/Alaskan Native (16-29%). There were a larger proportion of American Indian/Alaskan Native patients in 2020 (after PA removal) compared to 2019 (before removal of the PA).

The Elixhauser Comorbidity Index was used to estimate disease burden in the population. The index is a weighted measure based on relevant diagnoses submitted on medical claims during the baseline period. The presence or absence of diagnoses are identified in medical claims and categorized into 29 comorbidity variables. Each category is assigned a weighted score from -7 to +12. Lower scores indicate lower disease burden whereas higher scores are indicative of higher disease burden. The index is reported as 2 separate measures which can be used to predict risk of in-hospital mortality (the "M" index) and risk for 30-day readmission (the "R" index).[7] Indices were similar for both groups indicating similar disease burden in the population over time. The most common diagnoses contributing to the Elixhauser comorbidity index were drug abuse (88-89%), depression (19-20%), and alcohol abuse (15%).

The majority of patients with paid claims for sublingual buprenorphine had a diagnosis of OUD in the prior 6 months (**Table 2**) with similar rates before and after removal of the PA (89% vs. 87%). Most patients prescribed sublingual buprenorphine formulations had paid claims for the combination therapy with buprenorphine/naloxone. In this subgroup, the proportion of patients with a diagnosis of OUD was similar before and after removal of the PA. In the subgroup of patients with paid claims for sublingual buprenorphine monotherapy, the proportion of patients without a diagnosis of OUD increased after removal of the PA criteria (from 6.5% to 20.6%). However, these patients still represent a small proportion of the overall population (4.4%).

Table 1. Demographics for paid FFS pharmacy claims

	Before		After	
	364	%	472	%
Female	173	47.5%	230	48.7%
Age – mean (range)	35	(2-63)	35	(17-63)
<18	1	0.3%	2	0.4%
18-35	215	59.1%	273	57.8%
36-64	148	40.7%	197	41.7%
>=65	0	0.0%	0	0.0%
Race				
White	138	37.9%	170	36.0%
Unknown	160	44.0%	148	31.4%
American Indian/Alaskan Native (HNA)	60	16.5%	136	28.8%
Other	6	1.6%	18	3.8%
*Average Elixhauser Score "M"	-6.79		-6.88	
*Average Elixhauser Score "R"	20.58		20.63	

*Weighted index based on diagnoses on medical claims in the baseline period.

Table 2. Patients with OUD diagnoses (F11x) and buprenorphine claims

	Before		After	
All IE	364		472	
OUD diagnosis in baseline period	324	89.0%	411	87.1%
No OUD diagnosis in baseline period	40	11.0%	61	12.9%
Buprenorphine/naloxone IE	333		370	
OUD diagnosis in baseline period	295	88.6%	330	89.2%
No OUD diagnosis in baseline period	38	11.4%	40	10.8%
Buprenorphine IE	31		102	
OUD diagnosis in baseline period	29	93.5%	81	79.4%
No OUD diagnosis in baseline period	2	6.5%	21	20.6%

Limitations

- Diagnostic data is based on claims history which may be incomplete or not accurately reflect true patient diagnoses. Social stigma associated with OUD diagnoses (from patients or providers) may result in incomplete or missing diagnoses billed on medical claims. Diagnostic data was evaluated only over a 6-month period, and diagnoses for patients on stable maintenance therapy may be missed if they had infrequent provider visits.
- A significant proportion of patients identified with paid FFS claims for sublingual buprenorphine were ineligible for inclusion in study due to required inclusion criteria. More than half of patients identified with a sublingual buprenorphine claim (53%) were ineligible because they had potentially incomplete claims data due to other primary insurance or were not eligible for Medicaid for the required 6-month baseline period. This study assumes that included patients are still representative of the entire Medicaid population.
- The post-study period from January to June 2020 included a significant period of time when provider offices were closed due to the COVID-19 public health emergency. From March 19, 2020 to April 27, 2020 non-emergency healthcare offices were closed in Oregon to preserve supplies of personal protective equipment (PPE). After this date, healthcare offices could open depending on sufficient supply of PPE. Phased opening for businesses, schools and other organizations began in May 2020. It is unclear how this closure may impact data collected in this study. Diagnoses collected for patients in 2020 may be incomplete if they were unable to see a provider during this period leading to a potential decline in OUD diagnoses in the study period. Similarly, it is unclear how this may have impacted number of patients with paid claims for prescriptions. Patients unable to access MAT via in-person provider visits may have transitioned to dispensing via pharmacies leading to increased pharmacy utilization in the period after the PA removal.
- This analysis does not evaluate use of MAT when administered in a clinical setting. MAT may be billed using a variety of mechanisms (both pharmacy and medical), but only pharmacy claims were included in this analysis.
- Removal of the PA criteria for preferred MAT products allowed increased access to MAT in the FFS population. However, ongoing national and state-wide efforts may have also enhanced access to or referral for treatment of OUD and may account for the increasing utilization of MAT. For example, factors which may impact utilization of MAT include changes in opioid prescribing patters, increased awareness and diagnoses of OUD, efforts to increase the number of prescribing providers for buprenorphine, and availability of medical clinics for treatment of OUD

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Appendix 1: Key Inclusion Criteria

	Key question #1: Diagnoses
Population	Patients with continuous Medicaid eligibility in the 6 months prior to the index event (the first sublingual buprenorphine claim in the treatment period)
Intervention	Initiation of sublingual buprenorphine (index event; see associated HSNs in methods)
Comparator	Patients with sublingual buprenorphine claims from 1/1/2019-6/30/2019 vs patients with sublingual buprenorphine from 1/1/2020-6/30/2020 (before vs. after removal of PA criteria)
Outcomes	Proportion of patients with sublingual buprenorphine use and an opioid use disorder diagnosis
Setting	Fee-for-Service

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Drug Use Evaluation: Therapy Duration for Sublingual Buprenorphine

Research Question:

1. Since removal of the prior authorization (PA) criteria for medication-assisted treatment (MAT) for opioid use disorder (OUD) in Fee for Service (FFS), has there been a change in duration of treatment?

Conclusions:

- In FFS patients who were treatment-naïve to MAT for OUD, removal of the PA criteria had no impact on time to treatment discontinuation. Data are significantly limited by time patients remain in FFS and the proportion of patients who transition into coordinated care organizations (CCOs) after initiation of therapy. A larger population may be needed to discern statistical differences between groups.

Recommendations:

- No policy changes recommended.

Background

Despite current guidelines which recommend MAT as a first-line treatment, many patients do not continue long-term pharmacological therapy for OUD. Clinically relevant, long-term outcomes for patients with OUD include prevention of relapse, overdose, and death. Untreated OUD may also be associated with increased risk of sexually transmitted infections, decreased functional status, and criminal involvement.[1] However, because these outcomes are often difficult to evaluate in randomized controlled trials or claims-based studies, duration of therapy is often used as a surrogate marker of treatment success. Studies evaluating impact of MAT on treatment retention in adolescents have demonstrated that pharmacologic treatment of OUD may lead to a more than 4-times greater likelihood of abstinence with extended courses (2 to 3 months) of buprenorphine compared to short courses (14 to 28 days; low strength of evidence).[1] Similarly, retention in treatment has been associated with decreased mortality.[2] There is no recommended maximum time limit for maintenance therapy, and long-term treatment (in some cases lifelong therapy) is recommended for many patients due to high rates of relapse and increased risk of overdose after treatment discontinuation. However, estimates of treatment retention at 3 months vary widely (ranging from 19 to 94%), and remain low in many populations.[2] In a previous analysis of the Oregon FFS Medicaid population in 2017, it was estimated that only 44% of patients had prescriptions for continuous therapy with MAT for more than 120 days.[3] Because of limitations in claims data, it is unclear how directly this estimate correlates with actual patient adherence.

Many factors may contribute to lack of long-term treatment. Factors could include administrative barriers to access, coverage policies, stigma associated with MAT, costs and logistical issues with obtaining and maintaining treatment (e.g., availability of providers and pharmacies to prescribe and dispense therapy), untreated or undertreated comorbid conditions, fragmented systems of care, or involuntary referrals for treatment (e.g., drug court settings).[2] Several observational studies have evaluated risk factors for treatment discontinuation specifically for Medicaid patients.[4,5] In Medicaid patients with an OUD diagnosis and claims for MAT from 2013 to 2015 (n=17,329), risk factors associated with discontinuation of MAT within the first 6 months of treatment included lower

initial buprenorphine dose, younger age, non-white race, capitated insurance, comorbid substance use disorder, comorbid hepatitis C, opioid overdose history, or any inpatient care.[5]

Beginning 1/1/2020, Oregon legislation was enacted which prohibited use of PA during the first 30 days of MAT for both opioid- and alcohol-related substance use disorders. The primary goal of this legislation was to remove any coverage policies which may be creating administrative barriers for patients initiating care. In accordance, the FFS policy was updated to remove PA for all products to treat OUD (even beyond 30 days). Quantity limits of buprenorphine 24 mg per day were maintained to limit use of high doses for off-label conditions.

The goal of this policy evaluation is to evaluate whether removal of PA impacted duration of therapy for medication assisted treatment for OUD.

Methods:
Patients were identified for inclusion in the study based on paid FFS claims for sublingual buprenorphine (identified using First Databank HICL sequence numbers [HSNs] 001762 or 024846; route: sublingual). The evaluation window for buprenorphine claims was from 1/1/2019 to 6/30/2019 for the control group and from 1/1/2020 to 6/30/2020 for the intervention group. Cohorts were assigned to the control or intervention groups based on the first paid FFS claim (the index event [IE]). For each patient, the baseline period was defined based on the 30 days prior to the IE (exclusive of the IE).

Inclusion Criteria:

1. At least one FFS paid claim for sublingual buprenorphine during the evaluation window for buprenorphine claims

Exclusion Criteria:

1. Patients not assigned to either the control or intervention groups
2. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow up periods
3. Patients with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the at any time during the baseline period. Patients were identified based on the following benefit packages:

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

4. Non-continuous Medicaid eligibility during the baseline period
5. Patients with a prior history of MAT use defined as patients meeting any of the following criteria:
    - Patients with claims for MAT in (based on all FFS or CCO medical or pharmacy paid claims) in the baseline period. See **Appendix 1**, **Table A1** and **Table A2** for codes associated with MAT for opioid use disorder; OR
    - Patients with IE submitted with at least 1 refill; OR
    - Patients without any billed medical claims between their Medicaid enrollment date and the IE.
6. Patients included in both the control and intervention groups.

Outcomes evaluated in this analysis included duration of buprenorphine therapy. Because individuals were eligible for varying durations after the IE, a survival analysis curve was used to estimate duration of therapy. Kaplan-Meier curves were performed using SAS® Analytics Software.

- The primary outcome was time to treatment discontinuation defined as the number of days from the IE to the first gap of at least 14 continuous days between the end of coverage of one pharmacy claim and the beginning of coverage of the next pharmacy claim (treatment discontinuation). MAT for OUD may be billed using a variety of mechanisms (both pharmacy and medical), but only pharmacy claims were used to estimate covered days over the treatment period as days' supply is not available on medical claims. Duration of buprenorphine treatment was defined using pharmacy claims, and days covered by a claim were calculated by adding the days' supply submitted on the claim to the date of service. This outcome was evaluated in the 6 months following the IE.
- Patients were censored from the analysis if any of the following circumstances occurred before treatment discontinuation. Time to censoring was calculated using the same method described above by adding the days' supply submitted on the most recent paid claim to the date of service.
    - Enrollment in a CCO (CCOA or CCOB with coverage for physical health drugs)
    - Lost Medicaid eligibility
    - Enrollment in Medicare
    - Coverage by other primary insurance

Results:

Demographics of patients with paid claims for sublingual buprenorphine are shown in **Table 1.** The majority of patients (60-63%) were young adults and 44-47% of patients identified as female. The largest racial groups identified in the study were patients identifying as White (34-35%) and patients identifying as American Indian/Alaskan Native (22-31%). There were a larger proportion of American Indian/Alaskan Native patients in 2020 (after PA removal) compared to 2019 (before removal of the PA).

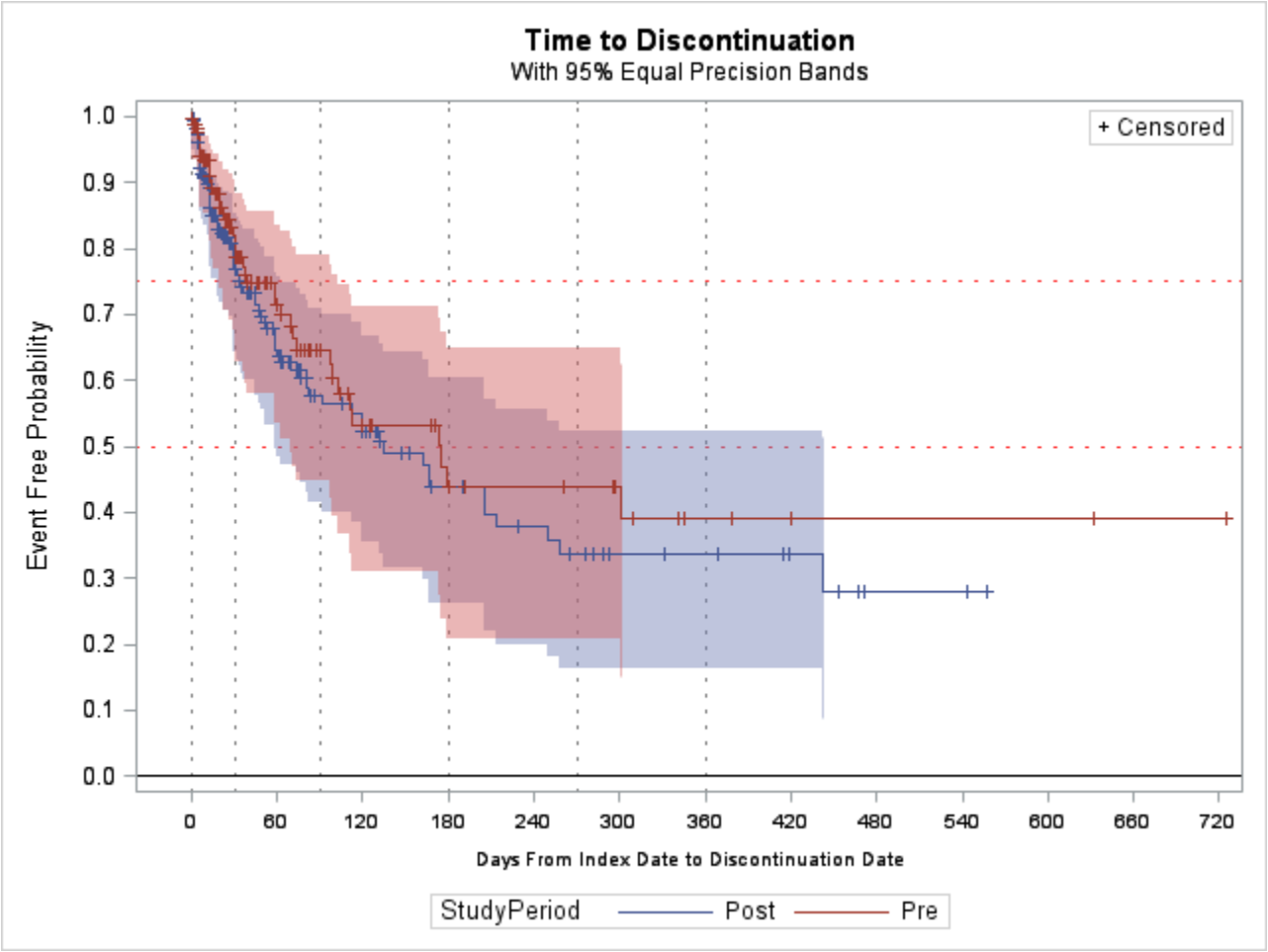
The Elixhauser Comorbidity Index, used to estimate disease burden in the population, was similar for both groups. The index is a weighted measure based on relevant diagnoses submitted on medical claims during the baseline period. The presence or absence of diagnoses are identified in medical claims and categorized into 29 comorbidity variables. Each category is assigned a weighted score from -7 to +12. Lower scores indicate lower disease burden whereas higher scores are indicative of higher disease burden. The index is reported as 2 separate measures which can predict risk of in-hospital mortality (the "M" index) and risk for 30-day readmission (the "R" index).[6] Given the short baseline period for this dataset (30 days prior to the IE), information on diagnoses may be incomplete. The most common diagnoses contributing to the Elixhauser Comorbidity Index included drug abuse (87-88%), alcohol abuse 11-12%), and depression (7-10%).

Table 1. Demographics for paid FFS pharmacy claims

	Before		After	
	297	%	395	%
Female	139	46.8%	173	43.8%
Age – mean (range)	34	(2-62)	35	(18-63)
<18	1	0.3%	0	0.0%
18-35	187	63.0%	237	60.0%
36-64	109	36.7%	158	40.0%
>=65	0	0.0%	0	0.0%
Race				
White	100	33.7%	138	34.9%
Unknown	123	41.4%	118	29.9%
American Indian/Alaskan Native (HNA)	65	21.9%	123	31.1%
Other	9	3.0%	16	4.1%
Average Elixhauser Score "M"	-6.91		-6.83	
Average Elixhauser Score "R"	17.45		17.31	

*Weighted index based on diagnoses on medical claims in the baseline period.
"M" score - in-hospital mortality index
"R" score - 30-day re-admission index

Figure 1. Kaplan-Meier Curve for Time to Treatment Discontinuation. Shading represents 95% confidence intervals.



Overall, there was no difference in time to treatment discontinuation before and after removal of PA criteria for MAT. The median time to treatment discontinuation was 175 days before removal of the PA criteria and 135 days after removal of the PA criteria. The analysis was significantly limited by the number of patients censored from the analysis prior to experiencing a treatment outcome. The primary reason for censoring was enrollment in a CCO (40-44%). Another 10% of patients lost Medicaid eligibility prior to treatment discontinuation.

Table 2. Reasons for censoring before buprenorphine treatment discontinuation

	Before		After	
	297	%	**395**	%
Enrollment in a CCO (CCOA or CCOB)	131	44.1%	157	39.7%
Lost Medicaid eligibility	31	10.4%	36	9.1%
Enrollment in Medicare	0	0.0%	0	0.0%
Coverage by other primary insurance	0	0.0%	0	0.0%

Limitations:

- Because many patients prescribed sublingual buprenorphine were new to Medicaid, the baseline period for assessment of diagnoses was limited to 30 days. However, a short baseline period significantly limits the number of medical claims that can be used to identify diagnoses and data used to estimate the Elixhauser Comorbidity Index is likely incomplete. Similarly diagnostic data based on claims may be inaccurate or not reflective of a patient's true diagnoses, especially for conditions associated with significant social stigma such as OUD.
- Medicaid includes a significant proportion of patients who are only transiently enrolled in FFS. Often patients are quickly enrolled into a CCO upon eligibility for Medicaid and remain in FFS for only a few months. In order to accurately capture data from this population in the analysis, a baseline period of only 30 days was required. However, this limitation led to several assumptions when identifying patients who may be treatment-naïve. Patients were assumed to be treatment-experienced if they met the following criteria: 1) had prior claims for MAT paid by Medicaid; 2) the pharmacy indicated that the first paid claim was a refill; or 3) the member did not have any paid medical claims between their enrollment date and the first paid claim for sublingual buprenorphine (with the assumption that members new to Medicaid but already on MAT would not have a recent provider visit). However, there are limitations to this definition, and it is possible that members who were actually treatment experienced may have been included. For example, patients who are new to Medicaid, but have frequent provider visits could have been included as a treatment-naïve patient when they may have been on MAT for some time.
- A significant proportion of patients were excluded because they had potentially incomplete claims data due to other primary insurance, were treatment experienced, or were not eligible for Medicaid for the required 30-day baseline period. Table 3 describes how individual exclusion criteria influenced number of patients eligible for inclusion in the study. After all exclusion criteria, about 30% of all patients with claims for sublingual buprenorphine were included in the study. This study assumes that included patients would still be representative of most treatment-naïve patients prescribed MAT in Medicaid.

Table 3. Population of included patients

	Before		After	
Number of included patients	#	%	#	%
With paid buprenorphine claim from 1/1/2019-6/30/2019 (pre) or from 1/1/2020-6/30/2020 (post)	**968**		**1,214**	
And after exclusion of limited benefit packages, Medicare, TPL in baseline period	843	87.1%	1,042	85.8%
And after continuous Medicaid enrollment requirement in the 30 days before the IE	730	75.4%	925	76.2%
And after treatment naïve restriction	323	33.4%	420	34.6%
And after removal of duplicate patients in control/experimental periods	299	30.9%	396	32.6%
And after removal of patients enrolled in a CCO-A at time of IE	297	30.7%	395	32.5%

- The COVID-19 public health emergency is also an external confounding factor which is not controlled for in this study. The post-study period from January to June 2020 included a significant period of time when provider offices were closed due to the COVID-19 public health emergency. From March 19, 2020 to April 27, 2020 non-emergency healthcare offices were closed in Oregon to preserve supplies of personal protective equipment (PPE). After this date, healthcare offices could open depending on sufficient supply of PPE. Phased opening for businesses, schools and other organizations began in May 2020. It is unclear how much impact these closures may have had on duration of therapy for patients. For example, patients may have been reluctant to visit their pharmacy to fill medications during closures and may have had difficulty obtaining refills if provider offices were closed.
- This analysis does not evaluate use of MAT when administered in a clinical setting. MAT may be billed using a variety of mechanisms (both pharmacy and medical), but only pharmacy claims were included in this analysis.
- This analysis was not limited to patients with a diagnosis of OUD. Patients may be prescribed sublingual buprenorphine for other indications and uses.
- There are also several limitations associated with use of a survival analysis to measure outcomes:
    - One assumption of a survival analysis is that the probability of treatment discontinuation is the same for subjects remaining in the analysis as those that are censored from the analysis. Because of this assumption, time to treatment discontinuation after the first censored patient is just an estimate. As more patients are censored, the reliability of this estimate decreases. Just under 50% of patients were censored from the analysis prior to treatment discontinuation (primarily because they were enrolled in a CCO) which is a significant limitation of this analysis.
    - Another assumption of survival analyses is that the probability of treatment discontinuation is the same for subjects starting treatment early in the study period compared to later in the study period. However, ongoing national and state-wide efforts have increased awareness and access to therapies for OUD over time, and it is unclear how this may impact duration of therapy for our population. For example, efforts to increase the number of prescribing providers for buprenorphine, availability of medical clinics for treatment of OUD, and enhanced coverage of supportive therapies may increase retention in treatment over time.
    - A third assumption of a survival analysis is that treatment discontinuation occurs at a specified time. For example, if a patient fills a 30-day prescription for buprenorphine without subsequent treatment, treatment discontinuation would be defined as the date 30 days after the prescription was filled, when in reality, treatment discontinuation could have occurred at any time in the prior 30 days.

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Appendix 1: Drug Coding

Table A1. Drug codes for MAT pharmacy claims

PDL Class	GSN	Form	Generic	PDL	Route
Substance Use Disorders, Opioid & Alcohol	060935	SUS ER REC	naltrexone microspheres	Y	IM
Substance Use Disorders, Opioid & Alcohol	029312	TAB SUBL	buprenorphine HCl	V	SL
Substance Use Disorders, Opioid & Alcohol	029313	TAB SUBL	buprenorphine HCl	V	SL
Substance Use Disorders, Opioid & Alcohol	077999	SOLER SYR	buprenorphine	Y	SQ
Substance Use Disorders, Opioid & Alcohol	078000	SOLER SYR	buprenorphine	Y	SQ
Substance Use Disorders, Opioid & Alcohol	051640	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	051641	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	066635	FILM	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	066636	FILM	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	070259	FILM	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	070262	FILM	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	071189	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	071190	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	073424	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	073425	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	074685	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL
Substance Use Disorders, Opioid & Alcohol	076981	TAB SUBL	buprenorphine HCl/naloxone HCl	Y	SL

Table A2. Drug codes for MAT medical claims

Code	Description
J3490, J3590,	Generic drug codes; Include only if associated with any of the pharmacy drug codes for MAT (see Table A1) or with methadone (GSNs 004237 004238; 004239; 004240; 004242; 023767)
H0033,	Oral Med Adm Direct Observe
T1502,	Medication Admin Visit
96372	Ther/Proph/Diag Inj Sc/Im; Include only if associated with any of the pharmacy drug codes for MAT (see Table A1) or with methadone (GSNs 004237 004238; 004239; 004240; 004242; 023767)
G2067	Medication Assisted Treatment, Methadone; Weekly Bundle Including Dispensing And/Or Administration,
G2068	Medication Assisted Treatment, Buprenorphine (Oral); Weekly Bundle Including Dispensing And/Or Admin
G2069	Medication Assisted Treatment, Buprenorphine (Injectable); Weekly Bundle Including Dispensing And/Or
G2070	Medication Assisted Treatment, Buprenorphine (Implant Insertion); Weekly Bundle Including Dispensing
G2071	Medication Assisted Treatment, Buprenorphine (Implant Removal); Weekly Bundle Including Dispensing A
G2072	Medication Assisted Treatment, Buprenorphine (Implant Insertion And Removal); Weekly Bundle Includin
G2073	Medication Assisted Treatment, Naltrexone; Weekly Bundle Including Dispensing And/Or Administration,
G2075	Medication Assisted Treatment, Medication Not Otherwise Specified; Weekly Bundle Including Dispensin
G2078	Take-Home Supply Of Methadone; Up To 7 Additional Day Supply (Provision Of The Services By A Medicar

G2079	Take-Home Supply Of Buprenorphine (Oral); Up To 7 Additional Day Supply (Provision Of The Services B
G2213	Initiation Of Medication For The Treatment Of Opioid Use Disorder In The Emergency Department Settin
G6053	methadone
H0020	Alcohol And/Or Drug Services; Methadone Administration And/Or Service (Provision Of The Drug By A Li
J0570	Buprenorphine Implant, 74.2 Mg
J0571	Buprenorphine, Oral, 1 Mg
J0572	Buprenorphine/Naloxone, Oral, Less Than Or Equal To 3 Mg Buprenorphine
J0573	Buprenorphine/Naloxone, Oral, Greater Than 3 Mg, But Less Than Or Equal To 6 Mg Buprenorphine
J0574	Buprenorphine/Naloxone, Oral, Greater Than 6 Mg, But Less Than Or Equal To 10 Mg Buprenorphine
J0575	Buprenorphine/Naloxone, Oral, Greater Than 10 Mg Buprenorphine
J0592	Injection, Buprenorphine Hydrochloride, 0.1 Mg
J1230	Injection, Methadone Hcl, Up To 10 Mg
J2310	Injection, Naloxone Hydrochloride, Per 1 Mg
J2315	Injection, Naltrexone, Depot Form, 1 Mg
Q9991	Injection, Buprenorphine Extended-Release (Sublocade), Less Than Or Equal To 100 Mg
Q9992	Injection, Buprenorphine Extended-Release (Sublocade), Greater Than 100 Mg
S0109	Methadone, Oral, 5 Mg

Table A3. Key Inclusion Criteria

	Key question #2: Duration
Population	new start patients with continuous Medicaid eligibility at least 30 days prior to the IE
Intervention	Initiation of buprenorphine SL (index event)
Comparator	Patients initiating buprenorphine SL from 1/1/2019-6/30/2019 vs Patients initiating buprenorphine SL from 1/1/2020-6/30/2020 (before vs. after removal of PA criteria)
Outcomes	Duration of buprenorphine therapy
Setting	FFS

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Drug Use Evaluation: Polypharmacy Associated with Sublingual Buprenorphine

Research Question 3:

1. Since removal of the prior authorization (PA) criteria for medication assisted treatment (MAT) of opioid use disorder (OUD), has there been a change in polypharmacy associated with buprenorphine and other controlled substances?

Conclusions:

- In patients prescribed sublingual buprenorphine, polypharmacy associated with controlled substance use decreased after removal of the PA criteria for MAT (from 51.4% to 42.5%).
- Few patients had claims for 3 or more controlled substances which overlapped with buprenorphine therapy during the study period (n=10; 7.8%).
- The most commonly prescribed concomitant sedating drugs with an overlap of at least 3 days included antiepileptic drugs (such as gabapentin; 20%), first-generation antihistamines (such as hydroxyzine; 15%), muscle relaxants (11%), and second-generation antipsychotics (10%).

Recommendations:

- No policy changes recommended.

Background

Based on accumulating evidence describing overdose risks associated with opioid use, there has been an increased number of notifications from regulatory agencies regarding safe opioid prescribing. Since 2014, the U.S. Food and Drug Administration (FDA) has recommended increased safety labeling changes for all opioids. While buprenorphine acts as a partial opioid agonist, it is associated with many of the same effects and risk factors as a full opioid agonist. Like other opioids, buprenorphine can be associated with respiratory depression, particularly when it is used in conjunction with other respiratory depressants. Buprenorphine is also associated with potential for addiction, abuse and misuse, and is currently classified as a Drug Enforcement Agency (DEA) schedule 3 controlled substance. In 2018, the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act required state Medicaid programs to enact policies to monitor prescribing of opioids and concurrent benzodiazepines or antipsychotics. While this requirement did not specifically apply to MAT for OUD, there is no high-quality evidence which demonstrates a lower risk of overdose or respiratory depression with buprenorphine compared to other opioids.[1] At least one small, short-term trial has described a plateau effect for respiratory depression with use of intravenous (IV) buprenorphine in a controlled clinical setting,[2] and much of the data documenting overdose risk is based on full opioid agonists rather than partial agonists.[3,4] However, data from well-designed clinical trials or large observational studies is lacking, and it is unclear if there is any difference in overdose risk when comparing buprenorphine to a full opioid agonist especially if combined with other central nervous system (CNS) depressants.[1]

In 2017, a safety communication from the FDA addressed use of MAT in combination with CNS depressants.[5] The FDA noted that MAT should not be withheld from patients taking other CNS depressants as the risks of untreated OUD likely outweigh potential harms associated with concurrent CNS depressant in most

patients.[5] However, they did note that concomitant use can be associated with increased risk of serious adverse effects and careful medication management may be warranted. Management strategies may include patient education regarding risks of concomitant use, management or monitoring of illicit drug use, tapering or discontinuation of the CNS depressant if possible, consideration of other treatment options for comorbid conditions, and coordination of care with other prescribers.[5]

In the Fee-for-Service (FFS) Oregon Health Plan, evaluation of concomitant prescribing of opioids and sedatives is currently performed via prospective drug utilization review (DUR) edits that notify the dispensing pharmacy of any overlapping therapy. The pharmacist can review these edits and choose to dispense the opioid or sedative if clinically appropriate. An override by the dispensing pharmacist is not currently required. Because use of polypharmacy with multiple controlled substances or sedating prescriptions may increase risk of overdose or be an early sign of potential buprenorphine misuse, the goal of this policy evaluation is to evaluate changes in polypharmacy associated with sublingual buprenorphine use since removal of the PA criteria for MAT in 2020.

Methods:

Patients were identified for inclusion in the study based on paid FFS claims for sublingual buprenorphine or buprenorphine-naloxone (identified using First Databank HICL sequence numbers [HSNs] 001762 or 024846; route: sublingual). The evaluation window for buprenorphine claims was from 10/1/2019 to 10/31/2019 for the control group and from 10/1/2020 to 10/31/2020 for the intervention group. Cohorts were assigned to the control or intervention groups based on the first paid FFS claim (the index event [IE]).

For each patient, the baseline and follow-up periods were based on the IE.

- The baseline period was defined as the 35 days prior to the IE (exclusive of the IE).
- The follow up period was defined as the 35 days following the IE (inclusive of the IE).

Inclusion Criteria:

1. At least one FFS paid claim for sublingual buprenorphine during the evaluation window for buprenorphine claims

Exclusion Criteria:

1. Patients not assigned to either the control or intervention groups
2. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow up periods
3. Patients with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods as data for these patients may be incomplete. Patients were identified based on the following benefit packages:

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

4. Non-continuous Medicaid eligibility during the baseline period
5. Non-continuous FFS eligibility during the follow-up period
6. Patients included in both the control or intervention groups

Outcomes evaluated in this analysis included the proportion of patients with polypharmacy associated with controlled substance use and types of therapy concomitantly prescribed.

- Claims for concomitant drug therapy were evaluated during the baseline and follow-up periods and included both FFS and coordinated care organization (CCO) claims. Patients were categorized as having concomitant drug therapy if the medication overlapped with buprenorphine treatment by at least 3 consecutive days. Days covered by a claim were calculated by adding the days' supply submitted on the claim to the date of service.

Results:

Demographics of patients with paid claims for sublingual buprenorphine are shown in **Table 1.** About 50% of patients were female and 60% were young adults (≤35 years of age). The largest racial groups identified in the study were patients identifying as American Indian/Alaskan Native (47-64%) and White (13-21%). There were a larger proportion of American Indian/Alaskan Native patients in 2020 (after PA removal) compared to 2019 (before removal of the PA).

The Elixhauser Comorbidity Index, used to estimate disease burden in the population, was comparable in both the before and after groups indicating similar disease burden in the population over time. The index is a weighted measure based on relevant diagnoses submitted on medical claims during the baseline period. The presence or absence of diagnoses are identified in medical claims and categorized into 29 comorbidity variables. Each category is assigned a weighted score from -7 to +12. Lower scores indicate lower disease burden whereas higher scores are indicative of higher disease burden. The index is reported as 2 separate measures which can predict risk of in-hospital mortality (the "M" index) and risk for 30-day readmission (the "R" index).[6]

Table 2 describes patients with paid claims for buprenorphine and overlapping therapy. In patients prescribed sublingual buprenorphine, polypharmacy associated with controlled substance use decreased after removal of the PA criteria for MAT (from 51.4% to 42.5%). The most common overlapping therapy included antiepileptic drugs (such as gabapentin or pregabalin; 20%), first-generation antihistamines (such as hydroxyzine; 15%), muscle relaxants (11%), and second-generation antipsychotics (10%). After removal of the PA, fewer patients had overlapping sedating drugs and buprenorphine compared to the control period. Similarly, the number of patients with overlapping use of controlled substances decreased from the before period to the after period. Forty-eight percent of patients in the before period had claims for only buprenorphine compared to 57% in the period after removal of the PA for buprenorphine. Very few patients prescribed buprenorphine had claims for 3 or more additional controlled substances (n=10; 7.9%).

Table 1. Demographics for paid FFS pharmacy claims

	Before		After	
	105	%	127	%
Female	52	49.5%	67	52.8%
Age – mean (range)	35	(20-63)	36	(19-63)
<18	0	0.0%	0	0.0%
18-35	68	64.8%	72	56.7%
36-64	37	35.2%	55	43.3%
>=65	0	0.0%	0	0.0%
Race				

White	22	21.0%	16	12.6%
Unknown	29	27.6%	29	22.8%
American Indian/Alaskan Native (HNA)	50	47.6%	82	64.6%
Other	4	3.8%	0	0.0%
Average Elixhauser Score "M"	-6.61		-7.82	
Average Elixhauser Score "R"	17.65		17.74	

*Weighted index based on diagnoses on medical claims in the baseline period.

Table 2. Patients with concomitant claims with at least 3 days overlap with sublingual buprenorphine

	Before		**After**	
Drug claims (by PDL class)	**Patient Count**		**Patient Count**	
SL Buprenorphine (denominator)	105	%	127	%
Benzodiazepines	3	2.9%	4	3.1%
Opioid (long-acting or short-acting)	2	1.9%	2	1.6%
Sedatives	1	1.0%	1	0.8%
Muscle relaxant, oral	8	7.6%	14	11.0%
Antihistamine, first generation	16	15.2%	19	15.0%
ADHD drugs (DEA schedule 2 only)	3	2.9%	10	7.9%
Other stimulants	0	0%	0	0%
Cough and cold	0	0%	2	1.6%
Antiepileptics (non-injectable)	27	25.7%	25	19.7%
Antipsychotics, 2nd-generation	17	16.2%	13	10.2%
Number of controlled substances (by HSN)				
0	51	48.6%	73	57.5%
1	34	32.4%	24	18.9%
2	15	14.3%	20	15.7%
3	4	3.8%	6	4.7%
4	1	1.0%	1	0.8%
5	0	0%	2	1.6%
6	0	0%	0	0%
7	0	0%	1	0.8%

Limitations:

- This study evaluates a short “snapshot” in time for patients with prescriptions for buprenorphine and data were based on claims history which may not accurately reflect true medication use. Ongoing therapy or polypharmacy for long periods was not assessed. Polypharmacy was defined as at least a 3

day overlap with buprenorphine for sedating or controlled substance drugs. However, a short overlap of 3 days could be explained by switches in therapy rather than ongoing concomitant treatment. In patients with multiple prescriptions for controlled substances, therapy could represent subsequent prescriptions for different medications rather than overlapping treatment for all drugs at the same time.

- Many controlled substances or sedating medications have their own utilization controls. For example, use of benzodiazepines or sedatives for longer than 30 days and use of opioids for longer than 7 days requires a PA. However, in circumstances where Medicaid has utilization controls, patients may elect to pay cash rather than navigate the PA process. This evaluation only included claims paid by Medicaid, and any potential cash claims would not be included.
- A significant proportion of patients were excluded because they had potentially incomplete claims data due to other primary insurance or were not eligible for Medicaid for the required 35-day baseline or follow-up periods. **Table 3** describes how individual exclusion criteria influenced the number of patients eligible for inclusion in the study. After all exclusion criteria, approximately 30% of all patients with claims for sublingual buprenorphine were included in the study. This study assumes that included patients would still be representative of most patients prescribed MAT in Medicaid.

Table 3. Population of Included Patients

	Before		After	
Number of included patients	#	%	#	%
With paid buprenorphine claim from 10/1/2019-10/31/2019 (pre) or from 10/1/2020-10/31/2020 (post)	**349**		**378**	
And after exclusion of limited benefit packages, Medicare, TPL in baseline period	292	83.7%	291	77.0%
And after continuous Medicaid enrollment requirement in the 35 days before the IE	276	79.1%	277	73.3%
And after continuous Medicaid enrollment requirement in the 35 days after the IE	186	53.3%	208	55.0%
And after removal of duplicate patients in control/experimental periods	105	30.1%	127	33.6%

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Appendix 1: Key Inclusion Criteria

	Key question #3: Polypharmacy
Population	patients with continuous Medicaid eligibility of at least 35 days prior to the index event (IE) and fee-for-service (FFS) eligibility in the 35 days after the IE
Intervention	Initiation of sublingual buprenorphine (index event)
Comparator	Patients initiating buprenorphine sublingual (SL) from 10/1/2019-10/31/2019 vs Patients initiating buprenorphine SL from 10/1/2020-10/31/2020 (before vs. after removal of prior authorization [PA] criteria)
Outcomes	Polypharmacy associated with concurrent controlled substances
Setting	FFS

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OHSU Drug Effectiveness Review Project Summary Report – Pharmacological Therapies for Attention-Deficit/Hyperactivity Disorder (ADHD)

Date of Review: June 2022

Date of Last Review: August 2020

Literature Search: 09/01/2020-03/01/2022

Current Status of PDL Class:

See **Appendix 1**.

Research Questions:

1. For adults and children, what is the comparative effectiveness of the included interventions (see **Table 1**) for attention-deficit/hyperactivity disorder (ADHD)?
2. For adults and children, what are the comparative harms of the included interventions (see **Table 1**) for ADHD?

Conclusions:

- The December 2021 drug class report on ADHD by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this review.[1] Evidence for the following comparisons informed the DERP report:
    - Stimulant vs. Stimulant
    - Stimulant vs. Nonstimulant
    - Nonstimulant vs. Nonstimulant
    - Newer drug vs. Placebo
- Stimulant versus another stimulant medication: there was low quality evidence of rare serious adverse events (SAEs) for lisdexamfetamine and osmotic release oral system (OROS) methylphenidate groups compared to methylphenidate immediate-release based on 2 randomized controlled trials (RCTs) (N=611) with high risk of bias.[1] There were no high, moderate, or low-quality studies identified that reported any differences in the reduction of ADHD symptoms between various methylphenidate formulations and mixed amphetamine salts.
- Stimulant versus nonstimulant medications: there was moderate quality evidence of no differences in global measures in 11 of 12 studies; one trial (N=267) reported that lisdexamfetamine treatment resulted in statistically significant reductions of ADHD symptoms compared to atomoxetine based on

assessments with the ADHD-Rating Scale (RS)-IV (*P*<0.001) and Weiss Functional Impairment Rating Scale [WFIRS] Parent Form (*P* = 0.05). Low quality evidence from 3 RCTs reported slightly more discontinuations due to adverse events (AEs) for atomoxetine (8%; 31/381) compared to methylphenidate immediate release (6%; 14/246).[1] Risk of bias was high in 7 of the 12 RCTs and moderate in 5 of the 12 RCTs.[1]

- Nonstimulant versus another nonstimulant: there was low quality evidence from 1 RCT (N = 338) that extended-release guanfacine (guanfacine XR) resulted in statistically significant reductions of ADHD symptoms compared to atomoxetine based on assessments with the ADHD-RS-IV (least square mean difference (LSMD): −5.1 (95% CI, −8.2 to −2.0); *P*=0.001).[1] Although adverse events were rare in both groups, a slightly higher proportion of patients treated with guanfacine XR reported SAEs compared to atomoxetine (2% vs 0%, respectively), while discontinuations due to adverse events were slightly higher with guanfacine XR treatment compared to atomoxetine (7.8% vs 4.5%).[1]
- Newer drug vs. placebo: there was low quality evidence from 2 RCTs (N=535) of 8 weeks duration that reported viloxazine treatment resulted in a statistically significant reduction in ADHD symptoms at doses from 200 mg to 400 mg per day compared to placebo as measured across multiple instruments (least squares [LS] mean change ADHD-RS 5 = -17.5 to -17.6, p<0.05; LS mean total score Clinical Global Impressions-Illness (CGI-I) = 2.6 for both 200 mg and 400 mg doses, with p=0.003 and <0.01, respectively; ADHD-RS-IV, total score, LS mean change: 200 mg, 300 mg = -18.4 to -18.6 (p=0.03) and 400 mg = -19.0 (p= 0.02).[1]

Recommendations:

- No changes to the current Oregon Health Plan (OHP) Preferred Drug List (PDL).
- Evaluate costs in the executive session to inform PDL status.

Summary of Prior Reviews and Current Policy

Prior reviews have found evidence to support that both stimulant and non-stimulant pharmacologic agents are beneficial in ADHD treatment compared to placebo.[2] Comparisons between different formulations (immediate release [IR] vs. various extended-release [ER], XR, or long acting [LA] versions]) within this class have not demonstrated consistent differences.[2] There has been insufficient evidence to directly compare differences in efficacy or safety outcomes for different ADHD drugs in children or adults, or in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), when taken with other medications, or when co-morbidities are present.[2] The most frequent adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; only low-quality evidence has been identified to suggest any differences in harms between various ADHD agents.[2]

To ensure safe and appropriate use within the OHP-FFS population, all medications within the ADHD class have limits based on patient age and quantity prescribed. Safety edits are in place to ensure that medication use reflects best practices. Any request for a non-preferred agent or for an agent that exceeds the age or quantity limit requires consultation with a specialist prescriber such as a psychiatrist or other mental health specialist.

Preferred agents within the ADHD class include atomoxetine, dexmethylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine dimesylate, and methylphenidate (see **Appendix 1**). Four of the medications within the ADHD class are part of the mental health carve-out and are exempt from traditional prior authorization (PA) requirements: atomoxetine, clonidine ER, guanfacine ER, and the newest agent viloxazine. All medications, regardless of PDL status, may be subject to clinical PA criteria to address any safety concerns or to ensure medically appropriate use.

Background

Attention-deficit/hyperactivity disorder is a neurodevelopmental disorder which affects approximately 9% of children and adolescents in the United States (U.S.) and is characterized by hyperactivity, impulsivity, and inattention.[3] Although ADHD has been thought of as a childhood disorder, symptoms may persist into

adulthood in as many as 1% to 4% of US adults aged 18 to 44 years.[1,4] According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosis is confirmed based on presence of at least 6 symptoms for greater than 6 months which interfere with function and are inappropriate for the patients developmental level (or at least 5 symptoms in patients greater than 16 years of age).[5] For adults, the Center for Disease Control (CDC) recommends the following criteria are met in adults for diagnosis of ADHD: 1) More than one symptom of ADHD has been present prior to 12 years of age; 2) several symptoms are present in 2 or more settings (i.e. home, school or work; with friends or relatives; in other activities); 3) evidence that the symptoms interfere with, or reduce the quality of work functioning, and 4) the symptoms are not explained by another mental disorder and do not happen only during the course of another psychotic disorder.[3-5]

ADHD may be classified into 3 general presentations: predominantly inattentive, hyperactive/impulsive, and combined.[6,7] ADHD that cannot be classified in one of the 3 main categories is referred to as ADHD other specified or unspecified type.[6,7] In predominantly inattentive ADHD, a child exhibits at least 6 months of 6 or more inattention symptoms (careless mistakes, lack of follow-through, loses things, forgetful, easily distracted, etc).[6,7] In hyperactive/impulsive type, a child shows 6 or more hyperactive or impulsive symptoms (fidgets, inappropriate running/climbing, difficulty with playing quietly, often interrupts/intrudes, etc.) for at least 6 months.[6,7] The third ADHD categorization is a combined presentation of inattentiveness and hyperactivity/impulsivity for at least 6 months or longer.[6,7] Predominantly hyperactive/impulsive- or combined type ADHD often becomes apparent from behavior problems as the child enters kindergarten/1st grade while predominantly inattentive ADHD generally has a later onset which is recognized by poor academic performance and organizational skills.[3,6-9] For adolescents older than 17 years old and adults, the DSM-5 ADHD Diagnostic Criteria is essentially identical but only requires that 5 or more symptoms of inattention and/or hyperactivity-impulsivity have persisted for at least 6 months and are inconsistent with the stage of development.[5]

Comorbid conditions which can be associated with a diagnosis of ADHD include mood disorders, tic disorders, developmental and learning disorders and anxiety disorders.[5] Many children and adults with ADHD have one or more comorbid psychiatric conditions with comparable symptoms that may hinder appropriate care and present unique challenges.[10,11] Some of the more common comorbidities in children and adolescents include anxiety, oppositional defiance disorder (ODD), learning disorders, and depression.[1,10,11] The presence of psychiatric disorders increases the risk of an ADHD diagnosis in adulthood.[10,11] Some common comorbidities present in adults also include anxiety and depression as well as other conditions such as substance use disorder (SUD) and bipolar disorder.[10]

Behavioral interventions such as cognitive behavioral therapy (CBT), skills training, and other supportive therapy is generally considered first-line therapy; however, a combination of psychosocial interventions and medications are increasingly employed and advocated by many guidelines.[6,12] It is estimated that 62% of children/adolescents and up to 80% of adults with ADHD use prescription medications to manage their symptoms.[3,6,10-12] In pediatric patients, recommendations from the American Academy of Pediatrics (AAP) are based on age and disease severity.[6] For pre-school aged children age 4-5 years, behavioral therapy is recommended as first-line treatment while methylphenidate may be used as a second-line therapy or in cases of moderate-to-severe functional impairment.[6] In children older than 6 years of age, either behavioral therapy or pharmacotherapy may be used as first-line therapy.[6] Evidence of efficacy is strongest for stimulant medications (e.g. methylphenidates, amphetamines) although non-stimulant medications including atomoxetine, clonidine ER and guanfacine ER are recommended as second-line therapy if stimulants are not tolerated or ineffective.[5,6] For adults, the National Institute for Health and Care Excellence (NICE) guidelines suggest lisdexamfetamine or methylphenidate as first-line pharmacological agents for adults with ADHD.[12] Atomoxetine is recommended as second line therapy for people that cannot tolerate stimulants or if they do not respond after 6 weeks of therapy.[12]

Researchers have investigated whether racial/ethnic disparities exist in ADHD diagnosis and medication use.[13] One longitudinal, multisite study of 5th-graders suggested an underdiagnosis and undertreatment of Black and Hispanic/Latino children compared to other races.[14] A study of children aged 6 to 17 years in Kentucky Medicaid also found that rates for receipt of an ADHD diagnosis were lowest for Hispanic/Latino and Asian children compared to other races.[15] In addition, racial/ethnic minority children were less likely to receive a stimulant medication, with Hispanic/Latino and Asian children having the lowest rates.[15]

However, the same study showed that non-Hispanic Black and Hispanic/Latino children had the highest rates of receiving psychosocial therapy interventions.[15] Most of the available studies are claims-based which are unable to determine the type or quality of services, whether the diagnosis/treatment was appropriate, or the accuracy of the optional fields in which race/ethnicity data are collected. More research is needed in this area to better understand whether differences in care are due to provider bias, child uniqueness, or cultural distinctions that impact treatment.

The goals of ADHD care may change as the patient matures, but generally, they focus on management of symptoms as well as improvements in function and quality of life.[6-8] Evaluation of symptom and functional improvement may employ a variety of behavior assessment scales and metrics which are usually completed by the parents, teacher, or patient with ADHD.[6-9,16,17] Assessment scales commonly used in clinical trials include the ADHD rating scale (ADHD-RS), the Weiss Functional Impairment Rating Scale (WFIRS), Permanent Product Measure of Performance (PERMP), the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), and Conners Parent Rating Scale (CPRS).[16,17] The ADHD-RS is based on DSM criteria for ADHD diagnosis which assesses symptoms of inattentiveness, hyperactivity, and impulsivity.[17] This 18-item scale has a range of 0 to 54 with more higher scores indicating more severe symptoms.[17] There has been some research to suggest that a 30% mean total score change difference between treatment groups (5.2 to 7.7 points) on the ADHD-RS represents a clinically meaningful change.[16] Although the Clinical Global Impressions scale is not specific to ADHD, it has been paired with the ADHD-RS to assess ADHD symptom changes.[1,16] The CGI Symptoms (CGI-S) component is employed as a baseline measurement and is based on a scale of 1 (no symptoms) to 7 (very severe symptoms). A 1-point difference on CGI-S has been reported to correlate with 8 to 10 points on ADHD-RS.[16] The CGI Improvement (CGI-I) scores follow changes from baseline where 1 to 3 means improvement, 4 means no change, and 5 to 7 means worsening symptoms.[16] It has been reported that a "much improved" (2-level improvement) on CGI-I correlates with 50 to 60% improvement on ADHD-RS.[16] Other scales such as the WFIRS is a 50-item instrument that assesses symptoms and degrees of impact on 6 clinically relevant functional areas.[17,18] WFIRS responses include "never or not at all", "sometimes or somewhat", "often or much", "very often or very much", and "N/A" (not applicable).[17,18] Any WFIRS item rating 2 or 3 within a section would indicate impairment.[17,18] The PERMP is a classroom assessment which evaluates attention using a skill-adjusted math test.[17,19] The total PERMP score is a sum of the number of math problems attempted and the number answered correctly.[17,19] Because PERMP score is specific to the ability of the patient, the minimum clinically significant difference (MCID) in PERMP score has not been determined. The SKAMP rating scale is another teacher-rated scale which evaluates attention and behavior in a laboratory classroom setting.[17] Scores assess 13 items including attention, quality of work, deportment and compliance.[17,20] Each item is assessed on a 0 to 6 point scale with total score ranging from 0 to 78 and higher scores associated with more severe impairment.[17,20] The CPRS scale evaluates a variety of ADHD symptoms, each assessed on a 0 to 3 scale corresponding to symptoms which are not present (0), just a little present (1), pretty much present (2), and very much present (3).[16] Minimal Clinically Important Differences (MCIDs) for ADHD outcomes related to the ADHD-RS, WFIRS, SKAMP, and CPRS scales are not presently well-defined.[1]

Methods:

The December 2021 drug class report by the DERP at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

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

Summary Findings:

The 2021 DERP report focused on the comparative efficacy and safety of drugs to treat ADHD and was an update of a previous DERP report completed in 2015.[1] The report focused on RCTs of FDA-approved stimulants and non-stimulants as well as off-label treatments.[1] DERP reviewers completed a systematic review

based on a literature search of studies published between January 1, 2015 and August 1, 2021.[1] Therapies were excluded if they were not RCTs, compared a branded agent to its generic equivalent, different doses of the same drug, placebo-controlled trials of older agents, trials that evaluated primarily multi-modal (non-drug) comparisons, and studies not published in English.[1]

Since the previous review, two new agents have received FDA approval for the treatment of ADHD.[1] Serdexmethylphenidate/dexmethylphenidate (AZSTARYS), an oral prodrug of the stimulant dexmethylphenidate, was approved in March 2021.[1,21] A new non-stimulant oral agent, viloxazine hydrochloride (QELBREE), was approved in April 2021.[1,22] Manufacturer's prescribing information for each of these products is presented in **Appendix 2**. Three ongoing head-to-head trials and 3 placebo-controlled RCTs for recently FDA- approved agents were identified but will not be discussed as results were pending.[1] The FDA approved drugs included in the ADHD DERP report are summarized by subclass and listed in **Table 1**.

Table 1. FDA-Approved and Selected Off-label Treatments for ADHD

Generic Name	Brand Name	Date of FDA Approval
Stimulants		
Serdexmethylphenidate dexmethylphenidate	AZSTARYS	March 2, 2021
Methylphenidate hydrochloride	ADHANSIA XR	February 27, 2019
Amphetamine sulfate	EVEKEO ODT	January 30, 2019
Methylphenidate hydrochloride	JORNAY PM	August 8, 2018
Amphetamine	ADZENYS ER	September 15, 2017
Mixed amphetamine salts	MYDAYIS	June 20, 2017
Methylphenidate	COTEMPLA XR-ODT	June 19, 2017
Lisdexamfetamine dimesylate	VYVANSE (CHEWABLE)	January 28, 2017
Amphetamine polistirex	ADZENYS XR-ODT	January 27, 2016
Methylphenidate hydrochloride	QUILLICHEW ER	December 4, 2015
Amphetamine	DYANAVEL XR	October 19, 2015
Methylphenidate hydrochloride	APTENSIO XR	April 17, 2015
Methylphenidate hydrochloride	QUILLIVANT XR	September 27, 2012
Amphetamine sulfate	EVEKEO	August 9, 2012
Lisdexamfetamine dimesylate	VYVANSE	February 23, 2007
Methylphenidate	DAYTRANA	April 6, 2006
Dexmethylphenidate hydrochloride	FOCALIN XR	May 26, 2005

Methylphenidate hydrochloride	METADATE CD	April 3, 2003
Methylphenidate hydrochloride	METHYLIN	December 19, 2002
Methylphenidate hydrochloride	RITALIN LA	June 5, 2002
Dexmethylphenidate hydrochloride	FOCALIN	November 13, 2001
Mixed amphetamine salts	ADDERALL XR	October 11, 2001
Methylphenidate hydrochloride (osmotic release)	CONCERTA	August 1, 2000
Methylphenidate hydrochloride	METHYLIN ER	May 9, 2000
Methylphenidate hydrochloride	RITALIN SR	March 30, 1982
Mixed amphetamine salts	ADDERALL	January 19, 1960
Methylphenidate hydrochloride	RITALIN	December 5, 1955
Nonstimulants		
Viloxazine hydrochloride	QELBREE	April 2, 2021
Clonidine hydrochloride (extended release)	KAPVAY	September 29, 2009
Guanfacine hydrochloride (extended release)	INTUNIV	September 2, 2009
Atomoxetine hydrochloride	STRATTERA	November 26, 2002
Off-Label treatment		
Armodafinil	NUVIGIL	June 15, 2007
Bupropion hydrochloride	WELLBUTRIN XL	August 28, 2003
Modafinil	PROVIGIL	December 24, 1998
Bupropion hydrochloride	WELLBUTRIN SR	October 4, 1996

Abbreviations. ADHD: attention deficit/hyperactivity disorder; CD: controlled dose; ER: extended release; LA: long acting; ODT: orally disintegrating tablet; SR: sustained release; XL/XR: extended release

There were 70 studies (N = 11,815) that met inclusion criteria. Of these trials, 50 involved populations from the United States that compared 2 active treatments.[1] Most participants were White between the ages of 6- and 12-years exhibiting ADHD symptoms of both inattention and hyperactivity or impulsiveness.[1] Fourteen studies had a moderate risk of bias while 56 studies had high risk.[1] The review compared findings for a stimulant versus another stimulant, a stimulant versus a nonstimulant, a nonstimulant versus another nonstimulant, and placebo compared to the new nonstimulant viloxazine.[1] **Table 2** is an overview of all the RCTs identified in the DERP review and the number of studies that met the minimum criteria for 8 weeks duration or longer.

Table 2: Overview of DERP Review Findings[1]

Comparators	Number of RCTs	Study Size Range	Total N	Study Duration (weeks)	Number of Studies 8 weeks or Longer
Stimulant vs. Stimulant	34	18 to 549	3,958	1 to 16	**3**
Stimulant vs. Nonstimulant	20	17 to 1,323	4,597	2 to 26	**13**
Nonstimulant vs. Nonstimulant	1	N/A	338	10 to 13	**1**
Newer drug vs. Placebo	11	59 to 477	2,786	1 to 8	**2**

Certainty of evidence was assessed using the GRADE criteria in RCTs that had a minimum of 8 weeks treatment (with or without follow-up) and was limited to 5 outcomes: symptom response, performance, quality-of-life (parent stress, parent satisfaction), discontinuations due to adverse events and SAEs.[1] Evidence certainty was assessed as "very low or moderate" for symptom response measures, "very low" for performance and quality of life measures, and "very low or low" for discontinuation due to AEs and SAEs.[1] All participants had ADHD symptom reduction compared to baseline without regard to what active treatment was employed and irrespective of age, race, gender, or ethnicity.[1] Studies comparing a stimulant to off-label treatment or placebo did not meet inclusion criteria.[1] In some cases, there were no eligible studies for a particular outcome or the included studies were rated as "Very low" certainty of evidence.[1] Only trials of 8-week or longer with High, Moderate, or Low quality of evidence for ADHD outcomes as will be highlighted in this DERP summary (see **Table 3** and **Table 4**).

Table 3: GRADE Criteria for Overall Quality of Evidence[1]

High	Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
Moderate	Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
Low	Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
Very Low	Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Table 4: Overview and Certainty of Evidence for Select ADHD Outcomes in RCTs of at least 8 weeks[1]

Comparators	ADHD Outcomes Studied and Certainty of Evidence (Low, Moderate, High)				
	Symptom Response	Performance	Quality of Life	Discontinuations Due to AEs	Serious AEs
Stimulant vs. stimulant					Low (2 RCTs; N = 611)
Stimulant vs. nonstimulant	Moderate (12 RCTs; N = 1,991)			Low (10 RCTs; N=1,716)	Low (3 RCTs; N = 493)
Nonstimulant vs. nonstimulant	Low (1 RCT; N = 338)			Low (1 RCT; N = 338)	Low (1 RCT; N = 338)
Nonstimulant vs. placebo	Low (2 RCTs; N = 535)				

Abbreviations. ADHD = attention deficit/hyperactivity disorder; AE = adverse effects; RCT = randomized controlled trial
Note: Table 4 includes only those studies assessed with GRADE criteria that also met the minimum 8-weeks of treatment requirement. Gray row shading indicates there were no eligible studies for a particular outcome, or the included studies rated as "Very low" certainty of evidence, therefore those results will not be discussed in this DERP summary.

Stimulant vs. Another Stimulant

A total of 34 RCTs (N=3958) were identified that compared one stimulant versus another that ranged from 3 to 16 weeks; however, only 3 studies were 8 weeks or longer.[1,23-25] Thirty-one studies involved children and adolescents with a mean age range of 7 to 18 years while 3 studies included adults up to 60 years of age (mean age range 33 – 36 years).[1] Thirty of the studies were rated as high risk of bias due to poor reporting and industry conflicts while 4 were moderate risk of bias due to inadequate methods reporting, lack of blinding, high (>20%) attrition, and other factors.[1] Adverse events were reported in only 13 of 33 studies.[1] Overall, there were no significant differences found in the reduction of ADHD symptoms between different methylphenidate formulations and mixed amphetamine salts.[1] There was low quality evidence from 2 RCTs (N=611) of rare SAEs, with one SAE reported in both the osmotic-release oral system methylphenidate and the lisdexamfetamine groups, and none in the immediate-release amphetamine group.[1,24,25] An overview of study characteristics for each trial is provided in **Table 5**.

Table 5: Overview of Study Characteristics for RCTs of at least 8-weeks Duration

Study Details						Population Eligibility			Outcomes				
Author, Year	Study Design	Duration + Follow-up (weeks)	Included United States	N Enrolled	Interventions	Ages or Other Criteria	ADHD Presentation	Other Comorbidities Allowed	Symptom Response	Performance	Quality of Life	AEs	Risk of Bias
Stimulant vs Another Stimulant													
Cikili Uytun, 2019[23]	RCT	16	No	103	ER-MPH OROS-MPH	6 to 16	Any	ODD	Yes	NR	NR	Yes	High
Steele, 2006[24]	RCT	8	No	147	IR-MPH OROS-MPH	6 to 12	Any	NR	Yes	NR	No	Yes	High
Newcorn, 2017[25] (flexi-dose)	RCT	8 + 1	Yes	464	LDX OROS-MPH PBO	13 to 17	Any	ODD	Yes	NR	NR	Yes	High
Newcorn, 2017[25] (forced dose)	RCT	6 + 1	Yes	549	LDX OROS-MPH PBO	13 to 17	Any	ODD	Yes	NR	NR	Yes	Mod
Stimulant vs Non-stimulant													
ÇEtİN, 2015[26]	RCT	26	No	145	ATX OROS-MPH	7 to 16	Any	None	Yes	NR	NR	Yes	Mod
Dittmann, 2013[27]	RCT	9	Yes	267	ATX LDX	6 to 17	Any	NR	Yes	Yes	NR	Yes	High
Garg, 2014[28]	RCT	8	No	84	ATX IR-MPH	6 to 14	Any	ODD	Yes	NR	NR	Yes	High
Kratochvil, 2002[29]	RCT	10	Yes	228	ATX MPH	Males, 7 to 15 Females, 7 to 9	Any	NR	Yes	NR	NR	Yes	High
Ni, 2017[30]	RCT	8 to 10	No	71	ATX IR-MPH	18 to 50 Drug naïve	Any	None	Yes	NR	NR	NR	Mod
Palumbo, 2008[31]	RCT	16	Yes	122	CLON +/-MPH MPH PBO	7 to 12	Any	NR	Yes	NR	NR	Yes	Mod

Shang, 2015[32]	RCT	24	No	160	ATX OROS-MPH	7 to 16 Drug naïve	Any	NR	Yes	NR	NR	Yes	Mod
Snircova, 2016[33]	RCT	8	No	78	ATX XR-MPH	5 to 16 Drug naïve	CM	None	Yes	NR	NR	NR	High
Su, 2016[34]	RCT	8	No	262	ATX OROS-MPH	6 to 16 Drug naïve	Any	NR	Yes	NR	NR	Yes	High
Tas Torun, 2020[35]	RCT	18	No	140	ATX OROS-MPH	6 to 12	Any	NR	Yes	NR	NR	Yes	High
Wang, 2007[36]	RCT	8	No	330	ATX MPH	6 to 16	Any	NR	Yes	NR	NR	Yes	High
Zhu, 2017[37]	RCT	8	No	104	ATX MPH	6 to 14	Any	NR	Yes	NR	NR	Yes	Mod
Tourette's Syndrome Study Group, 2002[38]	RCT	16	Yes	136	CLON MPH MPH + CLON PBO	6 to 14	Any	Tourette's	Yes	NR	NR	Yes	High
Non-stimulant vs Non-stimulant													
Hervas, 2014[39]	RCT	10 to 13	Yes	338	ATX GXR PBO	6 to 17	Any	ODD	Yes	NR	NR	Yes	Mod
Non-stimulant vs Placebo													
Nasser, 2021[40]	RCT	8	Yes	313	VLX	6 to 11	Any	None	Yes	NR	Yes	Yes	High
Johnson, 2017[41]	RCT	8	Yes	222	VLX	6 to 12	Any	None	Yes	NR	NR	Yes	High

Note: Table includes those studies of 8 weeks or longer and applicable new studies which were assessed with GRADE criteria.
Abbreviations. ADHD: attention deficit/hyperactivity disorder; AE: adverse event; ER: extended release; IR: immediate release; LA: long acting; LDX: lisdexamfetamine; MPH: methylphenidate; NR: not reported; ODD: oppositional deviance disorder; OROS: osmotic-release oral system; PBO: placebo; RCT: randomized controlled trial; SAE: serious adverse event; XR: extended release

Stimulant vs. Nonstimulant

A total of 20 RCTs (N=4,597) were identified that compared a stimulant to a non-stimulant and the studies ranged in length from 2 to 26 weeks.[1] Eighteen studies involved children and adolescents with a mean range of 9 to 11 years while only 2 studies involved adults (mean range of 31 to 41 years).[1] Twelve studies were rated as high risk of bias due to poor reporting of methods, short treatment and follow-up periods, and industry involvement while 8 studies were rated as moderate risk of bias.[1] Only 13 of the 20 studies met the minimum 8-week treatment requirement.[1,26-38] The MCIDs were not well defined for various outcomes. In children and adolescents, one 9-week trial (N=267) reported that lisdexamfetamine treatment resulted in statistically significant reductions of ADHD

symptoms compared to atomoxetine based on assessments with the ADHD-RS-IV (p<0.001) and the WFIRS (p = .05).[1,27] In participants who received a combination of methylphenidate and clonidine, there was a statistically significant reduction in ADHD symptoms compared with those who received clonidine alone based on the Conners Abbreviated Symptoms Questionnaire [ASQ] Teacher version (p = 0.03).[1,31] No differences were found in the reduction of ADHD symptoms among standard formulations of methylphenidate and atomoxetine or guanfacine XR.[1] There was low quality evidence of no difference in SAEs based on 3 RCTs (N=493) with methylphenidate versus clonidine, lisdexamfetamine versus atomoxetine, or methylphenidate versus atomoxetine.[1] Ten trials (N=1,716) of 8 weeks or longer reported discontinuations due to adverse events (AEs). In 4 of the studies (N=729) with standard methylphenidate versus atomoxetine, there were 49 total discontinuations reported.[1] Low quality evidence from 3 of these RCTs reported 8% discontinuations due to AEs for atomoxetine (31/381) compared to 6% for standard methylphenidate or immediate-release methylphenidate (14/246).[1,28,29,36] Similar results were observed in a trial of atomoxetine versus lisdexamfetamine.[1,27] Although specific frequencies of individual AEs were not consistently reported, the most common AEs that led to discontinuation highlighted by the authors are listed in **Table 6**.

Table 6: Reported Adverse Events Leading to Discontinuation for Atomoxetine versus Lisdexamfetamine or Methylphenidate[1,27-29,36]

	Atomoxetine (N = 518)	**Lisdexamfetamine** (N = 133)	**Methylphenidate** (N = 243)
Total Discontinuations (%)	41 (8%)	8 (6%)	14 (6%)
Daytime drowsiness/somnolence	X	X	
Decreased appetite /decreased weight/anorexia	X	X	X
Nausea/abdominal pain	X	X	X
Tachycardia/palpitations/chest pain	X		X
Headache	X		X
Agitation and/or irritability	X	X	
Other	skin-related issues	tic	mania

Nonstimulant vs. Another Nonstimulant

One 13-week RCT (N=338) compared a non-stimulant to another non-stimulant.[1,39] The study involved children and adolescents with a range of 6 to 17 years and 56% of participants also had a comorbid diagnosis of ODD.[1,39] The study was rated as moderate risk of bias due to poor reporting of methods, short treatment and follow-up periods, and industry involvement.[1,39] The MCIDs were not well defined for various outcomes. The study reported that guanfacine XR treatment resulted in statistically significant reductions of ADHD symptoms compared to atomoxetine based on assessments with the ADHD-RS-IV (LSMD: −5.1 (95% CI, −8.2 to −2.0; p=0.001).[1,39] In patients treated with guanfacine XR compared to atomoxetine, there was low quality evidence that found a slightly higher proportion of patients with discontinuations due to AEs (7.8% vs 4.5%, respectively).[1,39] In the same trial, serious AEs were rare with 2 (1.7%) reported in guanfacine XR-treated patients and none in those treated with atomoxetine (low quality evidence).[1,39]

Recently Approved Nonstimulant vs. Placebo

Two 8-week RCTs (N=535) compared a newer nonstimulant to placebo.[1,40,41] The studies included children and adolescents between 6 and 12 years of age without comorbidities.[1,40,41] The studies reported viloxazine treatment resulted in a statistically significant reduction in ADHD symptoms at doses from 200 mg to 400 mg per day compared to placebo as measured across multiple instruments (LS mean change ADHD-RS 5 = -17.5 to -17.6, p<0.05; LS mean total score Clinical Global Impressions-Illness (CGI-I) = 2.6 for both 200 mg and 400 mg doses, with p=0.003 and <0.01, respectively; ADHD-RS-IV, total score, LS mean change: 200 mg, 300 mg = -18.4 to -18.6 (p=0.03) and 400 mg = -19.0 (p= 0.02).[1,40,41] A dose-response effect was reported as larger reductions of symptoms were noted at the 200 mg and 400 mg doses.[1,40,41] No significant differences were found in symptom improvement with any other clinical instrument (e.g. Conners PS or WFIRS-Parent).[1,40,41] **Table 7** summarizes the participant characteristics and outcomes studied for viloxazine.

Table 7: Participant Characteristics and Outcomes for RCTs: Recently Approved Nonstimulant vs. Placebo for ADHD Treatment[1,40,41]

First Author, Year Duration + Follow-up N Randomized n of N Reported	Participant Characteristics	Mean Dose Symptom Response	AEs Quality of Life
Nasser, 2021[40] 8 weeks N = 313 • VLX: 204 of 301 PBO: 97 of 301	Participant characteristics, n of 301 (%) • Age, mean years (SD): 8.5 (1.7) • Male: 191 (63.4) • Race or ethnicity AI/AN: 3 (1.0) Asian: 1 (0.3) Black: 125 (41.5) Multiple: 13 (4.3) White: 159 (52.8) • ADHD presentation, NR Comorbidities, NR	Mean dose, NR **Symptom Response, vs. PBO** ADHD-RS−5, total score LS mean change (SE) • 200 mg, −17.6 (1.4); *P* <0.05 • 400 mg, −17.5 (1.5); *P* < 0.05 CGI-I, total score, LS mean (SE) • 200 mg, 2.6 (0.12); *P* = 0.003 • 400 mg, 2.6 (0.12); *P* < 0.01 Conners 3-PS, composite score, difference of LS means (SE) • 200 mg, −3.8 (1.39; 95% CI, −6.5 to −1.1); *P* = .006 • 400 mg, no difference WFIRS-Parent, no difference	AEs • AEs: VLX, 114 of 207 (55.1) vs. PBO, 47 of 103 (45.6) • SAEs: VLX, 7 of 207 (3.4) vs. PBO, 4 of 103 (3.9) • Discontinuation: VLX, 10 of 207 (4.8) vs. PBO, 3 of 107 (2.9) **Quality of Life, vs. PBO** PSI-4-SF, total score 200 mg, no difference 400 mg, LS mean (SD): −11.6 (2.01); *P* = 0.04
Johnson, 2017[41] weeks N = 222 • VLX: 182 of 206 PBO: 24 of 206	Participant characteristics, n of 206 (%) • Age, median years (range) 9.0 (6 to 12) • Male: 138 (67.0) Race or ethnicity AI/AN: 2 (1.0) Asian: 2 (1.0) Black/AA: 79 (38.3) Multiple: 6 (2.9) White: 117 (56.8) ADHD presentation, NR	Mean dose, NR **Symptom response, vs. PBO** ADHD-RS-IV, total score, LS mean change: • 100 mg, no difference • 200 mg, −18.4 (*P* = 0.03) • 300 mg, −18.6 (*P* = 0.03) • 400 mg, −19.0 (*P* = 0.02)	AEs • Any AE: VLX, 132 of 182 (72.5) vs. PBO, 11 of 24 (45.8) • SAEs: 0 for all groups Discontinuation: VLX, 13 of 182 (7.1) vs. PBO, 0

	Comorbidities, NR		

Abbreviations. AA: African American; ADHD: attention deficit/hyperactivity disorder; ADHD-RS-IV: ADHD Rating Scale IV; ADHD-SRS: ADHD Self-Rating Scale; AE: adverse event; AI: American Indian; AN: Native American; CGI-S: Clinical Global Impressions-Improvement; CI: confidence interval; C(3)PRS: Conners Parents Rating Scale; LS: least square; NR: not reported; PBO: placebo; PSI(4)SF: Parenting Stress Index, Short Form; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VLX: viloxazine; WFIRS: Weiss Functional Impairment Rating Scale

Limitations

There were several limitations conveyed by the DERP review authors. Roughly 1/3 of the trials (25/70) were RCTs between 1 and 7 weeks in length, however, guidelines including those from the American Academy of Pediatrics (AAP) recommend a minimum of 6 weeks of therapy for adequate assessment of therapy. A similar proportion of included RCTs (26/70) were crossover design with 1 to 3-week phases and no washout period. In addition, many of the trials titrated the medication doses over several weeks so the target or optimal dose was only maintained for 1 to 2 weeks. There were numerous cases where performance was measured in a single day after a short treatment period which may have resulted in uncertainty of evidence. Lastly, most of the studies overtly excluded patients with comorbidities.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL	Carveout
atomoxetine HCl	ATOMOXETINE HCL	CAPSULE	Y	Y
atomoxetine HCl	STRATTERA	CAPSULE	Y	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	CPBP 50-50	Y	
dexmethylphenidate HCl	FOCALIN XR	CPBP 50-50	Y	
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	TABLET	Y	
dexmethylphenidate HCl	FOCALIN	TABLET	Y	
dextroamphetamine/amphetamine	ADDERALL XR	CAP ER 24H	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	CAP ER 24H	Y	
dextroamphetamine/amphetamine	ADDERALL	TABLET	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	TABLET	Y	
lisdexamfetamine dimesylate	VYVANSE	CAPSULE	Y	
lisdexamfetamine dimesylate	VYVANSE	TAB CHEW	Y	
methylphenidate	DAYTRANA	PATCH TD24	Y	
methylphenidate HCl	METHYLPHENIDATE HCL CD	CPBP 30-70	Y	
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	CPBP 30-70	Y	
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET	Y	
methylphenidate HCl	RITALIN	TABLET	Y	
clonidine HCl	CLONIDINE HCL ER	TAB ER 12H	V	Y
clonidine HCl	KAPVAY	TAB ER 12H	V	Y
guanfacine HCl	GUANFACINE HCL ER	TAB ER 24H	V	Y
guanfacine HCl	INTUNIV	TAB ER 24H	V	Y
viloxazine HCl	QELBREE	CAP ER 24H	V	Y
amphetamine	ADZENYS ER	SUS BP 24H	N	
amphetamine	AMPHETAMINE	SUS BP 24H	N	
amphetamine	DYANAVEL XR	SUS BP 24H	N	
amphetamine	ADZENYS XR-ODT	TAB RAP BP	N	
amphetamine sulfate	EVEKEO ODT	TAB RAPDIS	N	
amphetamine sulfate	AMPHETAMINE SULFATE	TABLET	N	
amphetamine sulfate	EVEKEO	TABLET	N	
dextroamphetamine sulfate	DEXEDRINE	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	SOLUTION	N	
dextroamphetamine sulfate	PROCENTRA	SOLUTION	N	
dextroamphetamine sulfate	DEXEDRINE	TABLET	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	TABLET	N	
dextroamphetamine sulfate	ZENZEDI	TABLET	N	

dextroamphetamine/amphetamine	MYDAYIS	CPTP 24HR	N
methamphetamine HCl	DESOXYN	TABLET	N
methamphetamine HCl	METHAMPHETAMINE HCL	TABLET	N
methylphenidate	COTEMPLA XR-ODT	TAB RAP BP	N
methylphenidate HCl	ADHANSIA XR	CPBP 20-80	N
methylphenidate HCl	METHYLPHENIDATE ER (LA)	CPBP 50-50	N
methylphenidate HCl	METHYLPHENIDATE LA	CPBP 50-50	N
methylphenidate HCl	RITALIN LA	CPBP 50-50	N
methylphenidate HCl	JORNAY PM	CPDR ER SP	N
methylphenidate HCl	APTENSIO XR	CSBP 40-60	N
methylphenidate HCl	METHYLPHENIDATE ER	CSBP 40-60	N
methylphenidate HCl	METHYLIN	SOLUTION	N
methylphenidate HCl	METHYLPHENIDATE HCL	SOLUTION	N
methylphenidate HCl	QUILLIVANT XR	SU ER RC24	N
methylphenidate HCl	QUILLICHEW ER	TAB CBP24H	N
methylphenidate HCl	METHYLPHENIDATE HCL	TAB CHEW	N
methylphenidate HCl	CONCERTA	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	N
methylphenidate HCl	RELEXXII	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	TABLET ER	N
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET ER	N
serdexmethylphen/dexmethylphen	AZSTARYS	CAPSULE	N

Appendix 2: Prescribing Information Highlights

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

AZSTARYS (serdexmethylphenidate and dexmethylphenidate) capsules, for oral use, CII [controlled substance schedule pending for serdexmethylphenidate]
Initial U.S. Approval: [pending controlled substance scheduling]

WARNING: ABUSE AND DEPENDENCE
See full prescribing information for complete boxed warning.

- **CNS stimulants, including AZSTARYS, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

----------INDICATIONS AND USAGE----------
AZSTARYS is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Pediatric Patients 6 to 12 years: Recommended starting dosage is 39.2 mg/7.8 mg orally once daily in the morning. Dosage may be increased to 52.3 mg/10.4 mg daily or decreased to 26.1 mg/5.2 mg daily after one week. Maximum recommended dosage is 52.3 mg/10.4 mg once daily. (2.2)
- Adults and Pediatric Patients 13 to 17 years: Recommended starting dosage is 39.2 mg/7.8 mg orally once daily in the morning. Increase the dosage after one week to 52.3 mg/10.4 mg once daily. (2.2)
- Administer with or without food. (2.3)
- Swallow capsules whole or open and sprinkle onto applesauce or add to water. (2.3)
- To avoid substitution errors and overdosage, do not substitute for other methylphenidate products on a milligram-per-milligram basis. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Capsules (serdexmethylphenidate/dexmethylphenidate): 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, 52.3 mg/10.4 mg. (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to serdexmethylphenidate, methylphenidate, or product components. (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *Serious Cardiovascular Reactions*: Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions*: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to AZSTARYS use. (5.4)
- *Priapism*: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon*: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth*: Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

---------- ADVERSE REACTIONS ----------
Based on accumulated data from other methylphenidate products, the most common (>5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Corium, Inc. at 1-616-656-4563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Antihypertensive Drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed. (7.1)
- Halogenated Anesthetics: Avoid use of AZSTARYS on the day of surgery if halogenated anesthetics will be used. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2021

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

QELBREE™ (viloxazine extended-release capsules), for oral use
Initial U.S. Approval: 2021

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

In clinical trials, higher rates of suicidal thoughts and behavior were reported in pediatric patients treated with Qelbree than in patients treated with placebo. Closely monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).

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

Qelbree is a selective norepinephrine reuptake inhibitor indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age (1)

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

- *Pediatric patients 6 to 11 years of age*: Recommended starting dosage is 100 mg once daily. May titrate in increments of 100 mg weekly to the maximum recommended dosage of 400 mg once daily (2.2)
- *Pediatric patients 12 to 17 years of age*: Recommended starting dosage is 200 mg once daily. May titrate after 1 week, by an increment of 200mg, to the maximum recommended dosage of 400 mg once daily (2.2)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce (2.3)
- Severe Renal Impairment: Initial dosage is 100 mg once daily. Titrate in weekly increments of 50 mg to 100 mg to a maximum recommended dosage of 200 mg once daily (2.4, 8.6)

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

Extended-release capsules: 100 mg, 150 mg and 200 mg (3)

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

- Concomitant administration of monoamine oxidase inhibitors (MAOI), or dosing within 14 days after discontinuing an MAOI (4, 7.1)
- Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (4, 7.1)

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

- Blood Pressure and Heart Rate Increases: Assess heart rate and blood pressure prior to initiating treatment, following increases in dosage, and periodically while on therapy (5.2)
- Activation of Mania or Hypomania: Screen patients for bipolar disorder (5.3)
- Somnolence and Fatigue: Advise patients to use caution when driving or operating hazardous machinery due to potential somnolence (including sedation and lethargy) and fatigue (5.4)

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

Most commonly observed adverse reactions (≥5% and at least twice the rate of placebo) were: somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Supernus Pharmaceuticals at 1-866-398-0833 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Moderate sensitive CYP1A2 substrates: Not recommended for coadministration with Qelbree. Dose reduction may be warranted (7.1)

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

- Pregnancy: May cause maternal harm; discontinue when pregnancy is recognized (8.1)
- Hepatic Impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised:4/2021

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover ADHD medications only for diagnoses funded by the OHP and medications consistent with current best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs on the enforceable preferred drug list.
- Regimens prescribed outside of standard doses and age range (Tables 1 and 2)
- Non-standard polypharmacy (Table 3)

Covered Alternatives:

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

Table 1. FDA-approved and OHP-funded Indications.

	STIMULANTS		NON-STIMULANTS			
Indication	**Methylphenidate and derivatives****	**Amphetamine and derivatives**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**	**Viloxazine**
ADHD	**Age ≥6 years**	**Age ≥3 years**	**Age ≥6 years**	**Children age 6-17 years only**	**Children age 6-17 years only**	**Children age 6- 17 years only**
Narcolepsy	**Age ≥6 years**	**Age ≥6 years**	**Not approved**	**Not approved**	**Not approved**	**Not approved**

See **Table 2 for off-label methylphenidate IR dosing for age ≥ 4 years

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine ER	3		20 mg
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg
CNS Stimulant	amphetamine/dextroamphetamine ER (Mydayis®)	13		25 mg for children 13-17 years 50 mg for adults 18-55 years
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	4		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
CNS Stimulant	serdexmethylphenidate/dexmethylphenidate	6		52.3 mg/ 10.4 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg for adjunctive therapy in ages 6-17 years and for monotherapy in ages 6-12 years 7 mg for monotherapy in ages 13-17 years
Non-Stimulant	viloxazine	6	17	400 mg

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

Table 3. Standard Combination Therapy for ADHD

Age Group	Standard Combination Therapy
Age <6 years*	**Combination therapy not recommended**
Age 6-17 years*	**1 CNS Stimulant Formulation (LA or IR) + Guanfacine LA** **1 CNS Stimulant Formulation (LA or IR) + Clonidine LA**
Age ≥18 years**	**Combination therapy not recommended**

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

* As recommended by the American Academy of Pediatrics 2019 Guidelines Wolraich ML, Hagan JF, Jr., Allan C, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4).

**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2015.

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 #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an approved FDA diagnosis defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9

Approval Criteria		
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *6/22 (DE); 8/20; 5/19; 9/18; 5/16; 3/16; 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*

Implementation: *11/1/2018; 10/13/16; 7/1/16; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*

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Drug Use Evaluation: Attention Deficit Hyperactivity Disorder (ADHD) Drugs

Research Questions:

- What percentage of patients were prescribed combination therapy for treatment of Attention Deficit Hyperactive Disorder (ADHD)?
- What are the characteristics of patients who are utilizing combination medication therapy for the treatment of ADHD?
- What is the incidence of emergency department (ED) visits and/or hospitalizations due to drug overdose or adverse events from patients utilizing combination medication therapy for ADHD?
- What proportion of patients utilizing combination medication therapy are prescribed ADHD treatment by a specialist (e.g. psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist)?
- How have prescribing patterns and utilization of ADHD medications in adults enrolled in Oregon Health Plan (OHP) changed over the previous 5 years?

Conclusions:

- Out of 39,351 patients with claims for an ADHD medication within the 2021 calendar year, 2835 (7.2%) used multiple agents concurrently (**Table 1**).
- Of those patients on combination therapy (n=2835), 2103 (74.2%) used a stimulant and non-stimulant combination, 454 (16.0%) used two different stimulants, and 278 (9.8%) used two different non-stimulant agents. (**Table 2**).
- Of those patients using a second non-stimulant (either in addition to a stimulant, or in combination with another non-stimulant), 68% had a recent diagnosis of either developmental or mental health disorders (**Table 2**). These patients were more likely to be male (74%) and young (62% age 12 or less; **Table 1**).
- The incidence of emergency department visits or hospitalization for those utilizing combination therapy for ADHD treatment was 24.6%, and did not significantly differ from those utilizing a single agent for ADHD treatment (24.3%) (**Table 4**).
- A high percentage of patients utilizing a pharmacological agent for the treatment of ADHD have a documented comorbid mental health disorder (45.3%) (**Table 2**), and suicidal ideation (1.3%) was the most common reason for emergency department visit or hospitalization (**Table 4**).
- Approximately 49% of individuals using a combination of agents for the treatment of ADHD had therapies prescribed by a specialist (**Table 2**).
- Utilization of ADHD medications in adults has increased by 95% per member per month (PMPM) from 2016 to 2021 (**Figure 1**).

Recommendations:

- No revisions to the current ADHD safety edits are recommended.
- Continue to monitor for the use of combination therapies for the treatment of ADHD, and evaluate for any changes in trends over time.
- Consider additional education about the need for appropriate treatment of mental health disorders in those with ADHD.

Background

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder of childhood which affects approximately 9.4% of all children within the United States (U.S.) between the ages of 2 and 17 years.[1] Approximately two-thirds of all children with ADHD will continue to have residual symptoms into adulthood, with the overall prevalence of ADHD in adults in the U.S. of 4.4%.[2,3] The current Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) criteria for diagnosis of ADHD include the presence of inattention, hyperactivity-impulsivity, or both. For diagnosis, symptoms should be present before 12 years of age as well as within two or more settings (e.g. school, work or home, and interfere with the quality of social, school, or work functioning.[4] Furthermore, the presence of these symptoms should not occur exclusively during the course of a psychotic disorder and are not better explained by another mental disorder (e.g. anxiety, personality disorder or substance withdrawal).

The 2019 guidelines from the American Academy of Pediatrics (AAP) recommend the use of FDA-approved stimulant medications for the treatment of ADHD in children and adolescents 12 through 17 years of age.[5] The AAP guidelines encourage the use of non-pharmacological modalities for treatment of ADHD in children less than 12 years of age; however, the use of a stimulant may be considered if the benefits outweigh the risks of delaying pharmacological treatment for those of at least 4 years of age. The Food and Drug Administration (FDA) approved stimulants for the treatment of ADHD in adolescents include short- or long-acting methylphenidate and amphetamine derivatives. Non-stimulant agents, which include atomoxetine, extended-release guanfacine, and extended-release clonidine, are recommended as second-line ADHD treatments. However, non-stimulants are less efficacious for the treatment of ADHD when compared to stimulants in both children and adolescents.[5] The National Institute of Health and Care Excellence (NICE) 2018 guidelines recommend methylphenidate as a first-line pharmacological option for ADHD in children 5 years and older.[6] Current NICE guidelines suggest a switch to lisdexamfetamine or dexamphetamine in situations where treatment with methylphenidate is not tolerated or unsuccessful. This recommendation is influenced by the familiarity to providers and licensing status of these medications in Europe. The use of non-stimulant agents is also discussed, but are only utilized "off-label" in this age group and are only appropriate for consideration if a stimulant agent has failed or is not tolerated.[6]

The 2012 American Academy of Family Physicians (AAFP) provides guidelines for the treatment of ADHD for adults, and recommend the use of stimulants or atomoxetine as first-line treatments for ADHD.[7] Recommendations regarding use of extended-release guanfacine or extended-release clonidine are not included in these guidelines, since studies for FDA approval of both guanfacine and clonidine did not include adult participants.[9,10]. However, the antidepressant bupropion has been identified as an appropriate second-line treatment option for ADHD in adults.[7] The NICE guidelines provide recommendations specific to the treatment of ADHD in adults, with lisdexamfetamine or methylphenidate being the preferred first-line treatment options.[6] Similar to their recommendations for children, a switch to dextroamphetamine may be considered for adults whose symptoms are responding to lisdexamfetamine treatment but can no longer tolerate the adverse effects.[6] The use of atomoxetine monotherapy is also recommended in the 2018 NICE guidelines for adults when stimulant therapy fails or is not tolerated.[6] Other drug therapies including extended-release guanfacine, extended-release clonidine, or atypical antipsychotics should not be offered to adults for treatment of ADHD without guidance from a specialist.[7]

If monotherapy with a stimulant is not fully effective or limited by side effects, addition of adjunctive therapy can be considered.[5] AAP guidelines recommend extended-release guanfacine or clonidine as appropriate adjunctive therapies for ADHD due to established evidence of therapeutic benefit and FDA approval for children and adolescents.[5,9,10] Limited guidance is available regarding adjunctive therapy for ADHD treatment for adults. Current AAFP guidelines state that there is insufficient evidence to establish the role of extended-release clonidine and extended-release guanfacine for ADHD treatment within adults.[7]. Similarly, NICE

guidelines do not provide statements on the role of adjunctive therapies for ADHD treatment in adults, and only encourage the use of extended-release guanfacine and extended-release clonidine with guidance from a specialist .[6] Additionally, there is insufficient evidence evaluating the role of alternative therapies, such as atomoxetine and modafinil for the treatment of ADHD.[11,12]

Currently, OHP policy criteria for the approval of ADHD medications is summarized within the "Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit" (**see Appendix 1)**. This safety edit ensures appropriate diagnosis and consistent prescribing with current best practices. Additionally, this policy confirms the oversight of a specialist when ADHD therapies are being utilized outside of current guidelines, including doses that exceed recommended maximum dosing or inappropriate combination therapy. Current preferred therapies for treatment of ADHD include certain formulations of methylphenidate, dexmethylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine, and atomoxetine. The use of viloxazine, guanfacine and clonidine are listed as voluntary non-preferred, but do not require a prior authorization for approval. A full list of specific preferred agents and non-preferred agents can be found in **Appendix 2.**

The purpose of this drug use evaluation is to research the use of combination ADHD medication therapy in children, adolescents, and adults in the Oregon Medicaid population.

Methods:
This is a retrospective, cohort study. The policy period of interest included any patient of all ages with a pharmacy claim for an ADHD drug with either a stimulant (S) or non-stimulant (NS) medication from 1/1/2021 to 12/31/2021. Pharmacy claims included both fee-for-Service (FFS) and Coordinated Care Organization (CCO) claims. Patients were excluded if they had additional insurance coverage through Medicare or had less than 75% FFS or CCO eligibility during 2021. The S and NS medications of interest can be found in the following table:

Drug Type	Generic Name
CNS Stimulant	amphetamine ER
CNS Stimulant	amphetamine/dextroamphetamine salts IR
CNS Stimulant	amphetamine/dextroamphetamine salts ER
CNS Stimulant	dexmethylphenidate IR
CNS Stimulant	dexmethylphenidate LA
CNS Stimulant	dextroamphetamine IR
CNS Stimulant	dextroamphetamine LA
CNS Stimulant	lisdexamfetamine
CNS Stimulant	methamphetamine
CNS Stimulant	methylphenidate IR
CNS Stimulant	methylphenidate LA
CNS Stimulant	methylphenidate transdermal
CNS Stimulant	serdexmethylphenidate/dexmethylphenidate
Non-Stimulant	atomoxetine
Non-Stimulant	clonidine LA
Non-Stimulant	guanfacine LA
Non-Stimulant	viloxazine

To describe the distribution of patients with ADHD, eligible patients with claims were divided into the following groups: S only, NS only, S+NS, S+S, and NS+NS. Combination therapy was defined as an overlap in claims for two different medications of 60 days and no more than a 14-day gap in overlapping therapy from the next expected fill date.

To describe the characteristics of patients who are utilizing combination therapy, data regarding eligible patients' age, sex, race/ethnicity, and pregnancy status (if applicable) were collected. Eligible patients who have an additional indication that commonly co-exists with or mimics ADHD were denoted (see **Appendix 3)**. Patients with an additional FDA approved condition for stimulant use were also identified, and include those with a history of narcolepsy, exogenous obesity, binge eating disorder, and obstructive sleep apnea. Additional comorbidities that may impact drug safety were reported including patients with a history of hypertension, coronary artery disease, and substance use disorders.

The most common combinations, number of patients on a dose above the recommended daily dose, and additional characteristics of interest (e.g. foster care) are reported.

To investigate the incidence of emergency department (ED) visits and hospitalizations due to drug overdose/adverse events from patients utilizing combination therapy for ADHD, eligible patients with claims for two agents (NS+NS, NS+S, S+S) were further evaluated for the presence of claims for ED visits or hospitalizations, and the corresponding diagnosis code relating to the reason for the visit is reported. Only events that occurred after the date of the first medication claim for the year of 2021 were reported.

For those prescribed combination therapy, the frequency of an ADHD drug claim prescribed by a specialist was reported. A "specialist" was defined as a provider who is listed as a psychiatrist, developmental pediatrician, psychologist, psychiatric nurse practitioner, sleep specialist, or neurologist. All other providers without the previously mentioned taxonomy were considered a general provider.

To describe how prescribing patterns and utilization of ADHD medications in adults enrolled in the Oregon Health Plan have changed over time, utilization for FFS ADHD pharmacy claims from 2016-2021 were reported as per member per month (PMPM) times 1000. Utilization of ADHD medications in adults with a diagnosis of opioid or alcohol dependence present within the previous year was also evaluated.

The frequency of approved prior authorizations for a stimulant or non-stimulant agent were determined using the number of both requested prior authorizations and denied prior authorizations within 2021 in the FFS population only. Follow-up events after a denied claim were reported, defined as any eligible patient with a FFS denied claim for an ADHD medication in the year 2021 with a paid pharmacy claim 90 days after the denied claim. The number of attempts for a submitted prior authorization and the percentage of those that were denied were also reported.

Results:

Demographics

Demographics of patients prescribed ADHD drugs are described in **Table 1**. Patient sex assigned at birth was similar for the total claim population (male 50.6%); however, males were more frequently prescribed combination therapy, particularly in the S+NS (74.2%) and NS+NS (74.5%) cohorts.

Table 1: Patients with Pharmacy Utilization of ADHD Drugs - Demographics

	Stimulant Only		Non-Stimulant Only		Stimulant + Non-Stimulant		Stimulant + Stimulant		Non-Stimulant + Non-Stimulant		Total		All Medicaid	
N =	29,472		5,648		2,103		454		278		39,351		1,396,520	
Mean age (range)	26	(2-74)	22	(3-65)	13	(3-61)	24	(5-64)	12	(4-60)	24	(2-74)	31	(0-108)
0-12	6,697	22.7%	1,850	32.8%	1,308	62.2%	147	32.4%	179	64.4%	10,751	27.3%	305,013	21.8%
13-17	4,454	15.1%	1,185	21.0%	589	28.0%	76	16.7%	73	26.3%	6,636	16.9%	128,691	9.2%
18+	18,321	62.2%	2,613	46.3%	206	9.8%	231	50.9%	26	9.4%	21,964	55.8%	941,002	67.4%
Sex														
Male	14,085	47.8%	3,058	54.1%	1,560	74.2%	268	59.0%	207	74.5%	19,910	50.6%	658,827	47.2%
Female	15,387	52.2%	2,590	45.9%	543	25.8%	186	41.0%	71	25.5%	19,441	49.4%	737,693	52.8%
Indication of pregnancy in 2021	545	1.8%	76	1.3%	5	0.2%	5	1.1%	0	0.0%	649	1.6%		
Race														
Unknown	15,426	52.3%	2,631	46.6%	878	41.7%	196	43.2%	112	40.3%	20,015	50.9%	694,023	49.7%
White	11,710	39.7%	2,520	44.6%	1,055	50.2%	227	50.0%	151	54.3%	16,159	41.1%	465,744	33.4%
Hispanic	1,113	3.8%	213	3.8%	43	2.0%	11	2.4%	5	1.8%	1,449	3.7%	144,023	10.3%
Black	496	1.7%	121	2.1%	67	3.2%	7	1.5%	6	2.2%	724	1.8%	30,156	2.2%
Native American	447	1.5%	124	2.2%	47	2.2%	6	1.3%	3	1.1%	652	1.7%	25,025	1.8%
Asian or Pacific Islander	280	1.0%	39	0.7%	13	0.6%	7	1.5%	1	0.4%	352	0.9%	35,858	2.6%

Table 2 depicts the distribution of utilization of ADHD drugs in the calendar year of 2021 by totals and specific combination therapy groupings respectively. A total of 39,351 patients with claims for ADHD drugs were identified with over half (55.8%) prescribed for adults 18 years and older (ages in **Table 1**). Most patients had claims for a stimulant only (75%), with 62.2% of stimulant monotherapy in those ages 18 or older. The most common combination therapy consisted of a stimulant plus non-stimulant (n=2,103, 5.3%), and 62.2% of this combination was prescribed to patients 12 years of age or younger with limited use in adults. There was limited use of stimulant plus stimulant (n=454; 1.2%) and non-stimulant plus non-stimulant (n=278; <1%) in the population. The presence of a comorbid mental health disorder was observed in 45.3% of patients. Comorbid mental health disorders were the most commonly seen category that co-exist or mimic ADHD within this population. A complete list of indications that co-exist or mimic ADHD can be found within **Appendix 3.** The frequency of a specialist prescriber for an index ADHD claim for the year 2021 was 31.2% for the total population, though frequency was higher within the NS only, S+NS, S+S, and NS+NS cohorts (44.9%, 48.5%, 45.2%, and 59.0% respectively) than in the S only population (26.9%). Of note, a higher percentage of individuals within foster care were identified in the combination therapy cohorts with at least one NS agent compared to patients with ADHD monotherapy (7.2% in S+NS and 7.6% in NS+NS versus 1.2% in S only and 4% in NS only).

Table 2: Patients with Pharmacy Utilization of ADHD Drugs by Combination Therapy Groupings

	Stimulant Only		Non-Stimulant Only		Stimulant + Non-Stimulant		Stimulant + Stimulant		Non-Stimulant + Non-Stimulant		Total	
	29,472		5,648		2,103		454		278		39,351	
Specialist Prescriber on Index Claim	7,931	26.9%	2,535	44.9%	1,019	48.5%	205	45.2%	164	59.0%	12,297	31.2%
ADHD Diagnosis (anytime in the prior 3 years)	21,608	73.3%	3,414	60.4%	1,560	74.2%	339	74.7%	193	69.4%	28,171	71.6%
Additional Indications that Co-exist or Mimic ADHD (anytime in 2021)												
Miscellaneous	535	1.8%	138	2.4%	104	4.9%	14	3.1%	14	5.0%	816	2.1%
Developmental Disorders	2,260	7.7%	922	16.3%	554	26.3%	74	16.3%	90	32.4%	4,076	10.4%
Mental Health Disorders	12,985	44.1%	2,857	50.6%	872	41.5%	234	51.5%	114	41.0%	17,828	45.3%
Seizure Disorders	244	0.8%	103	1.8%	33	1.6%	6	1.3%	7	2.5%	407	1.0%
Aditional FDA Approved Indications for Stimulant Use (anytime in 2021)												
Narcolepsy	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Exogenous Obesity	1,753	5.9%	412	7.3%	111	5.3%	28	6.2%	14	5.0%	2,430	6.2%
Binge Eating Disorder	208	0.7%	72	1.3%	11	0.5%	6	1.3%	2	0.7%	322	0.8%
Obstructive Sleep Apnea	25	0.1%	5	0.1%	0	0.0%	0	0.0%	0	0.0%	31	0.1%
Additional Data Points of Interest												
Foster Care	359	1.2%	228	4.0%	152	7.2%	11	2.4%	21	7.6%	817	2.1%
Index claim exceeded max dose	685	2.3%	21	0.4%	31	1.5%	14	3.1%	2	0.7%	757	1.9%
Index claim outside of recommended age range	107	0.4%	332	5.9%	57	2.7%	5	1.1%	18	6.5%	567	1.4%

The distribution of specific S or NS index drugs within each cohort can be found in **Table 3.** The volume of patients prescribed S agents far outweigh the number of patients on NS and the majority were preferred agents on the OHP preferred drug list. The utilization of NS agents is consistent with current guidelines, with

atomoxetine being most common in the NS only cohort. Guanfacine is the most common NS agent prescribed as the index drug in the S + NS cohort (44.0%) and NS + NS (47.1%) cohorts.

Table 3: Patient Count by Index ADHD Drug

	Stimulant Only		Non-Stimulant Only		Stimulant + Non-Stimulant		Stimulant + Stimulant		Non-Stimulant + Non-Stimulant		Total	
Patient Count by Index Drug	29,472		5,648		2,103		454		278		39,351	
Stimulants												
dextroamphetamine/amphetamine	16,592	56.3%			258	12.3%	153	33.7%	8	2.9%	17,245	43.8%
methylphenidate HCl	10,320	35.0%			480	22.8%	88	19.4%	19	6.8%	11,310	28.7%
lisdexamfetamine dimesylate	1,318	4.5%			82	3.9%	103	22.7%	2	0.7%	1,459	3.7%
dexmethylphenidate HCl	604	2.0%			77	3.7%	24	5.3%	4	1.4%	740	1.9%
dextroamphetamine sulfate	587	2.0%			16	0.8%	33	7.3%	1	0.4%	617	1.6%
methylphenidate	39	0.1%			2	0.1%	4	0.9%	0	0.0%	44	0.1%
amphetamine	8	0.0%			0	0.0%	1	0.2%	0	0.0%	8	0.0%
methamphetamine HCl	3	0.0%			0	0.0%	0	0.0%	0	0.0%	3	0.0%
amphetamine sulfate	1	0.0%			0	0.0%	0	0.0%	0	0.0%	1	0.0%
Non-Stimulants												
atomoxetine HCl			3,151	55.8%	113	5.4%	5	1.1%	75	27.0%	3,868	9.8%
guanfacine HCl			2,030	35.9%	925	44.0%	38	8.4%	131	47.1%	3,377	8.6%
clonidine HCl			463	8.2%	150	7.1%	5	1.1%	38	13.7%	675	1.7%
viloxazine HCl			4	0.1%	0	0.0%	0	0.0%	0	0.0%	4	0.0%
Also had a stimulant at any time	29,472	100.0%			2,103	100.0%	454	100.0%	110	39.6%	33,703	85.6%
Also had a non-stimulant at any time			5,648	100.0%	2,103	100.0%	118	26.0%	278	100.0%	9,879	25.1%

Safety Outcomes with ADHD Drug Use

Table 4 includes comorbidities of concern with ADHD drug use and frequency of ED visits and hospitalizations within the calendar year of 2021. A total of 7.7% of all individuals had a cardiovascular comorbidity and 5.2% had a substance use disorder diagnosis (**Appendix 4)** These were lower in the combination groups. There were a total of 8,778 ED visits and 952 hospitalizations. There did not appear to be higher rates of either in the combination groups compared to monotherapy. **Table 4** additionally includes the most common reasons for hospitalizations present for individuals with claims for ADHD drugs in 2021. The most common associated diagnosis for either ED visits or hospitalization was suicidal ideation, which was reported as a low percentage across all cohorts (range 0.4% to 2%) but was nearly twice as high in cohorts that utilized a non-stimulant as monotherapy or combination therapy when compared with those cohorts using stimulants only.

Table 4: Comorbidities of Concern and Frequency of Emergency Department Visit or Hospitalization

	Stimulant Only		Non-Stimulant Only		Stimulant + Non-Stimulant		Stimulant + Stimulant		Non-Stimulant + Non-Stimulant		Total	
N=	29,472		5,648		2,103		454		278		39,351	
Co-Morbidities Impacting Safety of Stimulant Use (anytime in 2021)												
Cardiovascular Disease	2,391	8.1%	448	7.9%	44	2.1%	28	6.2%	10	3.6%	3,041	7.7%
Substance Abuse Disorder	1,473	5.0%	430	7.6%	17	0.8%	24	5.3%	4	1.4%	2,033	5.2%
Negative Safety Outcomes within 2021 (on or after the index date)												
Death	28	0.1%	9	0.2%	0	0.0%	0	0.0%	0	0.0%	37	0.1%
ED Visit - All cause	6,271	21.3%	1,440	25.5%	466	22.2%	106	23.3%	78	28.1%	8,778	22.3%
Hospitalization - All cause	683	2.3%	164	2.9%	34	1.6%	12	2.6%	3	1.1%	952	2.4%
ED or Hospitalization with Diagnosis for:												
Suicidal ideation	297	1.0%	112	2.0%	43	2.0%	2	0.4%	5	1.8%	501	1.3%
Syncope	139	0.5%	35	0.6%	8	0.4%	0	0.0%	0	0.0%	192	0.5%
Abnormal Electrocardiogram	3	0.0%	0	0.0%	1	0.0%	0	0.0%	0	0.0%	4	0.0%

ADHD Medication Utilization

Figure 1 illustrates trends of FFS ADHD pharmacy claims for adults from 2016 to early 2022, adjusted to Per Member Per Month (PMPM) x1000. From 2016 to February 2022, the total utilization in adults has increased from 8.75 PMPM to 18.3 PMPM. **Figure 2** illustrates adult patients with FFS ADHD claims for adults from 2016 to early 2022 who have a diagnosis of substance use disorder present within the year prior of the ADHD drug index claim, which was previously reviewed in June 2019. While a gradual, increasing trend is noted from 2016 to 2020, the increasing trend begins to plateau in 2020 and ranges between 3.68 PMPM to 2.68 PMPM from January 2020 to December 2021. The orange and purple lines within each figure denotes when the SUPPORT Act legislation was signed and the beginning of the COVID-19 pandemic respectively.

Figure 1: FFS ADHD Medication Utilization by Month

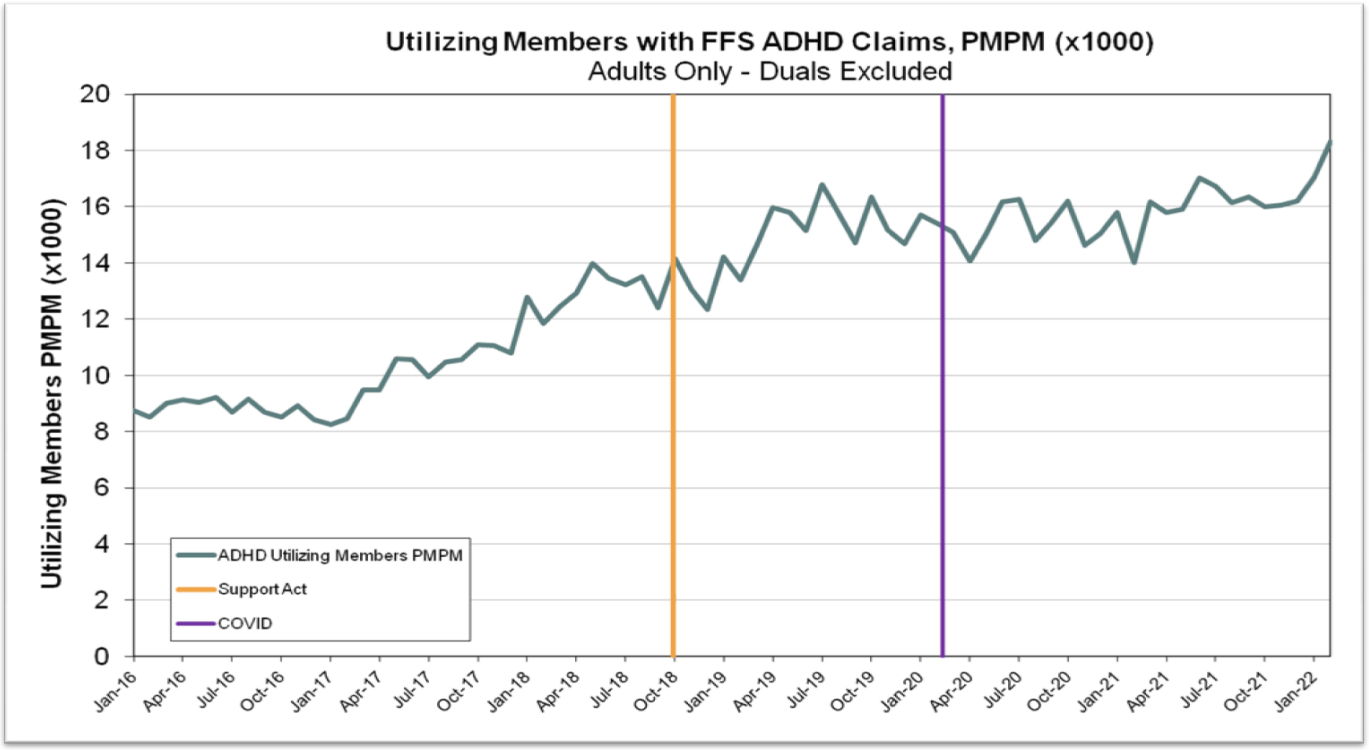

Figure 2: Adult Patients with FFS ADHD Claim by Month, With SUD Diagnosis in Year Prior

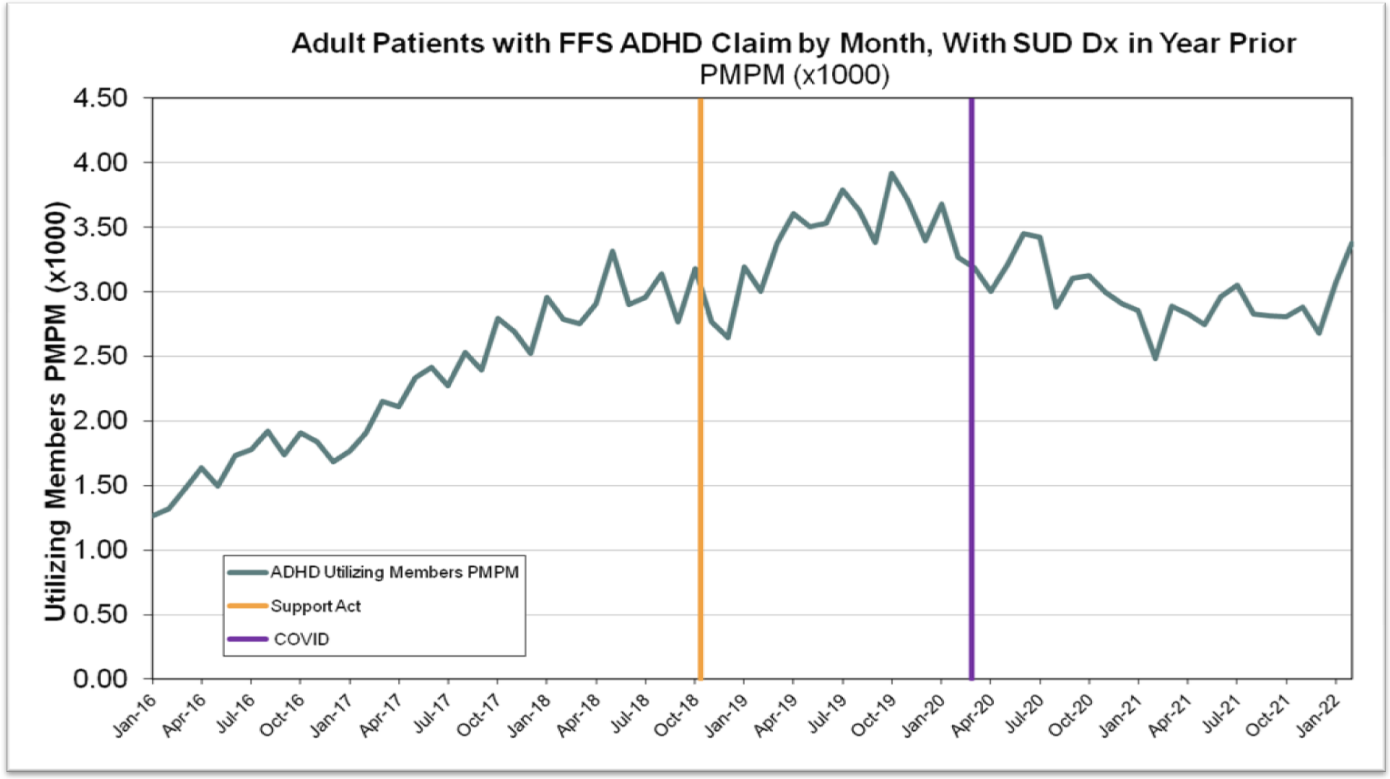

Table 5 depicts the frequency of ADHD drug index claim denials (FFS only) within the calendar year 2021. There was a total of 8083 patients with denied FFS claims for the year 2021. Of the denied claims, 79% had a claim paid within 30 days after the denial. The most common reasons for an initial claim denial that eventually had a claim paid within the next 90 days included brand formulation of the medication was required, the drug quantity per day limit was exceeded, a non-preferred medication was being requested, or the claim did not meet the age limit criteria set by the ADHD safety edit. Of the 15% of patients with denied claims and no paid claim within 90 days, a prior authorization was not requested for 83% of these patients. **Table 6** displays FFS ADHD prior authorization requests for the 2021 calendar year. Of the total PA requests submitted to FFS in 2021 for ADHD medications (n=2385), 93% were approved. While this is a high percentage of prior authorizations that were approved, it should be noted that not all denied claims resulted in a prior authorization request. Of the 7% of prior authorizations that were denied, 97% cited that the claim did not meet the criteria for approval established by the current ADHD safety edit (see **Appendix 1**), with 91% being considered not medically appropriate. A complete list of reason codes for denied prior authorization requests can be found in **Appendix 5.** Of note, a denied prior authorization request was allowed to have more than one reason code for denial.

Table 5: ADHD Drug Index Claim Denials by Patient

Patients with an ADHD Denied Claim	8,083	
└ ADHD claim paid within 30 days after the denial	6,357	79%
ADHD claim paid within 31-90 days after denial	500	6%
Never had an ADHD paid claim within 90 days of denial	1,226	15%
└ PA requested within 5 days before or 90 days after the denial	204	17%
PA denied within 5 days before or 90 days after the denial	72	6%
No PA requested	1,022	83%

Table 6: All ADHD Prior Authorization Requests for the 2021 Calendar Year

	Unique PAs	
Approved PAs	2208	93%
Denied PAs	117	7%
Total PAs	2385	100%

Discussion:

This analysis identified a total of 39,351 patients on Oregon Medicaid with a paid claim for an ADHD medication during the calendar year 2021. A total of 71.6% of these had a charted diagnosis of ADHD within 3 years prior to the index claim. Over half of individuals on an ADHD medication in the Medicaid population were 18 years of age or older (55.8%), which is consistent with the increasing trend of ADHD diagnoses within adults.[7,13] Within the study population, a total of 7.2% of individuals were utilizing combination therapy for treatment of ADHD, with the majority utilizing the S + NS combination. Of those utilizing a S + NS combination, 90.2% were ages 3-17, indicating that the utilization of these NS agents is consistent with the current guideline recommendations for ADHD treatment.[4,6]

The use of NS ADHD agents was more common by males, with the NS monotherapy, S+NS, and NS+NS cohorts being 54.1%, 74.2% and 74.5% male respectively. This trend of male gender being the most prevalent within each of the cohorts is consistent with the current trends reported within the literature, with the prevalence of ADHD between gender ranging from a male: female ratio of 2:1 to 10:1.[14] Of note, the male: female ratio was only consistently greater in the NS containing cohorts, and was 1:1 for the total population within this evaluation. It should be noted that no current guidelines recommend the use of multiple NS therapies concomitantly for the treatment of ADHD.[5,6,7]. The most common stimulants utilized within the S+NS cohort included methylphenidate and dextroamphetamine/amphetamine. The most commonly utilized NS within this cohort was guanfacine. The notable difference between NS agent utilization as monotherapy versus in combination with a stimulant may be explained by atomoxetine and viloxazine lacking FDA approval as adjunctive treatments for ADHD and viloxazine only receiving initial FDA approval to enter the market April 2021.

This analysis did not investigate the appropriateness of treatment of concomitant mental health disorders. However, a large proportion of individuals (45.3%) had a documented mental health disorder. While the impact upon ADHD from mental health disorders is not well defined, the presence of a mental health disorder can act as a confounder for the diagnosis for ADHD, as typical symptoms of depression and anxiety can mimic symptoms that are included in ADHD.[6]

Furthermore, stimulant therapy can further exacerbate the control of anxiety based upon the known side effect profile of this medication class. Current guidelines for the treatment of ADHD for adults recommend treatment of the comorbid conditions before ADHD treatment is initiated.[6]

Within the study population, 31.2% of individuals had an ADHD medication prescribed by a specialist. Those utilizing a stimulant agent only were more likely to have the medication prescribed by a non-specialist provider rather than a specialist (26.9%). While there is no current evidence available regarding a specific threshold for when a patient with ADHD should be referred to a specialist for management of ADHD, all available guidelines encourage referral to a specialist, especially in the presence of moderate to severe impairment with ADHD symptoms or the presence additional comorbid conditions including mental health disorders.[5,6,7] Of note, this evaluation did not assess the access to specialists or geographic distribution of those receiving therapy from a specialist versus non-specialist.

Overall, the incidence of emergency department visits or hospitalizations relating to potential negative adverse effects from ADHD medications was low. The most common reason for both emergency department visits and hospitalization was for suicidal ideation, which may be influenced by the high prevalence of concomitant mental health disorders seen within this population. The incidence of all cause hospitalization or emergency department visit was not significantly different between cohorts. The incidence of ED visits or hospitalization due to an overdose from a stimulant medication use was not able to be retrieved.

The trend of ADHD medication utilization in adults has continued to increase over time, from 8.75 PMPM to 18.3 PMPM from January 2016 to February 2022. In individuals with a diagnosis of substance use disorder present within the year prior to an FFS ADHD claim, the trend of utilizing members with FFS ADHD claims increased from 1.27 PMPM to 3.91 PMPM from January 2016 to October 2019. Afterwards, the trend began to decline from 3.91 PMPM to a low of 2.48 in February 2021, though it has recently begun to climb once more. The decrease in trend may be influenced by the passing of the SUPPORT Act in October 2018, which has been able to increase the availability of treatment for substance use disorder by allocating more funds to Medicaid programs and requiring all FDA approved medication assistance therapies to be covered.[15] The increase in access to these services in turn may have had an effect on the dependence of pharmacological agents for treatment of ADHD symptoms. Furthermore, the passing of the Support Act required states to increase monitoring requirements for prescribed opioids, which in turn leads to a higher likelihood of identifying and addressing patients with a substance use disorder. Additionally, another disruptor resulting in the downward trend could be related to the beginning of the COVID-19 pandemic in March of 2020, although the degree and method of this disruption is unknown.

The present ADHD Safety Edit criteria is aligned with the recommended dosing ranges per ADHD agent and the current recommendations for treatment of ADHD for children, adolescents, and adults.

Limitations:

The use of claims data limits the ability to directly correlate a patient's diagnosis with the medications being prescribed. When utilizing claims history data, the assumption is made that the medications of interest are being prescribed for the diagnosis of interest. Additionally, patients enrolled within coordinated care organizations may have missed diagnoses due to a time lag during the submission and processing of medical claims data. Potential discrepancies from use of provider taxonomy codes to determine provider type may cause underreporting of claims prescribed by what this review defined as a "specialist". Medication claims for specific combinations utilized (**Table 3**) were limited to the index agent and the distribution may not fully represent agent distribution if both agents in combination therapy were able included in table. This review additionally included data that coincided with the COVID-19 pandemic, which limited in-person learning and may directly affect the utilization of ADHD therapies for school-aged children and adolescents. Furthermore, with the increased burden placed

upon the health system from the COVID-19 pandemic, access to providers and the ability to maintain consistent follow-up with patients was also adversely affected.

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Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover ADHD medications only for diagnoses funded by the OHP and medications consistent with current best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs on the enforceable preferred drug list.
- Regimens prescribed outside of standard doses and age range (Tables 1 and 2)
- Non-standard polypharmacy (Table 3)

Covered Alternatives:

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

Table 1. FDA-approved and OHP-funded Indications.

	STIMULANTS		NON-STIMULANTS			
Indication	**Methylphenidate and derivatives****	**Amphetamine and derivatives**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**	**Viloxazine**
ADHD	**Age ≥6 years**	**Age ≥3 years**	**Age ≥6 years**	**Children age**	**Children age**	**Children age 6- 17 years only**

				6-17 years only	**6-17 years only**	
Narcolepsy	**Age ≥6 years**	**Age ≥6 years**	**Not approved**	**Not approved**	**Not approved**	**Not approved**

See **Table 2 for off-label methylphenidate IR dosing for age ≥ 4 years

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine ER	3		20 mg
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	4		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg

CNS Stimulant	serdexmethylphenidate/dexmethylphenidate	6		52.3 mg/ 10.4 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg for adjunctive therapy in ages 6-17 years and for monotherapy in ages 6-12 years 7 mg for monotherapy in ages 13-17 years
Non-Stimulant	viloxazine	6	17	400 mg

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

Table 3. Standard Combination Therapy for ADHD

Age Group	Standard Combination Therapy
Age <6 years*	**Combination therapy not recommended**
Age 6-17 years*	**1 CNS Stimulant Formulation (LA or IR) + Guanfacine LA** **1 CNS Stimulant Formulation (LA or IR) + Clonidine LA**
Age ≥18 years**	**Combination therapy not recommended**

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

* As recommended by the American Academy of Pediatrics 2011 Guidelines www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654

**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2011.

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 #3	**No:** Pass to RPh. Deny; not funded by OHP.

Approval Criteria		
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an approved FDA diagnosis defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9

Approval Criteria		
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *8/20 (DE); 5/19; 9/18; 5/16; 3/16; 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*

Implementation: *11/1/2018; 10/13/16; 7/1/16; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*

Appendix 2: Preferred Drug List

Generic	Brand	Route	Form	PDL
atomoxetine HCl	ATOMOXETINE HCL	ORAL	CAPSULE	Y
atomoxetine HCl	STRATTERA	ORAL	CAPSULE	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	ORAL	CPBP 50-50	Y
dexmethylphenidate HCl	FOCALIN XR	ORAL	CPBP 50-50	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	ORAL	TABLET	Y
dexmethylphenidate HCl	FOCALIN	ORAL	TABLET	Y
dextroamphetamine/amphetamine	ADDERALL XR	ORAL	CAP ER 24H	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	ORAL	CAP ER 24H	Y
dextroamphetamine/amphetamine	ADDERALL	ORAL	TABLET	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	ORAL	TABLET	Y
lisdexamfetamine dimesylate	VYVANSE	ORAL	CAPSULE	Y
lisdexamfetamine dimesylate	VYVANSE	ORAL	TAB CHEW	Y
methylphenidate	DAYTRANA	TRANSDERM	PATCH TD24	Y
methylphenidate HCl	METHYLPHENIDATE HCL CD	ORAL	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	ORAL	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL	ORAL	TABLET	Y
methylphenidate HCl	RITALIN	ORAL	TABLET	Y
clonidine HCl	CLONIDINE HCL ER	ORAL	TAB ER 12H	V
guanfacine HCl	GUANFACINE HCL ER	ORAL	TAB ER 24H	V
guanfacine HCl	INTUNIV	ORAL	TAB ER 24H	V
viloxazine HCl	QELBREE	ORAL	CAP ER 24H	V
amphetamine	ADZENYS ER	ORAL	SUS BP 24H	N
amphetamine	AMPHETAMINE	ORAL	SUS BP 24H	N
amphetamine	DYANAVEL XR	ORAL	SUS BP 24H	N
amphetamine	ADZENYS XR-ODT	ORAL	TAB RAP BP	N
amphetamine sulfate	EVEKEO ODT	ORAL	TAB RAPDIS	N
amphetamine sulfate	AMPHETAMINE SULFATE	ORAL	TABLET	N
amphetamine sulfate	EVEKEO	ORAL	TABLET	N
dextroamphetamine sulfate	DEXEDRINE	ORAL	CAPSULE ER	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	ORAL	CAPSULE ER	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	ORAL	SOLUTION	N
dextroamphetamine sulfate	PROCENTRA	ORAL	SOLUTION	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	ORAL	TABLET	N
dextroamphetamine sulfate	ZENZEDI	ORAL	TABLET	N

dextroamphetamine/amphetamine	MYDAYIS	ORAL	CPTP 24HR	N
methamphetamine HCl	DESOXYN	ORAL	TABLET	N
methamphetamine HCl	METHAMPHETAMINE HCL	ORAL	TABLET	N
methylphenidate	COTEMPLA XR-ODT	ORAL	TAB RAP BP	N
methylphenidate HCl	ADHANSIA XR	ORAL	CPBP 20-80	N
methylphenidate HCl	METHYLPHENIDATE ER (LA)	ORAL	CPBP 50-50	N
methylphenidate HCl	METHYLPHENIDATE LA	ORAL	CPBP 50-50	N
methylphenidate HCl	RITALIN LA	ORAL	CPBP 50-50	N
methylphenidate HCl	JORNAY PM	ORAL	CPDR ER SP	N
methylphenidate HCl	APTENSIO XR	ORAL	CSBP 40-60	N
methylphenidate HCl	METHYLPHENIDATE ER	ORAL	CSBP 40-60	N
methylphenidate HCl	METHYLIN	ORAL	SOLUTION	N
methylphenidate HCl	METHYLPHENIDATE HCL	ORAL	SOLUTION	N
methylphenidate HCl	QUILLIVANT XR	ORAL	SU ER RC24	N
methylphenidate HCl	QUILLICHEW ER	ORAL	TAB CBP24H	N
methylphenidate HCl	METHYLPHENIDATE HCL	ORAL	TAB CHEW	N
methylphenidate HCl	CONCERTA	ORAL	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	ORAL	TAB ER 24	N
methylphenidate HCl	RELEXXII	ORAL	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	ORAL	TABLET ER	N
serdexmethylphen/dexmethylphen	AZSTARYS	ORAL	CAPSULE	N

Appendix 3: Indications that Co-Exist or Mimic ADHD

Mental Health Disorders

- Generalized Anxiety disorder
- Social Anxiety Disorder
- Depression
    - Depressive episode
    - Recurrent depressive disorder
    - Bipolar affective disorder
    - Other mood disorders
    - Dysthymia

Developmental Disorders

- Speech and Language disorders
- Autistic disorder
- Learning disability

Seizure disorders

- Epilepsy
- Status epilepticus

Miscellaneous

- Fetal alcohol syndrome
- Fragile X syndrome
- Oppositional defiant disorder
- Obstructive sleep apnea
- Restless leg syndrome
- Chronic fatigue syndrome

Appendix 4: Cardiovascular Comorbidities and Substance Use Disorders of Interest

Cardiovascular Diseases

- Hypertension
- Angina pectoris
- Chronic ischemic heart disease
- Complications and ill-defined descriptions of heart disease
- Sequelae of cerebrovascular disease
- Peripheral artery disease
- Myocardial Infarction

Substance Use Disorders

- Sedative, Hypnotic, and Anxiolytic Use Disorder
- Alcohol Use Disorder
- Opioid Use Disorder
- Methamphetamine Use Disorder

Appendix 5: Denied Prior Authorizations by Reason Code

ALL ADHD PA Requests

Calendar year 2021

	Unique Prior Authorizations	
Denied PAs*	177	
ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) SAFETY EDIT	172	97%
After review of the documentation provided, this request was determined not medically appropriate per OAR 410-121-0040(2)(a) and (b), and 410-121-0040(3), 410-141-3830 (1) and (2), 410-141-3820 (1)(a-d), 410-120-1320(2), and 410-120-0000(145)(a - e)&(	161	91%
The drug requested is not FDA approved for your condition, is considered experimental or investigational and is not covered per OAR 410-120-1200(2)(i)	9	5%
DISPENSE AS WRITTEN-1 (DAW-1) REIMBURSEMENT RATE	7	4%
DMAP does not allow payment for services that are considered similar or identical to items that achieve the same purpose and result in the same anticipated outcome at a lower cost per OAR 410-121-0040(2)(a) and (b), 410-121-0040(3), and 410-120-1200(2)(n)	6	3%
The treatment for your condition is not a covered service on the Oregon Health Plan per OAR 410-121-0040(2)(a) and (b), and 410-121-0040(3), 410-141-3830 (1) & (2) , and OAR 410-141-3820 (1)(c) (10) and (11).	5	3%

*= Denied prior authorizations can include more than one reason code

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Drug Class Update with New Drug Evaluation: Diuretics

Date of Review: June 2022

Date of Last Review: June 2020
Dates of Literature Search: 11/22/2019 – 03/31/2022
Brand Name (Manufacturer): Kerendia® (Bayer)
Dossier Received: Yes

Generic Name: finerenone

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

Purpose for Class Update:

- Evaluate new comparative evidence for the effectiveness and safety of diuretics for the prevention of mortality and cardiovascular disease (CVD) in patients with hypertension (HTN), heart failure (HF) and chronic kidney disease (CKD).
- Evaluate the data supporting the efficacy and safety of finerenone and determine its appropriate place in therapy.

Research Questions:

1. Is there any new comparative evidence for diuretics in reducing mortality or CV outcomes in patients treated for HTN, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), or CKD?
2. Is there any new comparative evidence for the safety of diuretics in patients treated for HTN, HFpEF, HFrEF, or CKD?
3. What are the comparative benefits and harms of finerenone in patients with CKD?

Conclusions:

- There is low quality evidence evaluating aldosterone antagonists on clinical outcomes in patients with CKD. There is very low-quality evidence of an uncertain effect on kidney failure (relative risk [RR] 3.00; 95% confidence interval [CI] 0.33 to 27.65) and moderate level evidence of an increased risk of hyperkalemia (RR 2.17; 95% CI 1.47 to 3.22; number needed to harm [NNH] 41).[1]
- There is moderate quality evidence of no significant effect on CV mortality with mineralocorticoid receptor antagonists (MRAs) compared to placebo or standard of care (RR 0.90; 95% CI 0.74 to 1.11; 3 studies) or all-cause mortality (RR 0.91; 95% CI 0.78 to 1.06; 5 studies) but a significant reduction in heart failure hospitalizations with MRAs (11% vs. 14%; RR 0.82; 95% CI 0.69 to 0.98; number needed to treat [NNT] 41).[2] There was high quality evidence based on six studies of an increased risk of hyperkalemia with MRAs compared to placebo or standard of care (16% vs. 8%; RR 2.11; 95% CI 1.77 to 2.51).[2]
- There is moderate quality evidence that finerenone reduces adverse renal outcomes compared to placebo in patients with CKD and type 2 diabetes (T2DM) (17.8% vs. 21.1%; hazard ratio [HR]0.82; 95% CI 0.73-0.93; NNT 29 over 3 years) on background therapy with an angiotensin converting enzyme inhibitor

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(ACEI) or angiotensin receptor blocker (ARB).[3] This was primarily driven by a reduction in sustained estimated glomerular filtration rate (eGFR) and renal failure.

- There is moderate quality evidence that finerenone increases the risk of hyperkalemia-related adverse events compared to placebo in patients with CKD and T2DM (18.3% vs. 9.0%, respectively), despite being a nonsteroidal aldosterone antagonist.[3]
- There is moderate quality evidence that finerenone modestly decreases a composite of time to CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or HF hospitalizations in patients with CKD and T2DM over a median duration of 3.4 years compared to placebo (12.4% vs. 14.2%; HR 0.87; 95% CI 0.76 to 0.98; p=0.03 NNT 56).[4] Results were primarily driven by a reduction in HF hospitalizations. There was no difference in MI or stroke between the groups.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended at this time.
- Evaluate comparative costs in executive session.
- Maintain finerenone as non-preferred on the PDL and include prior authorization to limit use to patients with CKD and T2DM on background therapy with an ACE-I and ARB.

Summary of Prior Reviews and Current Policy

- High quality evidence suggests thiazide-type diuretics should continue to be recommended as a first-line option for hypertension due to benefit at reducing mortality and stroke. High-dose diuretic regimens have been shown to reduce mortality and stroke (moderate quality evidence), while low-dose regimens have been found to reduce mortality, stroke, coronary heart disease, and total CV events (high quality evidence). Evidence for use of "low" dose thiazide-type diuretics is stronger than "high" dose thiazide-type diuretics.[5-10] Low doses are less than chlorthalidone (CTDN) 50 mg per day, indapamide (INDAP) 5 mg per day or hydrochlorothiazide (HCTZ) 50 mg per day.[5] High doses are CTDN 50 mg or more each day, INDAP 5 mg more each day, or HCTZ 50 mg or more each day.[5]
- Thiazide-like diuretics [e.g. CTDN and INDAP] are preferred over thiazide diuretics [e.g HCTZ] by certain high quality guidelines for the treatment of HTN,[7-9] while another guideline has no preference between the two agent types.[10] These recommendations were all based on the same body of literature. High quality randomized controlled trials (RCTs) of CTDN and INDAP show cardiovascular benefits as well as pharmacokinetic superiority in the form prolonged half-life compared to HCTZ, but there is insufficient evidence to *directly* compare these agents for efficacy and safety.[7-12]
- Loop diuretics are recommended for edema in HF but they have not been shown to reduce mortality, and there is insufficient evidence to differentiate between agents.[13-17] (low quality evidence)
- There is high quality evidence that aldosterone receptor antagonists (spironolactone or eplerenone), unless contraindicated, reduce morbidity and mortality when added to evidence-based HF therapy in patients with systolic HF and reduced LVEF. There is insufficient evidence comparing spironolactone with eplerenone.
- There is moderate quality evidence that adding spironolactone to patients with systolic HF and preserved LVEF reduces hospitalizations; however, spironolactone does not yield any additional morbidity or mortality benefit.

Background:
The diuretics class encompasses multiple sub-classes of agents which differ mechanistically.[18] The most familiar agents are loop diuretics, thiazide-type diuretics, and potassium-sparing diuretics.[18] Potassium sparing diuretics are divided into agents which directly block sodium channels without antagonism of mineralocorticoid receptor (e.g., amiloride) and agents which function with direct inhibition of the mineralocorticoid receptor (e.g., spironolactone).[18] Additionally, there are a number of miscellaneous medications such as carbonic anhydrase inhibitors, osmotic diuretics, or vasopressin antagonists which function with diuretic properties; however, their clinical use varies significantly from disease states commonly treated with loop, thiazide-type, and potassium sparing agents.[18] These miscellaneous agents were excluded for the purpose of this review.

Loop, thiazide-type, and potassium-sparing diuretics are most commonly used for hypertension and HF.[9,15] Elevated blood pressure increases risk of complications such as MI, stroke, HF, and kidney disease.[9] It was the leading cause of death and disability-adjusted life years worldwide in 2010.[9] Hypertension has been the cause of more CV deaths than any other modifiable risk factor.[9] Risk for developing HTN increases with age and is more common in African-Americans than other races.[9] Diuretics, with thiazide-type agents being used most commonly for HTN, work by causing a net excretion of water, resulting in decreased blood pressure.[18] Depending upon comorbidities and electrolyte levels, different diuretic sub-types can be combined[9], though combinations require close monitoring to avoid adverse effects such as electrolyte abnormalities, dehydration, and acute kidney injury.[18]

Heart failure is a clinical syndrome involving structural or functional impairment of ventricular filling or ejection of blood.[16] It primarily manifests with symptoms of dyspnea, fatigue, and fluid retention.[16] There is a 20% lifetime risk for development of HF in Americans 40 years of age and older, and risk increases with increasing age.[16] Diuretics, primarily loop agents, find utility in reducing symptoms of fluid overload in heart failure.[16] Potassium-sparing agents with mineralocorticoid inhibition have also been shown to improve outcomes,[16] likely due to a reduction of the adverse effects of excess aldosterone on the heart.[18]

Progression from CKD to kidney failure is rising due to increasing prevalence of diabetes and HTN worldwide. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are the standard of care to slow progression of CKD in patients with proteinuria.[19] More recently, sodium-glucose co-transporter-2 (SLGT2) inhibitors have shown to reduce the risk of development of microalbuminuria or progression to overt nephropathy.[20] Furthermore, aldosterone blockade may reduce the development of hypertensive kidney disease, vascular injury, myocardial fibrosis, and glomerulosclerosis in those with CKD.[21] However, many of the steroidal aldosterone antagonists are limited in use due to the risk of hyperkalemia and gynecomastia. Finerenone is a nonsteroidal mineralocorticoid receptor antagonist (MRA) that is highly selective for the mineralocorticoid receptor.[21] It was FDA approved in 2021 to reduce the risk of eGFR decline, end stage renal disease (ESRD), CV death, nonfatal MI, and hospitalization for HF in adults with CKD associated with T2DM.

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

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

Systematic Reviews:
After review, 13 systematic reviews were excluded due to poor quality[22-29] (e.g., indirect network-meta analyses), wrong study design of included trials[30-32] (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied[33,34] (e.g., non-clinical). The additional four are summarized below.

Chronic Kidney Disease

- A Cochrane Collaboration systematic review evaluated the effects of aldosterone antagonists, including steroidal (spironolactone and eplerenone) and non-steroidal (finerenone), in combination with ACEI or ARB in adults with CKD and proteinuria on kidney failure, major CV events, death, and adverse events.[1] There were 44 studies (n=5745) identified that were included in the review with follow-up for generally 3 to 12 months.[1] Twenty-three studies included participants who had kidney disease due to diabetes. The majority used the non-selective aldosterone antagonist, spironolactone, and 3 studies used finerenone, the non-steroidal mineralocorticoid antagonist. Risk of bias was unclear or high in many studies due to unclear allocation concealment, unclear blinding of outcome assessors, incomplete outcome reporting, and inadequate random sequence generation. None of the studies were powered to detect differences in clinical outcomes including death, or major CV events. There was very low-quality evidence of uncertain effects on kidney failure (RR 3.0; 95% CI 0.33 to 27.65; 2 studies) with aldosterone antagonists plus ACEI/ARB compared to placebo or standard care.[1] There was moderate quality evidence that aldosterone antagonists increase risk of hyperkalemia (RR 2.17; 95% CI 1.47 to 3.22; 17 studies; NNH 41) compared to placebo or standard of care.[1] There was low quality evidence of an uncertain outcome on death, CV events, and proteinuria. There was low quality evidence that aldosterone antagonists may reduce mean eGFR by 3.0 ml/min (95% CI 5.51 to 0.49) compared to placebo or standard of care.[1] There was not enough evidence to make comparisons to other active treatments on clinical outcomes, including diuretics, calcium channel blockers, or ACEI.

- Another Cochrane Collaboration systematic review evaluated the benefits and harms of aldosterone antagonists in comparison to placebo or standard care in people with CKD requiring hemodialysis (HD).[35] A literature search for RCTs, cross-over trials, and quasi-RCTs in patients with end stage renal disease was completed. The primary outcomes were death, CV death, CV events, and hyperkalemia. A total of 16 studies were included (n=1446). Fourteen of these studies included spironolactone at doses of 12.5 to 50 mg/day and one study evaluated eplerenone 50 mg/day. [35] Most studies had an unclear or low risk of bias. However, six studies had a high risk of attrition bias. Overall, there was moderate quality evidence that compared to placebo or standard care aldosterone antagonists probably reduce the risk of all-cause death (RR 0.45; 95% CI 0.30 to 0.67; 9 RCTs; NNT 14), CV death (RR 0.37; 95% CI 0.22 to 0.64; 6 RCTs; NNT 16), and CV events (RR 0.38; 95% CI 0.18 to 0.76; 3 RCTs; NNT 12).[35] There was low quality evidence that in those with CKD requiring HD, aldosterone antagonists may not significantly increase the risk of hyperkalemia (RR 1.41; 95% CI 0.72 to 2.78; 9 studies; NNH 27). [35]

Chronic Heart Failure with Preserved Ejection Fraction

- A Cochrane Collaboration systematic review was done to determine if beta blockers, ACEIs, ARBs, and MRAs are beneficial in people with HFpEf. [2] For the purpose of this review, only evidence including MRAs will be summarized. A total of 13 studies evaluating aldosterone antagonists were included (n=4459). Eight studies included placebo as a comparator and five included standard of care. Ten of the studies evaluated spironolactone and the mean age of participants ranged from 54 to 80 years. Most studies had unclear (selection bias and reporting bias) or low risk of bias. There was moderate quality evidence of no significant effect on CV mortality with MRAs compared to placebo or standard of care (RR 0.90; 95% CI 0.74 to 1.11; 3 RCTs) or all-cause mortality (RR 0.91; 95% CI 0.78 to 1.06; 5 studies) but a significant reduction in HF hospitalizations with MRAs (11% vs. 14%; RR 0.82; 95% CI 0.69 to 0.98; NNT 41). There was high quality evidence based on six studies of an increased risk of hyperkalemia with MRAs compared to placebo or standard of care (16% vs. 8%; RR 2.11; 95% CI 1.77 to 2.51).

Hypertension

- A Cochrane Collaboration systematic review was conducted to determine if there are differences in clinical outcomes between initiating monotherapy for the treatment of HTN versus initiating combination therapy.[36] An initial 14 RCTs were identified. Subgroup data focusing on treatment initiation were requested from study authors and therefore only four studies were included in the meta-analysis. Overall risk of bias was low in all 4 studies. However, other bias was unknown since data came from subgroups of participants and the outcome of interest was not the primary outcome in any of the included trials. [36] The total number of participants (n=568) and events was very low, limiting ability to make conclusions about clinical outcomes. Therefore, despite low risk of bias, the overall certainty of the evidence was very low. There was very low-quality evidence of no difference in overall mortality (RR 1.35; 95% CI 0.08 to 21.72), CV mortality (RR not estimable), CV events (RR 0.98; 95% CI 0.22 to 4.41), serious adverse events (RR 0.77; 95% CI 0.31 to 1.92) or withdrawals due to adverse events (RR 0.85; 95% CI 0.53 to 1.35). [36] The authors concluded the quality of evidence is very low and no conclusions can be made about the relative efficacy of monotherapy versus combination therapy for the initial treatment of primary HTN. [36]

New Guidelines:
After review, 1 guideline was excluded due to limited applicability[37].

High Quality Guidelines:

Heart Failure

The European Society of Cardiology (ESC) updated guidelines for the treatment of acute and chronic HF in 2021, with a focus on diagnosis and treatment.[38] The guidelines continue to recommend an ACEI or angiotensin receptor-neprilysin inhibitor, beta-blocker, MRA and a sodium-glucose co-transporter 2 (SLGT2) inhibitor (dapagliflozin or empagliflozin) in all patients with HFrEF unless contraindicated or not tolerated to reduce the risk of HF hospitalization and death (Class I, Level A). The evidence-based drugs and doses included for an MRA include spironolactone target dose of 50 mg daily or eplerenone target dose of 50 mg daily. Caution should be used when MRAs are used in patients with impaired renal function and in those with serum potassium concentrations > 5.0 mmol/L. There is also a Class I recommendation based on Level C evidence that diuretics are recommended in patients with HFrEF to reduce HF symptoms, improve exercise capacity and reduce HF hospitalizations. The guidelines comment that the evidence for diuretics is poor and their effects on morbidity and mortality have not been studied in RCTs.

For those with HF and mildly reduced ejection fraction (HFmEF) (including those with ejection fraction of 41-49%), there is a Class IIb recommendation based on Level C evidence to consider an MRA to reduce the risk of HF hospitalization and death. This is based on a retrospective analysis of the TOPCAT trial demonstrating a reduction in hospitalizations and CV Death in those with HFmEF. Due to no treatment showing a reduction in mortality and morbidity with HFpEF, the guidelines give no specific recommendations for use of MRAs despite a possible decrease in hospitalizations.

Blood pressure in Chronic Kidney Disease

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the management of blood pressure in CKD was published in 2021.[19] The updated guidelines include a weak recommendation based on moderate quality evidence that adults with HTN and CKD be treated to a target systolic blood pressure (SBP) of < 120 mm Hg, when tolerated. The guidelines include a strong recommendation for starting an ACEI or ARB for those with HTN, CKD and severely increased albuminuria and a weak recommendation for moderately increased albuminuria. The following additional recommendations are included regarding diuretic therapy:

- MRAs are effective for management of refractory HTN but may cause hyperkalemia or a reversible decline in kidney function (Practice Point)

Hypertension

In 2022, National Institute for Health and Care Excellence (NICE) updated the 2019 guidelines for the diagnosis and management of hypertension in non-pregnant adults, including those with T2DM.[39] Treatment is recommended in stepwise fashion, and is based on various age, race, and comorbidity factors. For step 1 therapy, initiation of an ACEI or ARB is recommended for patients with T2DM or for non-African/African-Caribbean patients who are under 55 years of age. [39] See **Table 1** before for full details of step therapy. For those initiating or changing diuretic treatment, thiazide-like agents, such as indapamide, are preferred over conventional thiazide diuretics of hydrochlorothiazide. Patients who are well controlled on conventional thiazides should continue those agents.

Table 1: NICE Guidelines Step Therapy for Hypertension[39]

Patient Characteristics	**Step 1**	**Step 2**	**Step 3**	**Step 4**
Type 2 diabetes mellitus • Regardless of age or family origin	ACEI or ARB	CCB or thiazide-like diuretic	Combination of: (ACEI or ARB) AND CCB AND thiazide-like diuretic	If potassium 4.5 mEq/L or less consider: Low-dose spironolactone Monitor potassium and use caution in patients with reduced renal function. If potassium 4.5 mEq/L or higher consider: Alpha-blockers or beta-blockers
Age 55 or older • **NOT** African or African-Caribbean origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic		
Age 55 and older • African or African-Caribbean Origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic **Consider ARB in preference to ACEI*		
Age under 55 years • **NOT** African or African-Caribbean origin	ACEI or ARB	ACEI or ARB or thiazide-like diuretic		
Age under 55 years • African or African-Caribbean Origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic **Consider ARB in preference to ACEI*		
Clinical suspicion of heart failure	Consider thiazide-like diuretic, then follow chronic heart failure guidelines			

New Formulations:
In June, 2021 a new once daily formulation of torsemide (Soaanz®) was FDA approved for the treatment of edema associated with heart failure and renal disease.[40] It is dosed once daily and has a diuretic effect lasting about 6 to 8 hours.

Randomized Controlled Trials:
A total of 44 citations were manually reviewed from the initial literature search. After initial review, 19 RCTs were selected for more detailed evaluation for inclusion. After further review, 13 citations were excluded because of wrong study design (e.g., observational)[41-46], comparator[47-50] (e.g., no control or placebo-controlled), or outcome studied[51-53] (e.g., non-clinical). The primary approval study for finerenone is included in Table 4. The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Filipattos, et al.[54] DB, PC, PG, RCT	Finerenone vs. placebo	Adults with T2D and CKD (n=5734)	New onset atrial fibrillation	Finerenone: 82 (3.2%) Placebo: 117 (4.5%) HR 0.71; 95% CI 0.53-0.94 P=0.016	Secondary analysis of a pre-specified outcome of the FIEDLIO-DKD trial
Agarwal, et al.[55] Pooled analysis or 2 RCTs	Finerenone vs. placebo	Adults with T2D and CKD (n=13,026)	Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure	Finerenone: 825 (12.7%) Placebo: 939 (14.4%) HR 0.86; 95% CI 0.78 to 0.95 P=0.018	Pooled analysis of FIEDELIO-DKD and FIGARO-DKD studies
Filippattos, et al.[56] DB, PC, PG, RCT	Finerenone vs. placebo	Adults with T2D and CKD (n=7352)	New onset heart failure	Finerenone: 65 (1.9%) Placebo: 95 (2.8%) HR 0.68; 95% CI 0.50-0.93 P=0.0162	Secondary analysis of a pre-specified outcome of the FIGARO-DKD trial
Pitt, et al.[4] Phase III, DB, PC, MC, RCT	Finerenone vs. placebo Mean follow up of 3.4 years	Adults with T2D and CKD (n=7437)	Time to CV death non-fatal MI, non-fatal stroke, or hospitalization for heart failure	Finerenone: 458 (12.4%) Placebo: 519 (14.2%) HR 0.87; 95% CI 0.76 to 0.98 P=0.03	FIGARO-DKD trial Composite outcome results primarily driven by heart failure hospitalizations
Abbreviations: CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; DB: double-blind; HR: hazard ratio; MC: multicenter; PC: placebo controlled; PG: parallel group; RCT: randomized controlled trial; T2D: type 2 diabetes					

NEW DRUG EVALUATION:

See **Appendix 4** 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:
Finerenone is a non-steroidal mineralocorticoid receptor antagonist (MRA) FDA approved to reduce the risk of sustained eGFR decline, end stage kidney disease (ESRD), CV death, non-fatal MI, and hospitalization for HF in adult patients with CKD associated with type 2 diabetes.[57] It was FDA approved based on one placebo-controlled, double-blind, RCT evaluating the efficacy and safety of finerenone (FIDELIO-DKD) (**Table 4**) in adults with type 2 diabetes and CKD on maximum dose of an ACE-I or ARB. [3] In this trial, CKD was defined as moderately elevated albuminuria (urinary albumin to creatinine ratio [UACR] 30-300 mg/g), eGFR of 25 to 60 ml/min and a history of diabetic retinopathy, or severely elevated albuminuria (UACR ≥ 300 mg/g) and eGFR 25-75 ml/min. The primary outcome was a time to event analysis of a composite of kidney failure (defined as end stage kidney disease or an eGFR of less than 15 ml/min), sustained decrease of at least 40% in eGFR from baseline, or death from renal causes.

The trial consisted of a 4–16-week run-in period to allow for optimization of standard of care (ACEI or ARB) and a 2-week screening period. Of the 13,911 patients initially enrolled, only 5,734 were randomized.[3] Over half (59%) patients were excluded during the run-in period mostly due to not meeting eligibility criteria. There was no further information on which eligible criteria were not met. Almost all (~98%) patients were on an ACEI or ARB at baseline. However only 22% of patients on an ACEI and 55% of an ARB were on maximum recommended doses. Very few patients (4.6%) were on background therapy with a SGLT-2 inhibitor and over half (56.6%) were on either a loop or thiazide diuretic. Most patients (87.5%) had significant albuminuria (UACR ≥ 300 mg/g) and the mean eGRF was 44.3 ml/min.[3] There were very few subjects with an eGFR < 25 ml/min (2.4%).

After a median follow up of 2.6 years, there was a reduction in the risk of the primary composite outcome with finerenone compared to placebo (17.8% vs. 21.1%; HR 0.825; 95% CI 0.732 to 0.928; p=0.0014).[3] This was largely driven by a reduction in sustained decrease in eGFR and kidney failure. There were very few renal deaths that occurred (<0.1%). This difference was seen starting around 12 months. This difference was less than the absolute benefit reported in clinical trials of SLGT2 inhibitors and there is insufficient evidence evaluating use of finerenone in addition to an SLGT2 inhibitor. There was also a very modest reduction in a composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF (13.0% vs. 14.8%; HR 0.86; 95% CI 0.75 to 0.99; p=0.04), with the largest effect seen in hospitalizations due to HF.

This trial had extensive inclusion and exclusion criteria and a run-in and screening period that excluded a significant number of patients. This decreases external validity and limits the study population to those most likely to benefit and most likely to tolerate the medication. Additionally, the trial was funded by the manufacturer who was significantly involved in the study design process. Lastly, there is unclear attrition bias due to high levels of attrition overall, but similar between the two groups (~29%).

A similarly designed trial (FIGARO-DKD) was published after FDA approval (**Table 2**) and found a modest benefit in a composite outcome of time to CV death, non-fatal MI, non-fatal stroke, or HF hospitalizations in patients with CKD and T2DM over a median duration of 3.4 years with finerenone compared to placebo (12.4% vs. 14.2%; p=0.03).[4] Patients in this trial had more moderate CKD (stage 2-4 with moderate albuminuria, or stage 1-2 with severe albuminuria) with a

mean eGFR of 69 ml/min compared to 44 ml/min in the previous trial. Results were primarily driven by a reduction in heart failure hospitalizations. There was no difference in MI or stroke between the groups.

Clinical Safety:

In the primary clinical study, serious adverse events occurred in 31.9% of patients on finerenone and 34.3% on placebo. More patients taking finerenone discontinued treatment due to adverse events than those in placebo (7.3% vs. 5.9%, respectively) and the most common reason for discontinuation was hyperkalemia. Finerenone is contraindicated with concomitant strong CYP3A4 inhibitors, due to a potential increase in area under the curve up to 531% seen in pharmacokinetic studies. FDA labeling also includes a warning for hyperkalemia and a contraindication in those with adrenal insufficiency. There was a higher rate of hyperkalemia related adverse effects with finerenone compared to placebo (18.3% vs. 9.0%), a higher rate of discontinuation due to hyperkalemia (2.3% vs. 0.9%), and more hospitalizations due to hyperkalemia (1.4% vs. 0.3%). It is not recommended to initiate therapy if serum potassium is greater than 5.0 mEq/L or if eGFR is < 25 ml/min. Other adverse reactions that occurred in more than 1% of patients on finerenone and more frequently than placebo include hypotension (4.8% vs. 3.4%) and hyponatremia (1.4% vs. 0.7%). Gynecomastia was uncommon in both arms (<0.5%). There are no data on the use of finerenone in pregnancy or lactation.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Cardiovascular death
2) End stage kidney disease
3) All-cause mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Time to first occurrence of the composite endpoint of onset of kidney failure, sustained decrease of eGFR ≥ 40% from baseline, or renal death

Table 3. Pharmacology and Pharmacokinetic Properties.[57]

Parameter	
Mechanism of Action	Blocks mineralocorticoid receptor mediated sodium reabsorption and overactivation in both epithelial and nonepithelial tissues. Mineralocorticoid receptor overactivation is thought to contribute to fibrosis and inflammation. Finerenone is nonsteroidal and has no affinity for androgen, progesterone, estrogen and glucocorticoid receptors.
Oral Bioavailability	44%
Distribution and Protein Binding	Volume of distribution: 52.6 L; Protein binding 92%
Elimination	80% in urine (<1% unchanged) and 20% in feces
Half-Life	23 hours
Metabolism	CYP3A4 (90%) and CYP2C8 (10%)

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
FIDELIO-DKD[3] Phase 3, DB, PC, MC, RCT	1. Finerenone 10-20 mg daily 2. Placebo Duration: 3 years On background ACEI or ARB	Demographics: Mean Age 66 y/o 70% male 63% white 19.8% Asian 3.5% Black ACEI 34.2% ARB 65.7% Key Inclusion Criteria: • ≥ 18 y/o • T2DM • CKD • On ACEI or ARB • K ≤ 4.8 mEq/L Key Exclusion Criteria: • Non-diabetic kidney disease • HgA1C > 12% • BP ≥ 160/100 • NYHA Class II-IV HF • Addison's disease • On potassium sparing diuretic • Strong CYP3A4 inducers or inhibitors • ACS or stroke in last 30 days • Child-Pugh C hepatic dysfunction	ITT: 2866 2868 FAS: 2833 2841 PP: 2011 2013 Attrition: 822; 29% 828, 29%	Primary Endpoint: Composite of kidney failure, a sustained decrease of ≥40% in eGFR, or death from renal causes 1. 504 (17.8%) 2. 600 (21.1%) HR 0.82; 95% CI 0.73-0.93 P = 0.001 Secondary Endpoints: Composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for heart failure 1. 367 (13%) 2. 420 (14.8%) HR 0.86; 95% CI 0.75-0.99 P = 0.04 All-cause mortality 1. 219 (7.7%) 2. 244 (8.6%) HR 0.90; 95% CI 0.75 to 1.01 P = 0.24	ARR 3.4% / NNT 29 ARR 1.8% / NNT 56 NS	Discontinuations due to adverse events: * 1. 207 (7.3%) 2. 168 (5.9%) RD 1.5% (95% CI 0.1% to 2.7%) Hyperkalemia related effects* 1. 18.3% 2. 9.0% *p-values not reported	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization managed centrally using an interactive voice and web response system. Groups similar at baseline. Performance Bias: low; double-blinded, double dummy design. Detection Bias: low: clinical event committee who adjudicated outcome events was blinded to study treatment assignment. Attrition Bias: unclear; high overall rates of attrition, but similar between groupsand for similar reasons (adverse events, physician choice, death and withdrew). Efficacy analysis done on FAS with ~1% due to study violations. Reporting Bias: low; study protocol available and all outcomes reported on. Other Bias: high; study funded by Bayer, medical writing was funded by Bayer, and Bayer was involved in study design. Many of the authors had financial conflicts of interest disclosed. Extensive run-in and screening periods. **Applicability**: Patient: Run-in period and screening period and extensive exclusion criteria limits generalizability. Very few patients included on background therapy with a SGLT2 inhibitor. Intervention: NA Comparator: No active comparator. Outcomes: Composite outcome with outcomes of different levels of significance Setting: 1024 centers in 48 countries; 16.6% in North America and 41.6% in Europe

Abbreviations [alphabetical order]: ACEI = ace inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; ARR = absolute risk reduction; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; CV =cardiovascular; DB = double-blind; eGRF = estimated glomerular filtration rate; FAS = full analysis set; HG = heart failure; HG = hazard ratio; ITT = intention to treat; K = potassium; MC = multicenter; Mg = milligram; MI = myocardial infarction; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; NYHA = new York heart association; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus; y/o = years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
amiloride HCl	AMILORIDE HCL	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE HCL W/HCTZ	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE-HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
bumetanide	BUMETANIDE	ORAL	TABLET	Y
chlorthalidone	CHLORTHALIDONE	ORAL	TABLET	Y
furosemide	FUROSEMIDE	ORAL	SOLUTION	Y
furosemide	FUROSEMIDE	ORAL	TABLET	Y
furosemide	LASIX	ORAL	TABLET	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	CAPSULE	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	SOLUTION	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
indapamide	INDAPAMIDE	ORAL	TABLET	Y
spironolact/hydrochlorothiazid	ALDACTAZIDE	ORAL	TABLET	Y
spironolact/hydrochlorothiazid	SPIRONOLACTONE-HCTZ	ORAL	TABLET	Y
spironolactone	ALDACTONE	ORAL	TABLET	Y
spironolactone	SPIRONOLACTONE	ORAL	TABLET	Y
torsemide	TORSEMIDE	ORAL	TABLET	Y
triamterene	TRIAMTERENE	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	MAXZIDE	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	MAXZIDE-25 MG	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	TABLET	Y
chlorothiazide	DIURIL	ORAL	ORAL SUSP	N
chlorthalidone	THALITONE	ORAL	TABLET	N
eplerenone	EPLERENONE	ORAL	TABLET	N
eplerenone	INSPRA	ORAL	TABLET	N
ethacrynic acid	EDECRIN	ORAL	TABLET	N
ethacrynic acid	ETHACRYNIC ACID	ORAL	TABLET	N
finerenone	KERENDIA	ORAL	TABLET	N
furosemide	FUROSEMIDE	ORAL	SOLUTION	N
metolazone	METOLAZONE	ORAL	TABLET	N
spironolactone	CAROSPIR	ORAL	ORAL SUSP	N
hydroflumethiazide	SALURON	ORAL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

1. Filippatos G, Bakris G, Pitt B, et al. Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes **J Am Coll Cardiol** 2021 Jul 13;78(2):142-152. doi: 10.1016/j.jacc.2021.04.079. Epub 2021 May 17.

Background: Patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) are at risk of atrial fibrillation or flutter (AFF) due to cardiac remodeling and kidney complications. Finerenone, a novel, selective, nonsteroidal mineralocorticoid receptor antagonist, inhibited cardiac remodeling in preclinical models.

Objectives: This work aims to examine the effect of finerenone on new-onset AFF and cardiorenal effects by history of AFF in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study.

Methods: Patients with CKD and T2D were randomized (1:1) to finerenone or placebo. Eligible patients had a urine albumin-to-creatinine ratio ≥30 to ≤5,000 mg/g, an estimated glomerular filtration rate (eGFR) ≥25 to <75 ml/min/1.73 m^2 and received optimized doses of renin-angiotensin system blockade. Effect on new-onset AFF was evaluated as a pre-specified outcome adjudicated by an independent cardiologist committee. The primary composite outcome (time to first onset of kidney failure, a sustained decrease of ≥40% in eGFR from baseline, or death from renal causes) and key secondary outcome (time to first onset of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) were analyzed by history of AFF.

Results: Of 5,674 patients, 461 (8.1%) had a history of AFF. New-onset AFF occurred in 82 (3.2%) patients on finerenone and 117 (4.5%) patients on placebo (hazard ratio: 0.71; 95% confidence interval: 0.53-0.94; p = 0.016). The effect of finerenone on primary and key secondary kidney and cardiovascular outcomes was not significantly impacted by baseline AFF (interaction p value: 0.16 and 0.85, respectively).

Conclusions: In patients with CKD and T2D, finerenone reduced the risk of new-onset AFF. The risk of kidney or cardiovascular events was reduced irrespective of history of AFF at baseline. (EudraCT 2015-000990-11 [A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease]; Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease [FIDELIO-DKD]; NCT02540993).

2. Agarwal R., Gilippatos G. Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. **Eur Heart J**. 2022 Feb 10;43(6):474-484.

Aims: The complementary studies FIDELIO-DKD and FIGARO-DKD in patients with type 2 diabetes and chronic kidney disease (CKD) examined cardiovascular and kidney outcomes in different, overlapping stages of CKD. The purpose of the FIDELITY analysis was to perform an individual patient-level prespecified pooled efficacy and safety analysis across a broad spectrum of CKD to provide more robust estimates of safety and efficacy of finerenone compared with placebo.

Methods and results: For this prespecified analysis, two phase III, multicentre, double-blind trials involving patients with CKD and type 2 diabetes, randomized 1:1 to finerenone or placebo, were combined. Main time-to-event efficacy outcomes were a composite of cardiovascular death, non-fatal myocardial infarction,

non-fatal stroke, or hospitalization for heart failure, and a composite of kidney failure, a sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death. Among 13 026 patients with a median follow-up of 3.0 years (interquartile range 2.3-3.8 years), the composite cardiovascular outcome occurred in 825 (12.7%) patients receiving finerenone and 939 (14.4%) receiving placebo [hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.78-0.95; P = 0.0018]. The composite kidney outcome occurred in 360 (5.5%) patients receiving finerenone and 465 (7.1%) receiving placebo (HR, 0.77; 95% CI, 0.67-0.88; P = 0.0002). Overall safety outcomes were generally similar between treatment arms. Hyperkalaemia leading to permanent treatment discontinuation occurred more frequently in patients receiving finerenone (1.7%) than placebo (0.6%).

Conclusion: Finerenone reduced the risk of clinically important cardiovascular and kidney outcomes vs. placebo across the spectrum of CKD in patients with type 2 diabetes.

3. Pitt B. Filippatos G. Agarwal R. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med. 2021 Dec 9;385(24):2252-2263. doi: 10.1056/NEJMoa2110956. Epub 2021 Aug 28.

Background: Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has favorable effects on cardiorenal outcomes in patients with predominantly stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. The use of finerenone in patients with type 2 diabetes and a wider range of CKD is unclear.

Methods: In this double-blind trial, we randomly assigned patients with CKD and type 2 diabetes to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300 and an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m^2 of body-surface area (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of at least 60 ml per minute per 1.73 m^2 (stage 1 or 2 CKD). Patients were treated with renin-angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary outcome, assessed in a time-to-event analysis, was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The first secondary outcome was a composite of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes. Safety was assessed as investigator-reported adverse events.

Results: A total of 7437 patients underwent randomization. Among the patients included in the analysis, during a median follow-up of 3.4 years, a primary outcome event occurred in 458 of 3686 patients (12.4%) in the finerenone group and in 519 of 3666 (14.2%) in the placebo group (hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P = 0.03), with the benefit driven primarily by a lower incidence of hospitalization for heart failure (hazard ratio, 0.71; 95% CI, 0.56 to 0.90). The secondary composite outcome occurred in 350 patients (9.5%) in the finerenone group and in 395 (10.8%) in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 1.01). The overall frequency of adverse events did not differ substantially between groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%).

Conclusions: Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo. (Funded by Bayer; FIGARO-DKD ClinicalTrials.gov number, NCT02545049.).

4. Filippatos G., Anker S., Agarwal R., et al. Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. Circulation. 2022 Feb 8;145(6):437-447.

Background: Chronic kidney disease and type 2 diabetes are independently associated with heart failure (HF), a leading cause of morbidity and mortality. In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trials, finerenone (a selective, nonsteroidal mineralocorticoid receptor antagonist) improved cardiovascular outcomes in patients with albuminuric chronic kidney disease and type 2 diabetes. These prespecified analyses from FIGARO-DKD assessed the effect of finerenone on clinically important HF outcomes.

Methods: Patients with type 2 diabetes and albuminuric chronic kidney disease (urine albumin-to-creatinine ratio ≥30 to <300 mg/g and estimated glomerular filtration rate ≥25 to ≤90 mL per min per 1.73 m2, or urine albumin-to-creatinine ratio ≥300 to ≤5000 mg/g and estimated glomerular filtration rate ≥60 mL per min per 1.73 m2), without symptomatic HF with reduced ejection fraction, were randomized to finerenone or placebo. Time-to-first-event outcomes included new-onset HF (first hospitalization for HF [HHF] in patients without a history of HF at baseline); cardiovascular death or first HHF; HF-related death or first HHF; first HHF; cardiovascular death or total (first or recurrent) HHF; HF-related death or total HHF; and total HHF. Outcomes were evaluated in the overall population and in prespecified subgroups categorized by baseline HF history (as reported by the investigators).

Results: Overall, 7352 patients were included in these analyses; 571 (7.8%) had a history of HF at baseline. New-onset HF was significantly reduced with finerenone versus placebo (1.9% versus 2.8%; hazard ratio [HR], 0.68 [95% CI, 0.50-0.93]; P=0.0162). In the overall population, the incidences of all HF outcomes analyzed were significantly lower with finerenone than placebo, including an 18% lower risk of cardiovascular death or first HHF (HR, 0.82 [95% CI, 0.70-0.95]; P=0.011), a 29% lower risk of first HHF (HR, 0.71 [95% CI, 0.56-0.90]; P=0.0043) and a 30% lower rate of total HHF (rate ratio, 0.70 [95% CI, 0.52-0.94]). The effects of finerenone on improving HF outcomes were not modified by a history of HF. The incidence of treatment-emergent adverse events was balanced between treatment groups.

Conclusions: The results from these FIGARO-DKD analyses demonstrate that finerenone reduces new-onset HF and improves other HF outcomes in patients with chronic kidney disease and type 2 diabetes, irrespective of a history of HF.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to April 01, 2022>

1 indapamide.mp. or Indapamide/ 1432
2 hydrochlorothiazide.mp. or Hydrochlorothiazide/ 9047
3 spironolactone.mp. or Spironolactone/ 9525
4 triamterene.mp. or Triamterene/ 1420
5 amiloride.mp. or Amiloride/ 12172
6 furosemide.mp. or Furosemide/ 17307
7 bumetanide.mp. or Bumetanide/ 3458
8 torsemide.mp. or Torsemide/ 448
9 chlorothiazide.mp. or Chlorothiazide/ 2549
10 Chlorthalidone/ or chlorthalidone.mp. 1928
11 metolazone.mp. or Metolazone/ 316
12 eplerenone.mp. or Eplerenone/ 1569
13 ethacrynic acid.mp. or Ethacrynic Acid/ 2871
14 finerenone.mp. 186
15 loop diuretics.mp. or Sodium Potassium Chloride Symporter Inhibitors/ 3142
16 Mineralocorticoid Receptor Antagonists/ 5458
17 Diuretics, Potassium Sparing/ or Diuretics/ 29112
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 76814
19 Heart Failure/dt [Drug Therapy] 26701
20 Hypertension/de, dt [Drug Effects, Drug Therapy] 66170
21 chronic kidney disease.mp. or Renal Insufficiency, Chronic/ 72158
22 19 or 20 or 21 161716
23 18 and 22 16616
24 limit 23 to (english language and humans and yr="2020 -Current" and (clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "systematic review")) 176
25 from 24 keep 1-2,4-6,8,19-20,22,26,34,41,44,46,48,51-52,59,62-64,67,69-70,75,85,88-89,96,100,105-106,108,115,125,129,146,150,157,162,166,168,171,174 44

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KERENDIA (finerenone) tablets, for oral use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

Kerendia is a non-steroidal mineralocorticoid receptor antagonist (MRA) indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D). (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dosage is 10 mg or 20 mg orally once daily based on estimated glomerular filtration rate (eGFR) and serum potassium thresholds. (2.1)
- Increase dosage after 4 weeks to the target dose of 20 mg once daily, based on eGFR and serum potassium thresholds. (2.3)
- Tablets may be taken with or without food (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg and 20 mg (3)

CONTRAINDICATIONS

- Concomitant use with strong CYP3A4 inhibitors. (4, 7.1)
- Patients with adrenal insufficiency. (4)

WARNINGS AND PRECAUTIONS

- Hyperkalemia. Patients with decreased kidney function and higher baseline potassium levels are at increased risk. Monitor serum potassium levels and adjust dose as needed. (2.1, 2.2, 2.3, 5.1)

ADVERSE REACTIONS

Adverse reactions occurring in ≥ 1% of patients on Kerendia and more frequently than placebo are hyperkalemia, hypotension, and hyponatremia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors: Use is contraindicated. (7.1)
- Grapefruit or Grapefruit Juice: Avoid concomitant use. (7.1)
- Moderate or weak CYP3A4 Inhibitors: Monitor serum potassium during drug initiation or dosage adjustment of either Kerendia or the moderate or weak CYP3A4 inhibitor, and adjust Kerendia dosage as appropriate (7.1)
- Strong or moderate CYP3A4 Inducers: Avoid concomitant use. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding not recommended (8.2)

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

Revised: 7/2021

Appendix 5: Key Inclusion Criteria

Population	Adults and Pediatrics
Intervention	Diuretic therapy
Comparator	Active control or placebo
Outcomes	Mortality, composite cardiovascular outcome, hospitalizations, safety outcomes
Timing	N/A
Setting	Inpatient or outpatient

Finerenone

Goal(s):

- Promote use of finerenone that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- 12 months

Requires PA:

- Finerenone (Kerendia™)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code; go to #2	
2. Is the patient 18 years or older with a diagnosis of type 2 diabetes?	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Does the patient have a diagnosis of chronic kidney disease?	**Yes:** Go to #4	**No:** Pass to RPh; deny for medical appropriateness.
4. Does the patient have a documented estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) < 25 ml/min **OR** require hemodialysis?	**Yes:** Pass to RPh; deny for medical appropriateness. Request eGFR if not provided	**No:** Document eGFR and go to #5 Recent eGFR: _____ Date:

Approval Criteria		
5. Is the patient currently on a maximally tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), OR have a documented contraindication to both?	**Yes:** Go to #6	**No:** Pass to RPh; deny for medical appropriateness.
6. Is the patient's serum potassium ≤ 5.0 mEq/L?	**Yes:** Approve for up to 12 months Recent potassium: _____ Date: _____	**No:** Pass to RPh; deny for medical appropriateness.

P&T / DUR Review: *06/22 (MH)*
Implementation:

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

OHSU Drug Effectiveness Review Project Summary Report– Atopic Dermatitis

Date of Review: June 2022

Date of Last Review: Oct 2020
Literature Search: 05/20/2021-02/14/2022

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

Research Questions:
1. For adults and children, what is the comparative effectiveness of the included interventions (see **Table 2)** for atopic dermatitis (AD)?
2. For adults and children, what are the comparative harms of the included interventions (see **Table 2**) for AD?

Conclusions:
- The February 2022 drug class report on AD by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this review.[1] Evidence for the following informed the DERP report:
    - The immunomodulators azathioprine, cyclosporine, methotrexate, mycophenolate, and omalizumab, which may be prescribed off-label for AD;
    - Crisaborole, tacrolimus, pimecrolimus and dupilumab which have Food and Drug Administration (FDA) approval for AD;
    - The targeted immune modulators (TIMs) with FDA approval for AD, including the topical Janus Kinase (JAK) inhibitor ruxolitinib, the injectable interleukin-13 (IL-13) antagonist tralokinumab, and the oral JAK inhibitor abrocitinib; and
    - The TIM, upadacitinib, which recently received an expanded indication for moderate-to-severe AD.

Off-Label Drugs for Atopic Dermatitis
- Azathioprine improved Six-Area, Six-Sign Atopic Dermatitis (SASSAD) severity scores compared to placebo based on moderate quality evidence from 2 small randomized controlled trials (RCTs).[1] There were no differences between azathioprine and methotrexate over 12 weeks for improvements in the Severity Scoring of Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), and Investigator's Global Assessment (IGA) scales based on moderate quality evidence.[1] More adverse effects (AEs) were reported with azathioprine versus placebo over 12 weeks based on moderate quality evidence, with gastrointestinal (GI) effects (nausea, vomiting, diarrhea, bloating and abdominal pain) more commonly noted with azathioprine.[1] Azathioprine had similar rates of AEs to methotrexate based on moderate quality evidence, except for higher rates neutropenia and lymphopenia observed with azathioprine.[1]
- Seven RCTs with a high risk-of-bias and 2 RCTs with moderate risk of bias which analyzed cyclosporine for treatment of AD were included in the 2022 DERP report.[1] The quality of evidence for the 7 RCTs was downgraded to very low due to small sample sizes (n=24 to 97), lack of blinding, and high attrition rates.[1] Low quality evidence found no differences in efficacy between cyclosporine and methotrexate in pediatric patients.[1] In adults, low quality evidence demonstrated no differences in efficacy between cyclosporine, mycophenolate, or prednisolone.[1] One low quality RCT found cyclosporine was more effective than methotrexate in adults.[1] In one RCT with moderate risk of bias, tacrolimus was superior to cyclosporine in improving SCORAD scores.[1] Three RCTs with high risk of bias favored cyclosporine over placebo but preferred efficacy endpoints like SCORAD, EASI or IGA were not assessed.[1] Regardless of

the comparator group, participants in the cyclosporine groups reported more AEs including hypertension, GI manifestations, and infections.[1] Cyclosporine may have a less favorable safety profile compared with placebo, methotrexate and mycophenolate, based on very low-quality evidence.[1]

- One RCT with low risk of bias compared omalizumab to placebo in pediatric patients with severe AD.[1] Omalizumab was more effective than placebo in improving SCORAD scores based on high quality evidence; however, the improvement fell short of achieving a minimal clinically important difference (MCID).[1] Rates of AEs between omalizumab and placebo were similar based on low-quality evidence.[1] The most commonly reported AEs for both groups were respiratory and GI symptoms.[1]

FDA-Approved Drugs for Atopic Dermatitis

- For the 2022 DERP update, no new studies were identified for crisaborole.[1] Crisaborole is only indicated for management of mild-to-moderate AD, which is not funded by the Oregon Health Plan (OHP).[2,3]
- No new comparative studies to evaluate dupilumab with an FDA-approved therapy were identified for the DERP update.[1] Dupilumab was compared to abrocitinib in one phase 3 RCT, but a statistical analysis was not completed.[4] Upadacitinib was also compared to dupilumab in a clinical trial which assessed the safety and efficacy of upadacitinib for management of moderate-to-severe AD.[5]
- One RCT with moderate risk of bias evaluating the safety and efficacy of pimecrolimus versus topical corticosteroids in infants with mild-to-moderate AD was identified for the DERP report.[1] Both groups reported treatment success defined as an IGA of 0 (clear) or 1 (almost clear) by week 3.[1] High incidences of AEs were reported in both groups, with over 95% of participants in both groups reporting any event by the end of the study period.[1] No new eligible studies were identified for tacrolimus.[1]

New FDA-Approved Drugs for Atopic Dermatitis

- The FDA-approved indication for the oral JAK-1 selective inhibitor abrocitinib is for the treatment of adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when the use of those therapies is inadvisable.[6] Four placebo-controlled RCTs with low risk of bias assessed the efficacy of abrocitinib in patients with moderate-to-severe AD.[1] In the phase 3 RCTs, abrocitinib was superior to placebo in achieving IGA response of 0 or 1 and EASI-75 (75% improvement from baseline on the EASI) by week 12 or 16 based on high-quality evidence, with a number needed to treat (NNT) ranging between 2 to 7 for each outcome.[1] In one RCT, abrocitinib 100 mg and 200 mg were similar to dupilumab in achieving EASI-75 response at week 16 based on low-quality evidence; however, the study was not adequately powered to detect differences between the study arms.[1] In all 3 trials, higher rates of GI disorders, acne, herpes, and thrombocytopenia were associated with abrocitinib based on high-quality evidence.[1] One trial found similar rates of AEs between abrocitinib and dupilumab based on moderate quality evidence except dupilumab had higher rates of conjunctivitis.[1]
- The FDA-approved indication for ruxolitinib 1.5% cream is for the short-term treatment of mild-to-moderate AD in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[7] High-quality evidence from 2 placebo-controlled, identical, phase 3 RCTs with low-to-moderate risk of bias showed ruxolitinib was effective in improving EASI and achievement of IGA 0/1 scores in patients with mild-to-moderate AD.[1] No differences were noted between placebo and ruxolitinib in incidence of AEs based on high-quality evidence.[1] Application site-pain was the most frequently reported AE in both ruxolitinib and placebo groups.[1]
- Tralokinumab is FDA-approved for the treatment of moderate-to-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[8] Four RCTs with low-to-moderate risk-of-bias evaluated the safety and efficacy of tralokinumab in treatment of moderate-to-severe AD.[1] In a phase 2 RCT, improvement in EASI was found with tralokinumab 150 mg and 300 mg doses in combination with topical corticosteroids compared with placebo at 12 weeks based on moderate-quality evidence.[1] In two phase 3 RCTs, tralokinumab monotherapy was superior to placebo in achieving EASI-75 at 12 weeks based on moderate-quality evidence with a NNT ranging from 5 to 9 in each trial.[1] Tralokinumab was superior to placebo in achieving IGA 0/1 at 12 weeks based on low-quality evidence (NNT = 9 to 12) in these trials.[1] The DERP authors downgraded the evidence assessment for IGA outcome due to inconsistency and indirectness.[1] Another trial provided moderate-quality evidence that

tralokinumab, when combined with topical mometasone, was superior to placebo in achieving IGA of 0 to 1 at 16 weeks.[1] Tralokinumab increased the risk of infection-related AEs versus placebo based on low-quality evidence.[1] The most commonly reported AEs reported in more than 5% of participants and occurring more frequently with tralokinumab than placebo were viral upper respiratory tract infections (15.7% vs. 12.2%), upper respiratory tract infections (5.6% vs. 4.8%), and conjunctivitis (5.4% vs. 1.9%).[1]

- Upadacitinib (RINVOQ), an oral JAK-I originally approved for rheumatoid arthritis (RA), received expanded approval for treatment of moderate-to-severe AD in January 2022.[9] Four RCTs with low-to-moderate risk of bias were conducted in adults and adolescents with AD.[1] Upadacitinib was superior to placebo in achieving EASI-75 and IGA 0/1 in 3 RCTs based on high-quality evidence.[1] Upadacitinib was superior to dupilumab in achieving EASI-75 in the fourth trial based on high-quality evidence.[1] Upadacitinib had similar AEs to placebo based on high-quality evidence, except for higher rates of acne observed with upadacitinib.[1] Similar rates of AEs were observed between upadacitinib and dupilumab, except for higher rates of acne, upper respiratory tract infections, and increased creatinine phosphokinase (CPK) observed with upadacitinib based on moderate-quality evidence.[1]

Policy Revisions

- In January 2022, Guideline Note 21 was updated by the Health Evidence Review Commission (HERC) to include vitiligo as an inflammatory skin condition and funded coverage was broadened to include facial involvement for severe inflammatory skin conditions.

Recommendations:

- Update clinical prior authorization (PA) criteria for all drugs used to manage AD to reflect updated 2022 HERC guidance from Guideline Note 21 which now includes facial involvement in the severity assessment of AD (**Appendix 5**) and severe vitiligo as a funded inflammatory skin condition.
- Revise title for topical therapies for AD and psoriasis to “Topical Agents for Inflammatory Skin Conditions”. Add topical ruxolitinib to the clinical PA criteria for “Topical Agents for Inflammatory Skin Conditions” and designate as non-preferred on the Preferred Drug List (PDL).
- Revise title of “Monoclonal Antibodies for Severe Asthma” PA criteria to “Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis”. Add oral abrocitnib and injectable tralokinumab to “Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis” PA Criteria and designate both agents as non-preferred on the PDL (**Appendix 5**).
- Include an assessment of severe AD as an FDA-approved diagnosis for upadacitinib in the clinical PA criteria for “Targeted Immune Modulators for Autoimmune Conditions”(**Appendix 5**).
- Evaluate costs in the Executive Session to inform PDL status.

Summary of Prior Reviews and Current Policy

- The Pharmacy and Therapeutics (P&T) Committee approved revising the PA criteria for topical antipsoriatic drugs to include agents used to manage AD in March 2018. Dupilumab was also made a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP) with clinical PA criteria for use in AD. After reviewing costs in executive session, tacrolimus 0.03% ointment, tacrolimus 0.1% ointment, and pimecrolimus 1% cream were designated as preferred agents and crisaborole was maintained as a non-preferred agent. The PDL status for topical and systemic medications used to manage AD is presented in **Appendix 1**.
- Over the next 3 years, dupilumab received expanded FDA-approved indications. Dupilumab was presented to the Committee in August 2021 as part of a DERP report focused on TIMs used to treat eosinophilic asthma. The Committee retired the stand-alone dupilumab clinical PA criteria and dupilumab was instead added to the “Monoclonal Antibodies for Severe Asthma” clinical PA criteria. The PA criteria for Topical Atopic Dermatitis and Antipsoriatic Treatments and the Monoclonal Antibodies for Severe Asthma can be reviewed in **Appendix 5**.

- In October 2020, the HERC revised Guideline Note 21 to broaden coverage of severe inflammatory skin diseases, which include psoriasis, AD, lichen planus, Darier disease, pityriasis ruba pilaris, and discoid lupus.[3] Severe forms of these conditions are funded on line 426 and are defined as having functional impairment AND one or more of the following:
    - At least 10% of body surface area (BSA) involved, OR
    - Hand, foot or mucous membrane involvement.

  The definition of functional impairment, previously defined as "inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction", was replaced by an assessment of severe disease using the Dermatology Life Quality Index (DLQI) (score ≥11), Children's Dermatology Life Quality Index (CDLQI) (score ≥13), or severe score on another validated tool.[3] If inflammatory skin conditions do not meet the criteria stipulated in Guideline Note 21, they are not funded by the OHP and are included on lines 482, 504, 532, 541, and 656. The Committee revised the clinical PA criteria for therapies used to treat AD in December 2020 to include an assessment of severe disease using a validated scoring tool such as the DLQI or CDLQI per HERC guidance.
- In January 2022, Guideline Note 21 was updated by the HERC to include vitiligo as an inflammatory skin condition and funded coverage was broadened to include facial involvement for severe inflammatory skin conditions. The revised 2022 Guideline Note 21 is included in **Appendix 3**.

Background

Atopic dermatitis is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation with a relapsing and remitting pattern.[10] The cause is unknown, but may be due to genetics or immunologic dysfunction.[11] Many patients also have allergic asthma, allergic rhinoconjunctivitis, food allergies, and other immediate hypersensitivity (type 1) allergies.[12] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries.[13] Estimated prevalence of AD for adults in the United States (U.S.) is 10%.[13] Both sexes are affected, and the prevalence varies among races and ethnic groups.[14] For example, in the U.S., the prevalence is higher among Black children (19.3%) than among White children (16.1%).[15] Onset of AD is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years.[16] AD can persist into adulthood in about one-third of affected individuals.[17] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life.[18]

Therapy for AD is selected according to the clinical stage of disease (mild, moderate, or severe), the extent and location of body-surface area involved, age, co-existing conditions and medications being taken by the patient, the severity of pruritus, the degree to which quality of life is impaired, and the goals of the patient.[19,20] For all disease stages, general measures include care with frequent application of an emollient to maintain the skin's epidermal barrier, avoidance of triggers, and anti-inflammatory therapy with a topical corticosteroid or a topical calcineurin inhibitor (e.g., pimecrolimus or tacrolimus) as needed.[11] The use of topical corticosteroid and topical calcineurin inhibitor therapies in AD is supported by The American College of Dermatology's 2014 guideline[21] and 2004 guidance from the National Institute for Health and Care Excellence.[22] Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of topical corticosteroid can result in telangiectasia, increased hair, skin tears, easy bruising, poor wound healing, acne and rosacea, and thinning/atrophic skin changes, which can be permanent.[23] Topical calcineurin inhibitors are considered a second-line option in both adults and children with AD who have not responded to topical corticosteroid or when those treatments are not advisable.[23] The main rationale for topical calcineurin inhibitor use is that they do not cause skin atrophy and are therefore of particular value in delicate skin areas such as the face, neck, and skin folds. All topical preparations can sting, but there is evidence that this is even more of a problem with topical calcineurin inhibitor preparations. Furthermore, FDA labeling for tacrolimus and pimecrolimus include boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with topical calcineurin inhibitor administration.[24,25]

Patients with severe AD that cannot be controlled with topical corticosteroid or topical calcineurin inhibitor therapy can be treated with short-term, narrow band ultraviolet B (UVB) phototherapy or systemic immunomodulators such as cyclosporine, azathioprine, methotrexate, mycophenolate and oral corticosteroids.[19] The use of systemic immunomodulators in AD is considered off-label and only oral prednisone is FDA-approved to treat AD. Treatment with cyclosporine carries important risks of acute and chronic nephrotoxicity, can have hemodynamic effects that result in hypertension,[26] and can increase the risk of infections and cancer.[27] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[26] As a result, treatment with cyclosporine for AD is typically limited to one year. National Institute for Health and Care Excellence (NICE) Guidance from 2004 recommends systemic corticosteroids, phototherapy, and systemic immunosuppressants as "treatments of last resort" in AD patients.[22] The 2014 American Academy of Dermatology guidelines reinforce the NICE recommendations for systemic immunomodulators as treatments for patients with refractory AD who fail all other therapies.[28]

Two additional agents with novel mechanisms of action are included in AD treatment algorithms. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor approved for mild-to-moderate AD in adults and children aged 3 months and older.[2] PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity is increased in AD.[29] Crisaborole is available as an ointment that is applied twice daily. Dupilumab is an injectable IL-4 antagonist monoclonal antibody approved as systemic therapy for moderate-to-severe AD refractory to topical treatments in children aged 6 years and older and adults.[30] The Canadian Agency for Drugs and Technologies in Health (CADTH) published updated recommendations for the use of dupilumab in atopic dermatitis April 2020.[31] Dupilumab should be initiated in patients with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable.[31] Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.[31] Within the past year, 3 new TIMs have received FDA-approval for management of AD. These therapies will be discussed later in this report.

Clinical studies have utilized several scales for defining the severity of AD, including the SCORAD index, the EASI, IGA, and SASSAD severity score. The SCORAD index was developed in 1993 by the European Task Force on Atopic Dermatitis and is the most widely referenced AD scoring instrument in literature.[32] The SCORAD has been validated for content and construct validity, interobserver reliability, and sensitivity to change in 26 different publications.[32] The SCORAD tool incorporates clinician estimates of disease extent and severity and subjective patient assessment of itching and sleep loss.[33] The extent of AD is graded using a percentage score by the clinician for specific areas of the body (head/neck, upper limbs, lower limbs, trunk and back). Severity includes a clinician assessment of the intensity of redness, swelling, oozing, dryness, scratch marks, and lichenification, which are graded on a 4-point scale rated as 0 (none), 1 (mild), 2 (moderate) or 3 (severe).[33] Subjective symptoms such as itching and sleeplessness are scored by the patient using a visual analog scale (VAS) from 0 (no symptoms) to 10 (worst imaginable) for a total score of 20. Combining extent, severity, and symptoms results in a total SCORAD score ranging between 1 to 100 and categorized as mild (<25), moderate (26-49), and severe (>50).[33]

The EASI was adapted from the Psoriasis Area and Severity Index in 1998.[32] The EASI assesses the severity of, and body surface area affected by, AD symptoms including erythema, induration/papulation/edema, excoriations, and lichenification.[34] Each symptom is graded systematically for specific anatomical regions (the head, trunk, arms and legs) and summarized in a composite score. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD.[34] An EASI score of 7 or lower is considered to indicate mild disease, 8 to 21 moderate disease, 22 to 50 severe disease, and 51 to 72 very severe disease.[12] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90. A limitation often cited is the EASI's intermediate interobserver reliability, especially compared to SCORAD scale.[32]

The IGA is a clinician-reported outcome measure that has been used to evaluate severity of AD at a given point in time.[35] This measure was used to evaluate clinical response to treatment in studies evaluating new AD therapies.[36,37] In these trials, a 5-point scale ranging from 0 (clear) to 4 (severe) was used to assess changes in the severity of skin lesions. In most trials, scores less than or equal to 1 were generally classified as "treatment success," whereas scores greater than

1 were considered "treatment failure."[38] The IGA does not assess disease extent as body regions are not included in the IGA scoring. One systematic review concluded that although the IGA is easy to perform, the lack of standardization precludes any meaningful comparisons between studies which impedes data synthesis to inform clinical decision making.[35] The Investigator's Static Global Assessment (ISGA) does not assess changes in severity of skin lesions with treatment and may use a 6-point scale ranging from 0 (clear) to 5 (very severe).

The SASSAD score was created in 1998 by the British Association of Dermatologists.[32] The SASSAD severity score is obtained by grading 6 signs (erythema, exudation, excoriation, dryness, cracking and lichenification) each on a scale of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe) at each of 6 sites; arms, hands, legs, feet, head, neck and truck.[39] As with many other tested atopic eczema scoring indices, the SASSAD index is subject to significant interobserver variation, reflecting the difficulties in reliably assessing eczema severity objectively.[40] It is not commonly used as an outcome measurement in the literature or in clinical practice as there are better options for scales in terms of simplicity and validity.[32]

Table 1 summarizes the 4 different measures used in clinical trials evaluating the efficacy of AD treatments. These scales are primarily used in clinical trials and rarely in clinical practice, as they were generally not designed for this purpose.[16] Quality of life in AD patients is assessed by the DLQI, a 10 question tool used to asses impact of AD on itch, embarrassment, clothing, work/school, and relationships.[41] Questions are rated on a 0 to 3 scale, for a total score between 0 and 30; higher scores indicate poorer quality of life.[41] A similar tool, the CDLQI is used in children aged 4 to 16 years.[42]

Table 1. Assessment of Atopic Dermatitis Severity in Clinical Trials[33,34,39,43]

	SCORAD	EASI	IGA/ISGA	SASSAD
Scoring	Range: 0 to 100 Score ≤ 25: Mild AD Score ≥ 50 : Severe AD	Range: 0 to 72 Mild AD: 7.1-21.0 Moderate AD: 21.1-50 Severe AD: 50.1-72	Range: 0 to 4 (IGA) *or* 0 to 5 (ISGA) Score of 0 or 1 indicates disease clearing	Range: 0 to 108 Higher scores indicate more severe disease
Scale	4 point scale assessing intensity of erythema, edema/papulation, oozing/crusts, excoriations, and lichenification: 0 - absent 1 - mild 2 - moderate 3 - severe	4 point scale assessing erythema, induration, infiltration/papulation, edema, excoriation, and lichenification: 0 - absent 1 - mild 2 - moderate 3 - severe	5 (IGA) or 6 (ISGA) point scale based on assessment of erythema and infiltration/papulation: 0 - clear 1 - almost clear 2 - mild disease 3 - moderate disease 4 - severe disease 5 - very severe disease (ISGA)	3 point scale used to assess 6 domains; erythema, exudation, excoriation, dryness, cracking, and lichenification: 0 - absent 1 - mild 2 - moderate 3 - severe
Body Regions	Distribution rated on a 0 to 4 scale for each body region (Head/Neck, Trunk Upper limbs, and Lower limbs): 0= no affected site 1 = 1 affected site 2 = 2 affected sites 3 = 3 affected sites	Proportionate values assigned to 4 separate body regions: • Upper limbs (20%) • Lower limbs (40%) • Trunk (30%) • Head/Neck (10%)	Not Used	Scores from 6 different body areas are added together for final score: • Head/Neck • Trunk • Hand • Feet • Arms

	4= more than 4 affected sites			• Legs
Additional Assessments	Patient assessment of itching and sleep loss on a 0 to 10 VAS	None	None	None
Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ISGA = Investigator's Static Global Assessment; SASSAD=Six-Area, Six-Sign Atopic Dermatitis; SCORAD = Severity Scoring of Atopic Dermatitis; VAS = Visual Analog Scale				

Methods:
The February 2022 drug class report on AD by the DERP at the Center for Evidence-based Policy at OHSU was used to inform recommendations for this drug class.[1] The original report is available to P&T Committee members upon request.

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

Summary Findings:
The 2022 DERP systematic review and meta-analysis on drugs to treat to AD was an update of the 2017 DERP report completed in 2017. The 2017 DERP report focused on comparative evidence for dupilumab, crisaborole, pimecrolimus, and tacrolimus.[38] Oral immunomodulators (azathioprine and cyclosporine) and the monoclonal antibody omalizumab, which are prescribed off-label for AD, were not included in the original report. For the 2022 report, DERP investigators conducted a systematic review based on RCTs published from January 2017 through August 2021.[1] Adults and children with moderate-to-severe AD using FDA-approved agents, off-label agents, and investigational therapies were evaluated. Forty-seven new documents met inclusion criteria and 6 RCTs were carried forward from the 2017 DERP report.[1] Outcomes included response to treatment (IGA), disease symptoms (EASI score, SCORAD, percentage of BSA affected, quality of life [DLQI]), AEs, and serious adverse events (SAEs).[1]

Three new TIMs have received FDA-approval for AD management. These include the topical JAK inhibitor ruxolitinib (OPZELURA; September 2021)[7]; the injectable IL-13 antagonist tralokinumab (ADBRY; December 2021)[8]; and the oral JAK inhibitor abrocitinib (CIBINQO; January 2022).[6] Manufacturer's prescribing information for each of these products is presented in **Appendix 4**. In addition, upadacitinib (RINVOQ), an oral JAK inhibitor originally approved for rheumatoid arthritis (RA), received expanded approval for AD management in January 2022.[9] Additional TIMs currently under investigation for AD include the oral JAK inhibitor baricitinib, currently approved for RA treatment, and 2 new injectable IL-13 antagonists, lebrikizumab and nemolizuamb. Lastly, a novel neurokinin-1 receptor antagonist, tradipitant, is being studied for AD. These pipeline agents will not be discussed in-depth as they have not yet received FDA approval for management of AD. Drug information for the AD drugs included in the DERP report are summarized in **Table 2.**

Table 2. Drug Information for the Atopic Dermatitis Drugs Summarized in the DERP Report

Generic Name	Brand Name	Mechanism of Action	Dosage Formulations	FDA Indication	FDA-Approved Ages
Off-Label Drugs for AD					
Azathioprine[44]	Generics; IMURAN	Immunosuppressant	Oral Tablet	--	--
Cyclosporine[45]	Generics; NEORAL, SANDIMMUNE	Immunosuppressant	Oral Capsules and Solution	--	--
Omalizumab[46]	XOLAIR	Monoclonal Antibody	Subcutaneous Injection	--	--
FDA-Approved Drugs for AD					
Crisaborole[2]	EUCRISA	PDE4 Inhibitor	2% Ointment	Mild-to-Moderate AD	≥ 3 months
Dupilumab[30]	DUPIXENT	IL-4 Antagonist	Subcutaneous Injection	Moderate-to-Severe AD	≥ 6 years
Pimecrolimus[24]	ELIDEL	Calcineurin Inhibitor	1% Cream	Mild-to-Moderate AD	≥ 2 years
Tacrolimus[25]	PROTOPIC	Calcineurin Inhibitor	0.03% Ointment 0.10% Ointment	Moderate-to-Severe AD	≥ 2 years ≥ 15 years
New FDA-Approved Drugs for AD					
Abrocitinib[6]	CIBINQO	JAK Inhibitor	Oral Tablets	Moderate-to-Severe AD	≥ 18 years
Ruxolitinib[7]	OPZELURA	JAK Inhibitor	1.5% Cream	Mild-to-Moderate AD	≥ 12 years
Tralokinumab[8]	ADBRY	IL-13 Antagonist	Subcutaneous Injection	Moderate-to-Severe AD	≥ 18 years
Upadacitinib[9]	RINVOQ	JAK Inhibitor	Oral Extended-Release Tablets	Moderate-to-Severe AD	≥ 12 years

Abbreviations: AD = Atopic Dermatitis; DERP = Drug Effectiveness Review Project; FDA = Food and Drug Administration; IL= Interleukin; JAK = Janus Kinase; PDE4 = Phosphodiesterase 4

1. Off-Label Drugs for Atopic Dermatitis

Azathioprine

Azathioprine is FDA-approved as an adjunct for the prevention of rejection in renal transplantation and to reduce symptoms of rheumatoid arthritis.[44] The off-label use of azathioprine for AD is recommended in compendial resources.[47] Two placebo-controlled RCTs with moderate risk of bias met inclusion criteria. These RCTs evaluated azathioprine 1 mg to 2.5 mg/kg/day versus placebo in adults with moderate-to-severe AD over 12 weeks in 2002 and 2006.[1] An additional single-blind, RCT with moderate risk of bias published in 2011 compared azathioprine 1.5 mg to 2.5 mg/kg/day to methotrexate 10 mg to 22.5 mg per week over 24 weeks in adults (n=41) who had previously failed cyclosporine therapy.[1] Participants (n=35) from the 2011 RCT could enroll in an open-label, extension study to provide comparative data between azathioprine and methotrexate over 5 years of follow-up.[1] By the end of the 5-year study period only 7 participants were still receiving methotrexate and 4 participants were receiving azathioprine, with the remainder switching to topical therapy (n=15), lost to follow-up (n=5) or discontinued therapy (n=5).[1] All 3 RCTs had small sample sizes ranging from 37 to 61 adults with short durations of treatment.[1] The primary outcome was the change in SASSAD severity score at the end of treatment for the older studies and the SCORAD scale for the 2011 RCT. Compared with placebo, moderate-quality evidence showed azathioprine improved SASSAD severity scores in the 2 small RCTs (n=37 and n=61).[1] Moderate-quality evidence showed there was no difference between azathioprine and methotrexate over 12 weeks for improvements in the SCORAD, EASI, and IGA assessments.[1] Low quality-evidence showed azathioprine was superior to placebo for improvements in quality of life assessed by the DLQI.[1] Moderate-quality evidence revealed more reported AEs with azathioprine versus placebo over 12 weeks, with GI effects (nausea, vomiting, diarrhea, bloating and abdominal pain) more commonly noted with azathioprine.[1] Moderate-quality evidence showed azathioprine had similar AEs to methotrexate with higher rates of neutropenia and lymphopenia observed with azathioprine.[1]

Cyclosporine

Cyclosporine is FDA-approved for prophylaxis of organ rejection in kidney, liver, and heart allogenic transplants and treatment of rheumatoid arthritis and plaque psoriasis.[45] The off-label use of cyclosporine for AD is included in compendial resources.[47] Seven RCTs with a high risk-of-bias and 2 RCTs with moderate risk-of-bias which analyzed cyclosporine for treatment of AD were identified for the 2022 DERP report.[1] Two RCTs compared cyclosporine with methotrexate 7.5 mg to 15 mg per week, 4 separate RCTs evaluated cyclosporine versus mycophenolate, prednisolone, topical tacrolimus, or topical betamethasone, and 3 RCTs compared cyclosporine with placebo. Doses of cyclosporine ranged from 3 mg to 5 mg/kg/day. The quality of the evidence was downgraded to very low due to small sample sizes (n=24 to 97), lack of blinding, and high attrition rates.[1] Most of the studies were conducted over 6 to 24 weeks. One noninferiority RCT comparing cyclosporine with mycophenolate was conducted over 48 weeks. None of the studies were conducted in the U.S.[1]

Five RCTs published after 2000 used SCORAD changes as the primary endpoint.[1] Very low-quality evidence from one RCT comparing cyclosporine with methotrexate in pediatric patients, and another RCT in adults, found no difference in SCORD score changes between the 2 drugs.[1] Very low-quality evidence from one RCT found no difference in SCORAD score improvements between cyclosporine and mycophenolate over 48 weeks.[1] Another low-quality RCT comparing cyclosporine with prednisolone found similar efficacy for both treatments for the primary outcome of changes in the SCORAD score.[1] The attrition rate for this RCT was 39%, so findings from this trial should be carefully interpreted.[1] Very low-quality evidence from one RCT showed differences in the SCORAD score favored tacrolimus over cyclosporine.[1] In one RCT with high risk-of-bias, no differences in AD symptoms were identified between cyclosporine and topical betamethasone.[1] Three RCTs with high risk of bias favored cyclosporine over placebo; but preferred efficacy outcomes such as SCORAD, EASI or IGA were not assessed.[1] Regardless of the comparator group, participants in the cyclosporine groups reported more AEs including hypertension, GI manifestations, and infections.[1] Very low-quality evidence demonstrated placebo, methotrexate and mycophenolate may have a more favorable safety profile compared with cyclosporine.[1] Given the moderate-to-high risk of bias in these studies, caution is warranted when interpreting the findings.[1]

Omalizuamb

Omalizumab is FDA-approved for treatment of moderate-to-severe persistent asthma, nasal polyps, and chronic idiopathic urticaria.[46] According the prescribing information, omalizumab Is not indicated for allergic conditions or other forms of urticaria.[46] Evidence for the off-label use of omalizumab in AD is not included in compendial resources. [47] In the 2022 DERP report, one RCT with low risk-of-bias comparing omalizumab to placebo in pediatric patients (n=62) with severe AD over 24 weeks is described.[4] High-quality evidence shows the change in SCORAD score at 24 weeks was improved with omalizumab compared with placebo (adjusted mean difference [MD] of -8.3 points; 95% confidence interval [CI] -15.1 to -1.1).[1] However, the change in SCORAD score did not achieve the MCID of -8.7 points.[1] Low-quality evidence showed quality of life was improved in the omalizumab group compared with placebo (mean score difference of -3.5; 95% CI -6.5 to -0.5), and did achieve the MCID of -3.3 defined by investigators.[1] Low-quality evidence revealed AEs between omalizumab and placebo were similar.[1] The most commonly reported AEs for both groups were respiratory and GI symptoms.[1]

2. FDA-Approved Drugs for Atopic Dermatitis

Crisaborole

The 2017 DERP report stated there is inadequate evidence to assess the relative efficacy and safety of crisaborole compared with topical calcineurin inhibitor and topical corticosteroid treatments.[38] For the 2022 DERP update, no new studies were identified for crisaborole.[1] Crisaborole is only indicated for management of mild-to-moderate AD, which is not funded by the OHP.[2,3]

Dupilumab

In the 2017 DERP report, results from 6 placebo-controlled trials were pooled to assess the likelihood of achieving an IGA response of 0 or 1 in participants with moderate-to-severe AD treated with dupilumab.[1] The pooled risk ratio (RR) for this outcome was 4.10 (95% CI 3.10 to 5.42; p<0.01).[1] The overall incidence of AEs was similar between dupilumab and placebo groups.[38] Serious adverse events and AEs leading to treatment discontinuation were uncommon.[38] There is insufficient evidence to compare dupilumab with topical calcineurin inhibitor monotherapy, systemic cyclosporine or phototherapy. No new comparative studies to evaluate dupilumab with an FDA-approved therapy were identified for the DERP update.[1] Dupilumab was compared to abrocitinib in 1 RCT, but a statistical analysis was not completed.[4] Upadacitinib was also compared to dupilumab in a trial that assessed the safety and efficacy of upadacitinib in management of moderate-to-severe AD.[5] The results of this trial will be discussed in the upadacitinib section.

Pimecrolimus and Tacrolimus

The 2017 DERP report evaluated 4 fair quality head-to-head trials of topical calcineurin inhibitors in management of moderate-to-severe AD and concluded short-term treatment response (6 to 12 weeks) was not consistently different between tacrolimus and pimecrolimus.[38] Short-term improvement in symptoms was modestly better with tacrolimus compared to pimecrolimus, using a symptom scale, reduction in the percentage of BSA affected, and ratings of pruritus.[38] The DERP meta-analysis of the comparative topical calcineurin inhibitor trials did not show a difference between pimecrolimus and tacrolimus in withdrawal of therapy due to AEs (pooled RR 1.16; 95% CI 0.43 to 3.14; I^2 = 0%).[38]

In the 2022 DERP update, one RCT with moderate risk of bias evaluating the safety and efficacy of pimecrolimus versus topical corticosteroids over 5 years in infants with mild-to-moderate disease was identified.[1] Both groups reported improvement treatment success defined as an IGA of 0 or 1 by week 3.[1] High incidences of AEs were reported in both groups, with over 95% of participants in both groups reporting any event by the end of the study period.[1] No new eligible studies were identified for tacrolimus in the recent DERP update.[1]

3. New FDA-Approved Drugs for Atopic Dermatitis

Abrocitinib

Four phase 3 placebo-controlled trials with low risk of bias assessed the safety and efficacy of abrocitinib, an oral JAK-1 selective inhibitor, for treatment of moderate-to-severe AD.[1] One study was a phase 2 dose-finding trial, while the others 4 studies were phase 3 RCTs. Two RCTs included adults, 2 RCTs included participants 12 years or older weighing at least 40 kilograms (kg), and one RCT included adolescents aged 12 to 17 years who weighed at least 25 kg. Study sample sizes ranged from 267 to 838 participants and were conducted over 12 to 16 weeks.[1] Moderate-to-severe AD was defined as an IGA of 3 or more, EASI score of 16 or more, and involving a total BSA of at least 10%.[1] Participants enrolled in the RCTs had either an inadequate response to 4 weeks of topical calcineurin inhibitors or topical corticosteroids or were unable to receive topical treatments within 12 months of the study.[1] Participants were permitted to use oral antihistamines and non-medicated emollients as adjunctive therapy during the trials.[1]

Abrocitinib demonstrated superior efficacy over placebo in achieving IGA response of 0 or 1 and EASI-75 by week 12 or 16 based on high-quality evidence from the phase 3 trials.[1] In one RCT, moderate-quality evidence showed both doses of abrocitinib were similar to dupilumab in achieving EASI-75 response at week 16; however, the study was not powered to detect significant differences between the 2 study arms.[4] A summary of study characteristics and primary outcome data is presented in **Table 3.**

Table 3. Study Characteristics and Results: Abrocitinib for Moderate-to-Severe Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Primary Outcome or Co-Primary Outcomes	Adverse Effects
Gooderham et al.[48] NCT02780167 Low	▪ Phase 2b ▪ DB, MC, PC, RCT ▪ n=267 ▪ Adults 18-75 yo ▪ 12 weeks	1. ABRO 10 mg po daily (n=46) 2. ABRO 30 mg po daily (n=45) 3. ABRO 100 mg po daily (n=54) 4. ABRO 200 mg po daily (n=48) 5. Oral Placebo daily (n=52)	**Proportion of participants who achieved IGA of 0 or 1** 1. ABRO 10 mg: 10.9% (n=5; NS) 2. ABRO 30 mg: 8.9% (n=4; NS) 3. ABRO 100 mg: 29.6% (n=16; p<0.001) 4. ABRO 200 mg: 43.8% (n=21; p<0.001) 5. Placebo: 5.8% (n=3)	**Total TEAEs for all study arms:** 16.5% (n=44) ▪ Worsening AD: 7.5% ▪ Eczema: 2.2% ▪ Abdominal pain: 0.7%
Simpson et al.[49] JADE MONO-1 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=387 ▪ Adults and adolescents ≥12 yo and weight ≥ 40 kg) ▪ 12 weeks	1. ABRO 100 mg po daily (n=156) 2. ABRO 200 mg po daily (n=154) **3.** Oral Placebo daily (n=77)	**Proportion of participants who achieved IGA response of 0 or 1** 1. ABRO 100 mg: 24% (n=37) Difference vs. placebo: 15.8% (95% CI 6.8 to 24.8; p<0.0001; NNT=7) 2. ABRO 200 mg: 44% (n=67) Difference vs. placebo: 36.0% (95% CI 26.2 to 46.57; p<0.0001; NNT=3) 3. Placebo: 8% (n=6) **Proportion of participants who achieved EASI-75** 1. ABRO 100 mg: 40% (n=62) Difference vs. placebo: 27.9% (95% CI 17.4 to 38.3; p<0.0001; NNT=4) 2. ABRO 200 mg: 63% (n=96) Difference vs. placebo: 51.0% (95% CI 40.5 to 61.5; p<0.0001; NNT=2) 3. Placebo: 12% (n=9)	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 3% (n=5) 2. ABRO 200 mg: 3% (n=5) 3. Placebo: 4% (n=3)
Silverberg et al.[50] JADE MONO-2 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=391 ▪ Adults and adolescents ≥ 12 yo and weight ≥ 40kg ▪ 12 weeks	1. ABRO 100 mg po daily (n=158) 2. ABRO 200 mg po daily (n=155) **3.** Oral Placebo daily (n=78)	**Proportion of participants who achieved IGA response** 1. ABRO 100 mg: 28.4% (n=44) Difference vs. placebo: 19.3% (95% CI 9.6 to 29.0; p<0.001; NNT=6) 2. ABRO 200 mg: 38.1% (n=59) Difference vs. placebo: 28.7% (95% CI 18.6 to 38.8; p<0.001; NNT=4) 3. Placebo: 9.1% (n=7) **Proportion of participants who achieved EASI-75**	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 3.2% (n=5) 2. ABRO 200 mg: 1.3% (n=2) 3. Placebo: 1.3% (n=1)

			1. ABRO 100 mg: 44.5% (n=69) Difference vs. placebo: 33.9% (95% CI 23.3 to 44.4; p<0.001; NNT=3) 2. ABRO 200 mg: 61% (n=94) Difference vs. placebo: 50.5% (95% CI 40 to 60.9; p<0.001; NNT=2) 3. Placebo: 10.4% (n=8)	
Beiber et al.[4] JADE COMPARE	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=838 ▪ Adults aged ≥ 18 yo ▪ 16 weeks	1. ABRO 100 mg po daily (n=238) 2. ABRO 200 mg po daily (n=226) 3. Dupilumab 600 mg SC x 1 dose, then 300 mg SC every other week (n=243) **4.** Oral Placebo daily (n=131)	**Proportion of participants who achieved IGA response of 0 or 1** 1. ABRO 100 mg: 36.6% (n=86) Difference vs. placebo: 23.1% (95% CI 14.7 to 31.4; p<0.001; NNT=5) 2. ABRO 200 mg: 48.4% (n=106) Difference vs. placebo: 34.8% (95% CI 26.1 to 43.5 ; p<0.001; NNT=3) 3. Dupilumab 300 mg: 36.5% (n=88) Difference vs. ABRO: NR 4. Placebo: 14% (n=18) **Proportion of participants who achieved EASI-75** 1. ABRO 100 mg: 58.7% (n=138) Difference vs. placebo: 31.9% (95% CI 22.2 to 41.6; p<0.001; NNT=4) 2. ABRO 200 mg: 70.3% (n=154) Difference vs. placebo: 43.2% (95% CI 33.7 to 52.7; p<0.001; NNT=3) 3. Dupilumab 300 mg: 58.1% (n=140) Difference vs. ABRO: NR 4. Placebo: 27.1% (n=35)	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 2.5% (n=6) 2. ABRO 200 mg: 0.9% (n=2) 3. Dupilumab 300 mg: 0.8% (n=2) 4. Placebo: 3.8% (n=5)
Eichenfield et al.[51] JADE TEEN Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=273 ▪ Adolescents aged ≥12 to 17 yo and weight ≥ 25 kg ▪ 12 weeks	1. ABRO 100 mg po daily (n=92) 2. ABRO 200 mg daily (n=91) **3.** Oral Placebo daily (n=90)	**Proportion of participants who achieved IGA score improvement** 1. ABRO 100 mg: 41.6% (n=37) Difference vs. placebo: 16.7% (95% CI 3.5 to 29.9; p<0.05; NNT=6) 2. ABRO 200 mg: 46.2% (n=43) Difference vs. placebo: 20.6% 3. (95% CI 7.3 to 33.9; p<0.05; NNT=5) 4. Placebo: 24.5% (n=23) **Proportion of participants who achieved EASI-75** 1. ABRO 100 mg: 68.5% (n=61)	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 0% 2. ABRO 200 mg: 1.1% (n=1) 3. Placebo: 2.1% (n=2)

			Difference vs. placebo: 26.5% (95% CI 13.1 to 39.8; p<0.05; NNT=4) 2. ABRO 200 mg: 72% (n=67) Difference vs. placebo: 29.4% (95% CI 16.3 to 42.5; p<0.05; NNT=4 **3.** Placebo: 41.5% (n=39)	
Abbreviations: ABRO=abrocitinib; AD=atopic dermatitis; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; kg=kilogram; MC=multi-center; mg=milligrams; N=number; NNT = number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; PO=oral; RCT=randomized controlled trial; SAEs=serious adverse events; SC=subcutaneous; TEAEs=treatment-emergent adverse effects; yo=years old				

One notable AE associated with abrocitinib is a transient drop in platelets during the first few weeks of treatment.[1] The thrombocytopenia appears to be dose-related and no participants discontinued clinical trials due to this AE.[1] In the phase 3 trials, high-quality evidence showed abrocitinib had higher rates of GI disorders, acne, herpes infections, headache, and thrombocytopenia compared with placebo.[1] One RCT demonstrated abrocitinib had similar AEs to dupilumab based on moderate-quality evidence; however dupilumab had higher rates of conjunctivitis.[1] As with other JAK inhibitors, abrocitinib prescribing information has a FDA black boxed warning regarding the risk of serious opportunistic infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis associated with abrocitinib administration.[6] Adverse events occurring in 1.5% or more of abrocitinib patients compared with placebo in clinical studies are described in **Table 4.**

Table 4. Adverse Events Reported In Clinical Trials Of Abrocitinib Compared With Placebo[6]

Adverse Event	Abrocitinib 200 mg (n=590)	Abrocitinib 100mg (n=608)	Placebo (n=342)
Nausea	14.5%	6.0%	2.1%
Nasopharyngitis	8.7%	12.4%	7.9%
Headache	7.8%	6.0%	3.5%
Acne	4.7%	1.6%	0.0%
Herpes Simplex	4.2%	3.3%	1.8%
Vomiting	3.2%	1.5%	0.9%
Increased blood creatinine phosphokinase	2.9%	2.3%	1.5%
Dizziness	2.9%	1.8%	0.9%
Urinary Tract Infection	2.2%	1.7%	1.2%
Upper Abdominal Pain	1.9%	0.6%	0.0%
Thrombocytopenia	1.5%	0.0%	0.0%

The FDA-approved indication for abrocitinib is for the treatment of adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when the use of those therapies is inadvisable.[6] The recommended starting abrocitinib dose is 100 mg orally once daily.[6] Abrocitinib should be avoided in patients with severe renal impairment, end-stage renal disease, or severe hepatic impairment.[6] If patients are taking strong inhibitors of CYP2C19, the recommended dose is 50 mg or 100 mg once daily.[6] Use of abrocitinib is not advised if patients are taking a moderate to strong inhibitor of both CYP2C19 and CYP2C9.[6] Antiplatelet therapies except for aspirin 81 mg per day or less are contraindicated during the first 3 months of treatment.[6] Laboratory monitoring is recommended due to potential changes in platelets, lymphocytes, and lipids.[6]

Ruxolitinib

Ruxolitinib is selective inhibitor of JAK1 and JAK2. Three RCTs analyzed the safety and efficacy of topical ruxolitinib for people with mild-to-moderate AD. One study was a phase 2, dose-finding RCT with low risk-of-bias, and 2 identical phase 3 RCTs with moderate risk-of-bias compared ruxolitinib with placebo in adolescents and adults with mild-to-moderate AD.[1] Sample sizes ranged from 307 to 631 participants.[1] Study durations were short, ranging from 4 weeks to 8 weeks.[1] Criteria for study enrollment was similar across the RCTs: diagnosis of AD for least 2 years; IGA score of 2 or 3; and total BSA involvement of up to 20%.[1] Study details and primary outcome results are presented in **Table 5**. Adverse events reported during clinical trials are summarized in **Table 6**.

The primary end point of the Phase 2 study was mean percentage change from baseline in EASI score at week 4 in patients treated with ruxolitinib 1.5% cream twice daily versus patients treated with placebo twice daily.[52] Ruxolitinib 1.5% cream twice daily demonstrated a greater mean percentage change from baseline in EASI scores versus placebo at week 4 (71.6% vs. 15.5%; 95% CI not reported; p<0.0001).[52] No significant differences in EASI improvement at week 4 were observed between ruxolitinib 1.5% and triamcinolone.[52]

In the phase 3 RCTs, high-quality evidence demonstrated a greater proportion of patients treated with ruxolitinib cream (both 0.75% and 1.5% strengths) achieved IGA-treatment success (defined as a score of 0 or 1 with ≥2-grade improvement in IGA from baseline) versus placebo (p<0.0001 for all comparisons).[53] High-quality evidence indicated there were no differences between placebo and ruxolitinib in AE incidence rates.[1] Application site pain was the most frequently reported AE in both ruxolitinib and placebo groups.[1] There are insufficient data on ruxolitinib long-term safety and potential adverse effects due to systemic absorption.[1]

Table 5. Study Characteristics and Results: Topical Ruxolitinib for Mild-to-Moderate Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Primary Outcome	Adverse Effects
Kim et al.[52] NCT03011892 Low	▪ Phase 2 ▪ DB, MC, PC, RCT ▪ n=307 ▪ Adults 18 to 70 yo ▪ 4 weeks	1. RUX 0.15% QD (n=51) 2. RUX 0.5% QD (n=51) 3. RUX 1.5% QD (n=52) 4. RUX 1.5% BID (n=50) 5. Triamcinolone 0.1% BID (n=51) 6. Placebo BID (n=52)	**Mean percentage change in EASI at week 4:** 1. RUX 0.15%: 45.4% (Statistics NR) 2. RUX 0.5%: 52.2% (Statistics NR) 3. RUX 1.5% QD: 67% RUX vs. Vehicle p<0.0001 RUX vs. Triamcinolone: NS 4. RUX 1.5% BID: 71.6% RUX vs. Vehicle p<0.0001 RUX vs. Triamcinolone: NS 5. Triamcinolone 0.1% BID: 59.8% 6. Placebo BID: 15.5%	**Patients with TEAEs** 1. RUX 0.15% QD: 37.3% 2. RUX 0.5% QD: 21.6% 3. RUX 1.5% QD: 33.3% 4. RUX 1.5% BID: 24% 5. Triamcinolone 0.1% BID: 33.3% 6. Placebo BID: 32.7%
Papp et al.[53] TRuE-AD1 Moderate	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=631 ▪ Adults and adolescents ≥ 12 yo ▪ 8 weeks	1. RUX 0.75% BID (n=252) 2. RUX 1.5% BID (n=253) 3. Placebo BID (n=126)	**Proportion of participants who achieved IGA score of 0 or 1 and ≥2 point improvement** 1. RUX 0.75%: 50.0% (n=126) Difference vs. placebo: 34.9% (95% CI 26.1 to 43.7; p<0.0001; NNT=3) 2. RUX 1.5%: 53.8% (n=136) Difference vs. placebo: 38.9%	**Patients with SAES (combined study analysis)** 1. RUX 0.75%: 0.8% (n=4) 2. RUX 1.5%: 0.6% (n=3) 3. Placebo: 0.8% (n=2)

			(95% CI 30.3 to 47.4; p<0.0001; NNT=3) 3. Placebo: 15.1% (n=19) **Proportion of participants who achieved EASI-75** 1. RUX 0.75%: 56.0% (n=142) Difference vs. placebo: 31.4% (95% CI 21.7 to 41.1; p<0.0001; NNT=4) 2. RUX 1.5%: 62.1% (n=158) Difference vs. placebo: 37.5% (95% CI 27.8 to 47.1; p<0.0001;NNT=3) 3. Placebo: 24.6% (n=31)	**Patients with TEAEs (combined study analysis)** **1.** RUX 0.75%: 26.5% (n=132) 2. RUX 1.5%: 29% (n=145) 3. Placebo: 33.2% (n=83) **Discontinuation due to TEAEs (combined study analysis)** 1. RUX 0.75%: 0.8% (n=4) 2. RUX 1.5%: 0.8% (n=4) **3.** Placebo: 3.2% (n=8)
Papp et al.[53] TRuE-AD2 Moderate	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=618 ▪ Adults and adolescents ≥ 12 yo ▪ 8 weeks	1. RUX 0.75% BID (n=248) 2. RUX 1.5% BID (n=246) 3. Placebo BID (n=124)	**Proportion of participants who achieved IGA score of 0 or 1 and ≥2 point improvement** 1. RUX 0.75%: 39.0% (n=91) Difference vs. placebo: 31.3% 95% CI 23.4 to 39.2; p<0.0001; NNT=4) 2. RUX 1.5%: 51.3% (n=117) Difference vs. placebo: 43.7% (95% CI 35.6 to 51.8; p<0.0001; NNT=3) 3. Placebo: 7.6% (n=9) **Proportion of participants who achieved EASI-75** 1. RUX 0.75%: 51.5% (n=128) Difference vs. placebo: 37.1% (95% CI 28.1 to 42.6; p<0.0001; NNT=3) 2. RUX 1.5%: 61.8% (n=140) Difference vs. placebo: 47.4% (95% CI 38.5 to 56.4; p<0.0001; NNT=3) 3. Placebo: 14.4% (n=17)	**See Above**
Abbreviations: AD=atopic dermatitis; BID=twice daily; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; MC=multi-center; N=number; NNT=number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; QD=once daily; RCT=randomized controlled trial; RUX=ruxolitinib; SAEs=serious adverse events; TEAEs=treatment-emergent adverse effects; yo=years old				

The FDA-approved indication for ruxolitinib 1.5% cream is for the short term and non-continuous treatment of mild-to-moderate AD in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with other topical prescription therapies or when those therapies are not advisable.[7] Treatments for mild-to-moderate AD are not funded by HERC.[3] Use of ruxolitinib with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.[7] The cream should be applied twice daily to affected areas of up to 20% of body surface area.[7] As with other JAK inhibitors, the label for topical ruxolitinib has a FDA black boxed warning regarding the risk of serious infections, mortality, MACE, and thrombosis associated with JAK inhibitor administration for inflammatory conditions.[7] Adverse events occurring in 1% or more of ruxolitinib patients compared with vehicle placebo in clinical studies are described in **Table 6.**

Table 6. Adverse Events Reported With Ruxolitinib In Clinical Trials compared with Placebo[7]

Adverse Event	Ruxolitinib (n=499)	Vehicle (n=250)
Nasopharyngitis	27%	33%
Bronchitis	3%	1%
Ear Infection	1%	0%
Decreased Eosinophil Count	1%	0%
Urticaria	1%	0%
Diarrhea	1%	<1%
Folliculitis	1%	0%
Tonsillitis	1%	0%
Rhinorrhea	1%	<1%

Tralokinumab

Tralokinumab is an IL-13 antagonist formulated for subcutaneous injection. Four placebo-controlled RCTs with low-to-moderate risk of bias assessed the safety and efficacy of tralokinumab for treatment of moderate-to-severe AD.[1] One dose-finding phase 2 trial and phase 3 RCTs enrolled participants diagnosed with moderate-to-severe AD with an EASI score of 12 or greater, IGA of 3 or more, and BSA involvement of 10% or more.[1] In the phase 2 trial, enrollees continued topical corticosteroids and could use rescue therapy as long it was not as systemic agent or topical calcineurin inhbitor.[1] In 2 of the phase 3 studies, ECZTRA 1 and ECZTRA 2, participants were permitted to use emollients twice daily, rescue topical corticosteroid therapy, and systemic glucocorticoids.[1] Patients who received rescue treatment (systemic and topical) were labeled as nonresponders by the investigators.[54] In the third phase 3 trial, ECZTRA 3, tralokinumab was combined with topical mometasone 0.1% cream as needed in patients with similar characteristics as those enrolled in ECZTRA 1 and ECZTRA 2. Studies were conducted over 12 to 16 weeks with relatively large sample sizes (n=340 to 800). Additional study details and results are presented in **Table 7**.

The primary endpoints for all studies were achievement of an IGA of 0 to 1 and improvement of EASI by 75% or more over 12 to 16 weeks. In the phase 2 RCT, EASI was improved with tralokinumab 150 mg and 300 mg doses in combination with topical corticosteroids compared with placebo at 12 weeks based on moderate-quality evidence.[1] In the ECZTRA 1 and ECZTRA 2 trials, there was moderate-quality evidence that showed tralokinumab monotherapy was superior to placebo in achieving EASI-75 at 12 weeks.[1] Tralokinumab was superior to placebo in achieving IGA 0 or 1 at 12 weeks based on low-quality evidence from these trials.[1] The DERP authors downgraded the evidence assessment for IGA outcome due to inconsistency and indirectness.[1] In ECZTRA 3, moderate-quality evidence demonstrated tralokinumab combined with topical mometasone was superior to placebo in achieving IGA of 0 to 1 and EASI-75 at 16 weeks.[1]

Table 7. Study Characteristics and Results: Tralokinumab for Moderate-to-Severe Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Co-Primary Outcomes	Adverse Effects
Wollenberg et al.[55] NCT02347176 Moderate	▪ Phase 2 ▪ DB, MC, PC, RCT ▪ n=204 ▪ Adults aged 18 -75 yo ▪ 12 wks	1. TRAL 45 mg SC every 2 wks (n=50) 2. TRAL 150 mg SC every 2 wks (n=51) 3. TRAL 300 mg SC every 2 wks (n=52) 4. Placebo every 2 wks (n=51)	**Change in EASI score from baseline to week 12** 1. TRAL 45 mg: -13.67 (NS) MD vs placebo: NS 2. TRAL 150 mg: -15.14 MD vs placebo: -4.36 (95% CI -8.22 to -0.51; p<0.05) 3. TRAL 300 mg: - 15.72 MD vs placebo: -4.94 (95% CI -8.76 to -1.13; p<0.05) 4. Placebo: -10.78 **Proportion of participants who achieved IGA score of 0 or 1** 1. TRAL 45 mg: 11.6% (n=6) Difference vs placebo: NS 2. TRAL 150 mg: 19.5% (n=10) Difference vs placebo: 7.7 (95% CI -6.1 to 21.5; NS) 3. TRAL 300 mg: 26.7% (n=13) Difference vs placebo: 14.8 (95% CI 0 to 29.7; NS) 4. Placebo: 11.8% (n=6)	**Patients with TEAEs** 1. TRAL 45 mg: 24% (n=12) 2. TRAL 150 mg: 17.6% (n=9) 3. TRAL 300 mg: 11.5% (n=6) 4. Placebo: 17.6% (n=9)
Wollenberg et al.[54] ECZTRA 1 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ N=802 ▪ Adults ≥ 18 yo ▪ 16 wks	1. TRAL 300 mg SC every 2 wks after 600 mg LD (n=601) 2. Placebo SC every 2 wks (n=197) • Monotherapy	**Proportion of participants who achieved IGA score of 0 or 1** 1. TRAL 300 mg: 15.8% (n=95) 2. Placebo: 7.1% (n=14) Difference: 8.6% (95% CI 4.1 to 13.1; p=0.002; NNT=12) **Proportion of participants who achieved EASI-75** 1. TRAL 300 mg: 25.0% (n=150) 2. Placebo: 12.7% (n=25) Difference: 12.1% (95% CI 6.5 to 17.7; p<0.001; NNT=9)	**Patients with SAES** 1. TRAL 300 mg: 3.9% (n=24) 2. Placebo: 5.6% (n=11)
Wollenberg et al.[54] ECZTRA 2	▪ Phase 3 ▪ DB, MC, PC, RCT	1. TRAL 300 mg SC every 2 weeks after 600 mg LD (n=591)	**Proportion of participants who achieved IGA score of 0 or 1**	**Patients with SAEs** 1. TRAL 300 mg: 1.68% (n=10)

Low	▪ N=794 ▪ Adults ≥ 18 yo ▪ 16 wks	2. Placebo SC every 2 wks (n=201) • Monotherapy	1. TRAL 300 mg: 22.2% (n=131) 2. Placebo: 10.9% (n=22) Difference: 11.1% (95% CI 5.8 to 16.4; p<0.001; NNT=9) **Proportion of participants who achieved EASI-75** 1. TRAL 300 mg: 33.2% (n=196) 2. Placebo: 11.4% (n=23) Difference: 21.6% (95% CI 15.8 to 27.3; p<0.001; NNT=5)	2. Placebo: 3% (n=6)
Silverberg et al.[56] ECZTRA 3 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ N=380 ▪ Adults ▪ 16 wks	1. TRAL 300 mg SC every 2 weeks after 600 mg LD (n=253) 2. Placebo SC every 2 weeks (n=127) • Both arms continued a topical corticosteroid during the study	**Proportion of participants who achieved IGA score of 0 or 1** 1. TRAL 300 mg: 38.9% (n=98) 2. Placebo: 26.2% (n=33) Difference: 12.4% (95% CI 2.9 to 21.9; p<0.001; NNT=4) **Proportion of participants who achieved EASI-75** 1. TRAL 300mg: 56.0% (n=141) 2. Placebo: 35.7% (n=45) Difference: 20.2% (95% CI 9.8 to 30.6; p<0.001; NNT=5)	**Patients with SAEs** 1. TRAL 300 mg: 0.8% (n=2) 2. Placebo: 3.2% (n=4)

Abbreviations: AD=atopic dermatitis; BID=twice daily; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; LD=loading dose; MC=multi-center; MD=mean difference; N=number; NNT= number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; QD=once daily; RCT=randomized controlled trial; SAEs=serious adverse events; SC=subcutaneous; TEAEs=treatment-emergent adverse effects; TRAL=tralokinumab; wks=weeks; yo= years old

Low-quality evidence demonstrated tralokinumab increased the risk of infection-type AEs over placebo.[1] Most AEs were mild to moderate. The most commonly reported AEs reported in more than 5% of participants and occurring more frequently with tralokinumab than placebo were viral upper respiratory tract infections, upper respiratory tract infections, and conjunctivitis.[1] The most frequently reported AEs in tralokinumab clinical trials are summarized in **Table 8**.[8]

Table 8. Adverse Events Reported in Clinical Trials with Tralokinumab and Placebo[8]

Adverse Reaction	Tralokinumab Monotherapy		Tralokinumab Combined with Mometasone	
	Tralokinumab (n=1180)	Placebo (n=388)	Tralokinumab (n=243)	Placebo (n=123)
Upper respiratory infection	23.8%	20.4%	30.0%	15.4%
Conjunctivitis	7.5%	3.1%	13.6%	4.9%
Injection Site Reactions	7.4%	4.1%	11.1%	0.8%
Eosinophilia	1.4%	0.5%	1.2%	0%

Tralokinumab is FDA-approved for the treatment of moderate-to-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[8] The recommended dose is an initial subcutaneous dose of 600 mg followed by 300 mg

administered every other week.[8] For patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment, the dose can be adjusted to 300 mg every 4 weeks.[8]

Upadacitinib

Upadacitinib is a selective JAK-1 inhibitor which is FDA-approved for management of RA in adults and treatment of moderate-to-severe AD in patients aged 12 years and older.[9] Four RCTs with low-to-moderate risk of bias were conducted in adults and adolescents with AD.[1] The phase 2 RCT was a dose-ranging study in patients with an AD diagnosis for at least 2 years, EASI score of 12 or greater, and total BSA involvement of at least 10%. Two identical phase 3 RCTs were placebo-controlled and an additional head-to-head phase 3 trial included dupilumab as an active comparator. In all 3 of the phase 3 RCTs participants had a confirmed moderate-to-severe AD diagnosis with an IGA score of 3 or more, EASI score of 16 or more, and total BSA involvement of least 10%.[1]

In one placebo-controlled phase 3 RCT, patients were randomized to upadacitinib 15 mg or 30 mg in combination with topical corticosteroid therapy in adults (18 to 75 years of age) and adolescents (12 to 17 years of age) with moderate-to-severe AD.[57] Rescue therapy was permitted with topical calcineurin inhibitors or crisaborole.[57] In the MEASURE UP 1 and MEASURE UP 2 RCTs, no additional therapies were allowed, although rescue therapy was permitted beginning at week 4.[58] These trials were conducted during the COVID-19 pandemic, so accommodations were made for site disruptions and remote visits.[1] In the HEADS UP trial, participants had to be candidates for systemic therapy which was defined as having an inadequate response to topical treatments, documented use of systemic treatment, or topical treatments were otherwise medically inadvisable.[5] Rescue therapy could be administered at any time per investigator discretion.[5]

Upadacitinib was superior to placebo in achieving EASI-75 and IGA 0 or 1 in 3 clinical trials based on high-quality evidence.[1] Upadacitinib was superior to dupilumab in achieving EASI-75 (NNT = 10) in the HEADS UP trial based on high-quality evidence.[1] Study details and results are presented in **Table 9**.

High-quality evidence showed upadacitinib had similar AEs to placebo with higher rates of acne observed with upadacitinib.[1] Moderate-quality evidence showed similar rates of AEs between upadacitinib and dupilumab with higher rates of acne, upper respiratory tract infections, and increased creatinine phosphokinase (CPK) observed with upadacitinib.[1]

Table 9. Study Characteristics and Results: Upadacitinib for Moderate-to-Severe Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Co-Primary Outcomes	Adverse Effects
Guttman-Yassky et al.[59] NCT02925117 Low	• Phase 2 • DB, MC, PC, RCT • N=167 • Adults ≥ 18 yo • 16 wks	1. UPAD 7.5 mg po once daily (n=42) 2. UPAD 15 mg po once daily (n=42) 3. UPAD 30 mg po once daily (n=42) 4. Placebo po once daily (n=41)	**Percentage improvement in EASI** 1. UPAD 7.5 mg: 39% Difference vs placebo: 16% (95% CI 1.4 to 31; p=0.03) 2. UPAD 15 mg: 62% Difference vs placebo: 39% (95% CI 24 to 54; p<0.001) 3. UPAD 30 mg: 74% Difference vs placebo: 51% (95% CI 36 to 67; p<0.001)	**Patients with SEAS** 1. UPAD 7.5 mg: 4.8% (n=2) 2. UPAD 15 mg: 2.4% (n=1) 3. UPAD 30 mg: 0% 4. Placebo: 2.5% (n=1)

			4. Placebo: 23%	
Reich et al.[57] AD Up Low	• Phase 3 • DB, MC,PC, RCT • N=901 • Adolescents and Adults ≥ 12 yo • 16 wks	1. UPAD 15 mg po once daily + TCS (n=300) 2. UPAD 30 mg po once daily + TCS (n=297) 3. Placebo po once daily + TCS (n=304)	**Proportion of participants who achieved EASI-75** 1. UPAD 15 mg: 65% (n=194) Difference vs placebo: 38.1% (95% CI 30.8 to 45.4; p<0.0001; NNT=3) 2. UPAD 30 mg: 77% (n=229) Difference vs placebo: 50.6% (95% CI 43.8 to 57.4; p<0.0001; NNT=2) **3.** Placebo: 26% (n=80) **Proportion of participants who achieved IGA score of 0 or 1** 1. UPAD 15 mg: 40% (n=119) Difference vs placebo: 28.5% (95% CI 22.1 to 34.9; p<0.0001; NNT=4) 2. UPAD 30 mg: 59% (n=174) Difference vs placebo: 47.6% (95% CI 41.1 to 54.0; p<0.0001; NNT=3) 3. Placebo: 11% (n=33)	**Patients with SEAS** 1. UPAD 15 mg: 2% (n=7) 2. UPAD 30 mg: 1% (n=4) 3. Placebo: 9% (n=3)
Guttman-Yassky et al.[58] Measure Up 1 Low	• Phase 3 • DB, MC, PC, RCT • N=847 • Adults and adolescents aged ≥ 12 yo • 16 wks	1. UPAD 15 mg po once daily (n=281) 2. UPAD 30mg po once daily (n=285) 3. Placebo po once daily (n=281)	**Proportion of participants who achieved EASI-75** 1. UPAD 15 mg: 69.6% (n=196) Difference vs placebo: 53.3% (95% CI 46.4 to 60.2; p<0.0001; NNT=2) 2. UPAD 30 mg: 79.7% (n=227) Difference vs. placebo: 63.4% (95% CI 57.1 to 69.8; p<0.0001; NNT=2) 3. Placebo: 16.3% (n=46) **Proportion of participants who achieved IGA score of 0 or 1** **1.** UPAD 15 mg: 48.1% (n=135) Difference vs placebo: 39.8% (95% CI 33.2 to 46.4; p<0.0001; NNT=3) **2.** UPAD 30 mg: 62% (n=177) Difference vs placebo: 53.6% (95% CI 47.2 to 60.0; p<0.0001; NNT=2) **3.** Placebo: 8.4% (n=24)	**Patients with SEAS** 1. UPAD 15 mg: 2% (n=6) 2. UPAD 30 mg: 3% (n=8) 3. Placebo: 8% (n=3)
Guttman-Yassky et al.[58] Measure Up 2 Low	• Phase 3 • DB, MC, PC, RCT • N=836	1. UPAD 15 mg po once daily (n=276) 2. UPAD 30mg po once daily (n=282) 3. Placebo po once daily (n=278)	**Proportion of participants who achieved EASI-75** 1. UPAD 15 mg: 60.1% (n=166) Difference vs placebo: 46.9% (95% CI 39.9 to 53.9; p<0.0001; NNT=3)	**Patients with SEAS** 1. UPAD 15 mg: 2% (n=5) 2. UPAD 30 mg: 3% (n=7) 3. Placebo: 8% (n=3)

	• Adults and adolescents ≥ 12 yo • 16 wks		2. UPAD 30 mg: 72.9% (n=206) Difference vs placebo: 59.6% (95% CI 53.1 to 66.2; p<0.0001; NNT=2) 3. Placebo: 13.3% (n=37) **Proportion of participants who achieved IGA score of 0 or 1** 1. UPAD 15 mg: 38.8% (n=107) Difference vs placebo: 34% (95% CI 27.8 to 40.2; p<0.0001; NNT=3) 2. UPAD 30 mg: 52% (n=147) Difference vs placebo: 47.4% (95% CI 41.0 to 53.7; p<0.0001; NNT=3) 3. Placebo: 4.7% (n=13)	
Blauvelt et al.[5] HEADS Up Moderate	• Phase 3 • DB, AC, MC, RCT • N=692 • Adults ≥ 18 yo • 16 wks	1. UPAD 30 mg po once daily (n=348) 2. Dupilumab 300 mg SC every 2 weeks after 600 mg LD (n=344)	**Proportion of participants who achieved EASI-75** UPAD 30 mg: 71% (n=247) Dupilumab 300 mg: 61.1% (n=210) Difference: 10% (95% CI 2.9 to 17.0; p=0.006; NNT=10)	**Patients with SEAS** 1. UPAD 30 mg: 2.9% (n=10) 2. Dupilumab 300 mg: 1.2% (n=4)

Abbreviations: AC=active-comparator; AD=atopic dermatitis; BID=twice daily; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; LD=loading dose; MC=multi-center; MD=mean difference; N=number; NNT=number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; po=oral; RCT=randomized controlled trial; SAEs=serious adverse events; SC=subcutaneous; TCS=topical corticosteroid; TEAEs=treatment-emergent adverse effects; UPAD=upadacitinib; wks=weeks; yo= years old

Summary

Current therapies for moderate-to-severe AD include topical creams, oral products and subcutaneous injections. Older therapies such as azathioprine and cyclosporine are effective, but carry risk of significant AEs including systemic immunosuppression.[1] Azathioprine showed mixed long-term efficacy with many participants discontinuing treatment over time due to AEs.[1] Studies for cyclosporine highlighted there is insufficient high-quality comparative evidence with other oral immunomodulators (methotrexate, mycophenolate, prednisolone).[1] Topical tacrolimus and pimecrolimus have demonstrated superiority to placebo and therapeutic equivalence.[1] Topical ruxolitinib showed good efficacy in achieving EASI-75 and IGA 0 or 1 for managing mild-to-moderate AD, which is not funded by OHP. The oral JAK-inhibitors, abrocitinib and upadacitinib, showed effective response rates in EASI-75 and IGA 0 or 1 in patients with moderate-to-severe AD. Tralokinumab, an injectable IL-13 antagonist, was shown to be superior to placebo in short-term trials. Further published studies are needed to demonstrate safety of ruxolitinib, abrocitinib, and tralokinumab with long-term use beyond 52 weeks.

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Appendix 1: Current Preferred Drug List

Atopic Dermatitis PDL Class (Topical Products)

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

Asthma Biologics (Select Systemic Products)

Generic	Brand	Route	Form	PDL
dupilumab	DUPIXENT PEN	SUBCUT	PEN INJCTR	N
dupilumab	DUPIXENT SYRINGE	SUBCUT	SYRINGE	N
tralokinumab-ldrm	ADBRY	SUBCUT	SYRINGE	N
abrocitinib	CIBINQO	ORAL	TABLET	

Targeted Immune Modulators (Select Systemic Products)

Generic	Brand	Route	Form	PDL
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1946 to February Week 1, 2022, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to February 16, 2022

1. Dermatitis, Atopic/	22299
2. Eczema/	11785
3. Calcineurin Inhibitors/	4191
4. Pimecrolimus.mp.	889
5. Tacrolimus/	16993
6. Crisaborole.mp.	124
7. Dupilumab.mp.	1100
8. exp Janus Kinase Inhibitors/	896
9. abrocitinib	40
10. ruxolitinib	1734
11. tralokinumab	97
12. upadacitinib	204
13. baricitinib	541
14. lebrikizumab	96
15. nemolizuamb	57
16. 1 or 2	32181
17. 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	23863
18. 16 and 17	505
19. limit 19 to (english language and humans and yr="2020 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	85

Appendix 3: Prioritized List Guideline Note

Extracted from the January 1, 2022 Prioritized List
Searchable Prioritized List 2022

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE
Lines 426,482,504,532,541,656

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus
G) Vitiligo

The conditions above are included on Line 426 if severe, defined as having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:

- At least 10% of body surface area involved
- Hand, foot, face, or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 482, 504, 532, 541 and 656.
For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.

For severe atopic dermatitis/eczema, first-line agents include topical moderate- to high- potency corticosteroids and narrowband UVB. Second line agents include topical calcineurin inhibitors (e.g. pimecrolimus, tacrolimus), topical phosphodiesterase (PDE)-4 inhibitors (e.g. crisaborole), and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids). Use of the topical second line agents (e.g. calcineurin inhibitors and phosphodiesterase (PDE)-4 inhibitors) should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to at least one agent from each of the following three classes: 1) moderate to high potency topical corticosteroids, 2) topical calcineurin inhibitors or topical phosphodiesterase (PDE)-4 inhibitors, and 3) oral immunomodulator therapy.

ICD-10-CM Q82.8 (Other specified congenital malformations of skin) is included on Line 426 only for Darier disease.

Appendix 4: Prescribing Information Highlights

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

CIBINQO$_{TM}$ (abrocitinib) tablets, for oral use
Initial U.S. Approval: 2022

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), and THROMBOSIS
See full prescribing information for complete boxed warning.

- **Increased risk of serious bacterial, fungal, viral and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Discontinue treatment with CIBINQO if serious or opportunistic infection occurs. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death, with another JAK inhibitor vs. TNF blockers in rheumatoid arthritis (RA) patients. CIBINQO is not approved for use in RA patients. (5.2)**
- **Malignancies have occurred with CIBINQO. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients. (5.3)**
- **MACE has occurred with CIBINQO. Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients. (5.4)**
- **Thrombosis has occurred with CIBINQO. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers. (5.5)**

----------INDICATIONS AND USAGE----------
CIBINQO is a Janus kinase (JAK) inhibitor indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. (1)

Limitation of Use: CIBINQO is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

----------DOSAGE AND ADMINISTRATION----------
- For recommended testing, evaluations and procedures prior to CIBINQO initiation, see Full Prescribing Information. (2.1)
- Recommended dosage is 100 mg orally once daily. (2.2)
- 200 mg orally once daily is recommended for those patients who are not responding to 100 mg once daily. (2.2)
- Moderate renal impairment: 50 mg once daily or 100 mg once daily for those patients who are not responding to 50 mg once daily. (2.3)
- CYP2C19 poor metabolizer: 50 mg once daily or 100 mg once daily for those patients who are not responding to 50 mg once daily. (2.4)
- For dosage modifications for certain adverse reactions, see Full Prescribing Information. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------
CIBINQO Tablets: 50 mg, 100 mg, and 200 mg (3)

----------CONTRAINDICATIONS----------
Antiplatelet therapies except for low-dose aspirin (≤81 mg daily), during the first 3 months of treatment. (4)

----------WARNINGS AND PRECAUTIONS----------
- Laboratory Abnormalities: Laboratory monitoring is recommended due to potential changes in platelets, lymphocytes, and lipids. (5.6)
- Immunizations: Avoid use of live vaccines prior to, during, and immediately after CIBINQO treatment. (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥1%) in subjects receiving 100 mg and 200 mg include:: nasopharyngitis, nausea, headache, herpes simplex, increased blood creatinine phosphokinase, dizziness, urinary tract infection, fatigue, acne, vomiting, oropharyngeal pain, influenza, gastroenteritis.
Most common adverse reactions (≥1%) in subjects receiving either 100 mg or 200 mg also include: impetigo, hypertension, contact dermatitis, upper abdominal pain, abdominal discomfort, herpes zoster, and thrombocytopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong inhibitors of CYP2C19: The recommended dose is 50 mg daily or 100 mg once daily for those patients who are not responding to 50 mg once daily. (2.5, 7.1)
- Moderate to strong inhibitors of both CYP2C19 and CYP2C9, or strong CYP2C19 or CYP2C9 inducers: Avoid concomitant use. (7.1)
- P-gp substrate where small concentration changes may lead to serious or life-threatening toxicities: Monitor or titrate dosage of P-gp substrate. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Breastfeeding not recommended. (8.2)
- Renal Impairment: Avoid use in patients with severe renal impairment or end-stage renal disease. (8.6)
- Hepatic Impairment: Avoid use in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2022

Opzelura™
(ruxolitinib) cream 1.5%

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

OPZELURA™ (ruxolitinib) cream, for topical use
Initial U.S. Approval: 2011

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Janus kinase inhibitors for inflammatory conditions. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.2)**
- **Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.3)**
- **Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.4)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.5)**

INDICATIONS AND USAGE

OPZELURA is a Janus kinase (JAK) inhibitor indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. (1)

Limitation of Use

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream: 1.5% ruxolitinib (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Serious Infections:* Serious bacterial, mycobacterial, fungal and viral infections have occurred. Regularly monitor patients for infection and manage it promptly. (5.1)
- *Non-melanoma Skin Cancers.* Basal cell and squamous cell carcinoma have occurred. Perform periodic skin examinations during treatment and following treatment as appropriate. (5.3)
- *Thrombosis.* Thromboembolic events have occurred. (5.5)
- *Thrombocytopenia, Anemia and Neutropenia:* Thrombocytopenia, anemia and neutropenia have occurred. Perform CBC monitoring as clinically indicated (5.6).

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥1%) are nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Incyte Corporation at 1-855-463-3463 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ADBRY™ (tralokinumab-ldrm) injection, for subcutaneous use
Initial U.S. Approval: 2021

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

ADBRY is an interleukin-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. ADBRY can be used with or without topical corticosteroids. (1)

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

- Prior to ADBRY initiation, complete all age appropriate vaccinations as recommended by current immunization guidelines (2.1)
- The recommended dosage of ADBRY is an initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. A dosage of 300 mg every 4 weeks may be considered for patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment. (2.2)
- Administer by subcutaneous injection. (2.2)

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

Injection: 150 mg/mL solution in a single-dose prefilled syringe with needle guard. (3)

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

Known hypersensitivity to tralokinumab-ldrm or any excipients in ADBRY. (4)

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

- Hypersensitivity: Hypersensitivity reactions, including anaphylaxis, and angioedema have occurred after administration of ADBRY. Discontinue ADBRY in the event of a hypersensitivity reaction. (5.1)
- Conjunctivitis and Keratitis: Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
- Parasitic (Helminth) Infections: Treat patients with pre-existing helminth infections before initiating treatment with ADBRY. If patients become infected while receiving ADBRY and do not respond to anti-helminth treatment, discontinue treatment with ADBRY until the infection resolves. (5.3)
- Risk of Infection with Live Vaccines: Avoid use of live vaccines. (5.4)

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

Most common adverse reactions (incidence ≥ 1%) are upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia. (6.1)

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

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

Revised: 01/2022

Topical Agents for Inflammatory Skin Disease

Goal(s):

- Restrict dermatological drugs only for funded OHP diagnoses. 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.

Length of Authorization:

- From 6 to 12 months

Requires PA:

- Non-preferred antipsoriatics
- All atopic dermatitis drugs
- STC = 92 and HIC = L1A, L5F, L9D, T0A
- This PA does not apply to 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 or Topical Atopic Dermatitis Drugs

Drug	Minimum Age
Crisaborole	3 months
Pimecrolimus	2 years
Ruxolitinib	12 years
Tacrolimus 0.03%	2 years
Tacrolimus 0.1%	16 years

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for mild or moderate inflammatory skin conditions?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the request for treatment of severe inflammatory skin disease? 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: 1. At least 10% body surface area involved OR 2. Hand, foot, face , or mucous membrane involvement	**Yes:** Go to #4	**No:** Pass to RPh; deny, not funded by the OHP
4. Is the diagnosis psoriasis?	**Yes:** Go to #8	**No:** Go to #5
5. Is the diagnosis atopic dermatitis?	**Yes:** Go to #6	**No:** Go to #10
6. Does the patient meet the age requirements per the FDA label (Table 1)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 first line agents (i.e. topical corticosteroids or tacrolimus) indicated for the treatment of severe AD? *Note ruxolitinib, pimecrolimus and crisaborole are FDA approved to manage mild to moderate AD, while tacrolimus is FDA approved to manage moderate to severe AD.	**Yes:** Document drug and dates trialed, and intolerances or contraindications (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested product preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #9
9. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Approve for length of treatment; maximum 1 year.
10. 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:** Deny, not funded by the OHP.

P&T/DUR Review: *6/22 (DM); 12/20 (DM); 10/20; 7/19 (DM); 5/19 (DM) 3/18 (DM); 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 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.Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx. Accessed March 1, 2022.

Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Restrict use of targeted immune modulators to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required an Emergency Department visit or hospitalization or for patients with severe atopic dermatitis.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria, mild-to-moderate atopic dermatitis).

Length of Authorization:

- Up to 12 months

Requires PA:

- Targeted immune modulators with indications for severe asthma or severe atopic dermatitis (see **Table 2** below) for pharmacy and provider-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)	Atopic Dermatitis (AD)
Abrocitinib CIBINQO							≥18 years
Benralizumab FASENRA	≥12 years						
Dupilumab DUPIXENT	≥6 years (or with oral corticosteroid dependent asthma)					≥18 years	≥6 years
Mepolizumab NUCALA	≥6 years			≥ 12 years	≥18 years	≥18 years	
Omalizumab XOLAIR		≥6 years				≥18 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).							

Table 3. Abrocitinib Dosing Adjustments for Atopic Dermatitis

Assessment	Recommended Dose
CYP2C19 Poor Metabolizer	50 mg once daily
GFR 30 to 60 mL/min	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

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

Approval Criteria		
3. Is the request for an FDA-approved indication and age (**Table 2**)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. 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 #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. 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 #7	**No:** Go to #14
7. 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 #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for abrocitinib?	**Yes:** Go to #9	**No:** Go to # 13

Approval Criteria		
9. 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 # 10 Document Lab and Date Obtained: Platelets:_____ Lymphocytes:_____ Lipids:_____ Hemoglobin:	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient currently taking other targeted immune modulators or oral immunosuppressants?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. If the patient has renal or hepatic impairment has the dose been adjusted as described in Table 3?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the patient 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? *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:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13

Approval Criteria		
13. 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
14. 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 #15
15. 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 #16
16. Is the request for treatment of nasal polyps?	**Yes:** Go to # 17	**No:** Go to #19
17. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to # 18	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
18. 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
19. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. 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 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 #21 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.
21. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.
22. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, or tezepelumab etc.,)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #23
23. Is the request for tezepelumab?	**Yes:** Approve for up to 12 months.	No: Go to # 24

Approval Criteria		
24. 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 #25
25. 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.

Renewal Criteria		
1. Is the request to renew therapy for eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), or hypereosinophilic syndrome (HES)?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #4	**No:** Go to #5

Renewal Criteria		
4. 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.
5. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the number of 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.

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

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

Targeted Immune Modulators for Autoimmune Conditions

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.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators for autoimmune conditions (both pharmacy and physician-administered claims)

Covered Alternatives:

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

Table 1. Approved and Funded Indications for Targeted Immune Modulators

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo			aGVHD ≥ 2 yo
Adalimumab (HUMIRA) and biosimilars	≥18 y	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥5 yo (Humira) ≥18 yo (biosimilars)		Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo			NOMID DIRA
Apremilast (OTEZLA)				≥18 yo	≥18 yo				Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo			
Brodalumab (SILIQ)				≥18 yo					
Canakinumab (ILARIS)			≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
									Stills Disease
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo			Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥4 yo (biosimilars)	≥18 yo	≥18 yo			
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo		≥2 yo active polyarticular course		≥2 yo	≥18 yo	≥18 yo (Simponi)		
Guselkumab (TREMFYA)				≥18 yo	≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab (TALTZ)	≥ 18 yo			≥6 yo	≥18 yo				Nr-axSpA ≥ 18 yo
Risankizumab-rzaa (SKYRIZI)				≥18 yo	≥ 18 yo				
Rituximab (RITUXAN) and biosimilars						≥18 yo			CLL ≥18 yo DLBCL≥6 yo BL≥6 yo B-AL≥6 yo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yo Pemphigus Vulgaris ≥18 yo (Rituxan only)
Sarilumab (KEVZARA)						≥18 yo			
Secukinumab (COSENTYX)	≥18 yo			≥6 yo	≥2 yo				ERA ≥ 4 yo Nr-AxSpA ≥18 yo
Tildrakizumab-asmn (ILUMYA)				≥18 yo					
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo			CRS ≥2 yo GCA ≥18 yo SSc-ILD ≥18 yo
Tofacitinib (XELJANZ)	≥18 yo		≥2 yo active polyarticular course		≥18 yo	≥18 yo	≥18 yo		

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Upadacitinib (RINVOQ)					≥18 yo	≥18 yo	≥18 yo	≥ 12 yo	
Ustekinumab (STELARA)		≥ 18 yo		≥6 yo	≥18 yo		≥18 yo		
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo		

Abbreviations: aGVHD = acute Graft Versus Host Disease; BD = Behcet's Disease; BL = Burkitt Lymphoma; B-AL = mature B-cell acute leukemia CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; DLBCL = Diffuse Large B-Cell Lymphoma; ERA = Enthesitis-Related Arthritis; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; MPA = Microscopic Polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; Nr-axSpA = Non-Radiographic Axial Spondyloarthritis; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP? Notes: A. Mild-to-moderate psoriasis is unfunded, severe psoriasis is funded. B. Mild Hidradenitis Suppurativa (HS) is unfunded, moderate-to-severe HS (e.g., Hurley Stage II or III) is funded.	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
3. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?* *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to # 4	**No:** Pass to RPh. Deny; medical appropriateness. If patient meets all other criteria, pharmacist may approve once for up to 3 months to allow time for screening for ongoing therapy to avoid interruptions in care.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the request for a non-preferred product and 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 Committee.	**Yes:** Inform prescriber of preferred alternatives. Go to #6	**No:** Go to # 6
6. Is the request for a medication and corresponding diagnosis indicated according to the “Other” column of table 1? AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to # 7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to # 8	**No:** Go to # 9

Approval Criteria		
8. Is this a request for a preferred agent OR if the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® branded product or an Enbrel® branded product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to # 10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in 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 involvement; OR • Hand, foot, face, or mucous membrane involvement?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); AND • At least one other topical agent: calcipotriene, tazarotene, anthralin; AND • Phototherapy; AND • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; AND • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for a drug FDA-approved for atopic dermatitis as defined in Table 1? Note: only *severe* atopic dermatitis is funded by the OHP.	**Yes:** Go to # 13	**No**: Go to #15
13. Is the atopic dermatitis severe in nature, which has resulted in 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 involvement; or • Hand and, foot, face, or mucous membrane involvement?	**Yes:** Go to # 14	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
14. 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
~~12.~~15. Is the diagnosis rheumatoid arthritis, juvenile idiopathic arthritis, or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 16	**No:** Go to # 19

Approval Criteria		
~~13.~~16. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; OR • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® branded product or an Enbrel® branded product for at least 3 months? AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to # 17 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
17. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to # 18	**No:** Approve for up to 6 months
18. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus OR cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis
19. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 20	**No:** Go to # 21

Approval Criteria		
20. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90 day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198 OHA Prioritized List	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness**.**
21. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 22	**No:** Go to # 24
22. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Go to #23	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
23. Is the request for a preferred product or has the patient tried and failed a 3 month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
24. Is the diagnosis for an FDA approved diagnosis and age as outlined in Table 1, and is the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis, plaque psoriasis, or rheumatoid arthritis?	**Yes:** Go to # 6	**No:** Go to # 2
2. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #3	**No:** Go to #4

Renewal Criteria		
3. Have the patient's symptoms improved with upadacitinib 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.~~4. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 5	**No:** Go to # 6
~~4.~~5. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: • a reduction of 25% or more in the total abscess and inflammatory nodule count, AND • no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
~~5.~~6. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
~~6.~~7. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *6/22(DM);10/21 (DM); 10/20 (DM); 2/20; 5/19; 1/19; 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *TBD; 1/1/22; 1/1/2021; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*

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Drug Class Update and New Drug Evaluation: Asthma Biologics

Date of Review: June 2022

Date of Last Review: August 2021
Dates of Literature Search: 05/01/2021 – 03/01/2022
Brand Name (Manufacturer): Tezspire (AstraZeneca/Amgen)
Dossier Received: Yes

Generic Name: Tezepelumab-ekko

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

Purpose for Class Update:
To review and evaluate the place in therapy for tezepelumab, a new monoclonal antibody approved for severe asthma, in addition to recent evidence and guideline recommendations for targeted immune modulators (TIMs) approved for the treatment of moderate-to-severe asthma and other conditions such as chronic rhinosinusitis with nasal polyps (CRSwNP).

Research Questions:
1. What is the efficacy of TIMs approved for the treatment of eosinophilic asthma including benralizumab, dupilumab, mepolizumab, and reslizumab?
2. What is the tolerability and frequency of adverse events (AEs) for benralizumab, dupilumab, mepolizumab, and reslizumab in the treatment of eosinophilic asthma?
3. What is the evidence on the benefits and harms of omalizumab for treatment of patients with moderate-to-severe allergic asthma?
4. What is the evidence on the benefits and harms of tezepelumab, a recently approved monoclonal antibody, for treatment of patients with severe asthma?
5. Are there subgroups of patients (e.g. groups defined by demographics, asthma severity, comorbidities) for which monoclonal antibodies used to treat asthma differ in efficacy or frequency of AEs?

Conclusions:
- Since the last review, one systematic review evaluating evidence for TIMs in treating chronic rhinosinusitis[1] and 4 high-quality guidelines with recommendations for the use of TIMs in treating severe asthma[2-5] were published.
- A 2021 Cochrane Review assessed the effects of dupilumab, mepolizumab, and omalizumab for the treatment of CRSwNP.[1] In patients with chronic rhinosinusitis, high-quality evidence shows dupilumab improves disease-specific, health-related quality of life (HRQoL) and moderate-quality evidence shows dupilumab may reduce disease severity compared to placebo.[1] At 16 and 52 weeks of follow-up, dupilumab may result in a reduction in serious adverse effects (SAEs) compared to placebo (low-quality evidence).[1] Mepolizumab may improve disease-related HRQoL (low-quality evidence), but it is uncertain if there is a difference in disease severity or the number of SAEs compared with placebo.[1] Omalizuamb may improve disease-related HRQoL (moderate-quality

evidence), but it is uncertain if there is a difference in the number of SAEs compared with placebo.[1] There is no evidence regarding the effect of omalizumab on disease severity.[1] The following limitations to the data were identified: 1) all studies were in adults, and there are no data for children; 2) there is a lack of long-term evidence, as only one study was conducted over 52 weeks; 3) sample sizes were insufficient and length of follow-up too short to comprehensively and adequately assess the risk of adverse effects.[1]

- The April 2021 Global Initiative for Asthma (GINA) guidance provides recommendations for management for severe asthma in adolescent and adult patients.[2] After referral for expert assessment and phenotyping, consider adding a monoclonal antibody for patients with exacerbations or poor symptom control on high-dose inhaled corticosteroid-long-acting beta-agonist (ICS-LABA) who have eosinophilic or allergic biomarkers, or the need for maintenance oral corticosteroids (OCS).[2] Targeted treatment should be considered using the following biomarkers: serum immunoglobulin E (IgE); baseline blood eosinophil cell counts; percentage of sputum eosinophils; or fractional exhaled nitric oxide (FeNO).[2] Frequency of asthma exacerbations and asthma that is allergy driven are additional factors to consider when adding a monoclonal antibody to asthma treatment regimens.[2]
- A clinical review of dupilumab for severe asthma was published August 2021 by the Canadian Agency for Drugs and Technologies in Health (CADTH).[3] The review summarized data from 3 randomized controlled trials (RCTs) that compared dupilumab to placebo in patients with moderate-to-severe asthma who were already receiving standard of care treatment.[3] None of the included studies had an active comparator and only 1 trial was 52 weeks in duration.[3] Based on a review of the evidence, CADTH recommended the following conditions for dupilumab utilization including: 1) inadequate asthma control despite use of high-dose inhaled ICS and one or more additional asthma controllers; 2) an eosinophil count greater than or equal to 150 cells/µL or OCS-dependent asthma; and 3) baseline assessment of asthma symptom control using a validated asthma control questionnaire prior to initiation of dupilumab treatment.[3]
- In February 2021, the National Institute for Health and Care Excellence (NICE) published guidance for the use of mepolizumab in treating severe eosinophilic asthma.[5] There is no evidence directly comparing mepolizumab with the other interleukin (IL)-5 pathway antagonists benralizumab and reslizumab.[5] Mepolizumab, as add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if it is used for adults who meet the following criteria: 1) have a blood eosinophil count of 300 cells/µL or more and have had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months; or 2) have had continuous OCS doses equivalent to at least prednisolone 5 mg per day over the previous 6 months; or 3) have blood eosinophil count of 400 cells/µL or more and have had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months.[5]
- In December 2021, NICE published guidance for the use of dupilumab for treating severe asthma.[4] Dupilumab is recommended as add-on maintenance therapy in people 12 years and older as an option for treating inadequately controlled severe asthma with Type 2 (T2) inflammation despite maintenance therapy with high-dose ICS and another maintenance treatment only if: 1) the person has a blood eosinophil count of 150 cells/µL or more, FeNO of 25 parts per billion (ppb) or more, and has had at least 4 or more exacerbations in the previous 12 months; and 2) the person is not eligible for mepolizumab, reslizumab or benralizumab (Interleukin [IL]-5 inhibitors are the standard of care for severe asthma management in the United Kingdom [UK]), or has asthma that has not responded adequately to these therapies.[4]
- In December 2021, tezepelumab received FDA-approval as add-on maintenance treatment for patients aged 12 years and older with severe asthma.[6] Tezepelumab binds to the cytokine thymic stromal lymphopoietin (TSLP) in the upstream inflammatory cascade.[6] Clinical data from 2 studies (NAVIGATOR and PATHWAY) were submitted to the FDA to support the licensing application for tezepelumab.[7] The dose-finding, phase 2, PATHWAY trial showed the use of tezepelumab at a dose of 70 mg every 4 weeks, 210 mg every 4 weeks, and 280 mg every 2 weeks resulted in annualized asthma exacerbation rates (AAER) at week 52 of 0.27, 0.20, and 0.23, respectively, as compared with 0.72 in the placebo group.[8] Moderate-quality evidence demonstrated asthma exacerbation rates were lower in the respective tezepelumab groups than in the placebo group by 62% (90% Confidence Interval [CI], 42 to 75; P<0.001), 71% (90% CI, 54 to 82; P<0.001), and 66% (90% CI, 47 to 79; P<0.001).[8]
- The phase 3 NAVIGATOR trial enrolled adults and adolescents aged 12 to 80 years old with severe, uncontrolled asthma in a multi-center, double-blind, randomized study.[9] Subjects must have had at least 2 asthma exacerbations during the 12 months prior to study enrollment.[9] The primary objective of the study was to assess the effect of 210 mg of tezepelumab administered every 4 weeks compared with placebo on AAER over a 52-week treatment period.[9]

Moderate-quality evidence showed that for the overall population, AAER was 0.93 events per patient year with tezepelumab and 2.10 events per patient year with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001).[9] In patients with a blood eosinophil count of less than 300 cells/µL, the AAER was 1.02 events per patient year with tezepelumab and 1.73 events per patient year with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P<0.001).[9] The annualized rate of asthma exacerbations was significantly lower with tezepelumab compared to placebo among adults and adolescents with severe, uncontrolled asthma, including those with low blood eosinophil counts at baseline.[9]

- In the NAVIGTOR and PATHWAY trials the frequencies and types of AEs did not differ meaningfully between tezepelumab and placebo.[8,9] In the pooled safety population, the most common adverse effects of tezepelumab (frequency 3% and greater) were pharyngitis, arthralgia, and back pain.[6] Since TSLP may be involved in the immunological response to some parasitic infections, such infections should be treated before starting tezepelumab.[6]
- The guidelines for monoclonal antibodies approved to manage eosinophilic asthma have different thresholds with respect to baseline levels of blood eosinophils. The GINA recommendations have the broadest guidance and recommend benralizumab, dupilumab, mepolizumab or reslizumab be initiated for difficult-to-treat, severe asthma when eosinophils range between 150 cells/µL and greater or 300 cells/µL and greater.[2]

Recommendations:

- Add tezepelumab injection to the Prior Authorization (PA) criteria for "Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis" and maintain as non-preferred on the Preferred Drug List (PDL).
- To align with current guidelines, revise PA criteria to reduce the threshold for blood eosinophils to 150 cells/µL for monoclonal antibodies prescribed for eosinophilic asthma, update definition of severe asthma exacerbation, and include use of OCS in asthma exacerbation criteria.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy:

A class update focused solely on use of monoclonal antibodies for treatment of severe asthma was presented at the August 2021 Pharmacy and Therapeutics (P & T) meeting. The August 2021 class update was informed by the February 2021 research report created by the Drug Effectiveness Review Project (DERP).[10] Recommendations from August 2021 meeting included:

- Create a PDL class entitled "Biologics for Severe Asthma" and include benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab in this PDL class.
- Modify "Monoclonal Antibodies for Severe Asthma" Prior Authorization (PA) criteria to include expanded indications for mepolizumab in treatment of HES and chronic rhinosinusitis with nasal polyps (CRSwNP) and omalizumab for treatment of nasal polyps.
- Retire dupilumab PA criteria and add dupilumab to "Monoclonal Antibodies for Severe Asthma" PA criteria.

The Oregon Health Plan (OHP) provides coverage with PA criteria for 4 monoclonal antibodies approved to manage eosinophilic asthma refractory to other asthma therapies: benralizumab, dupilumab, mepolizumab, and reslizumab. An additional biologic, omalizumab, is also part of the monoclonal antibodies for asthma PA criteria and provides coverage for patients with severe allergic asthma. Omalizuamb is also indicated for management of chronic urticaria, a diagnosis which is not currently funded according to the Health Evidence Review Commission (HERC) prioritized list. Current criteria require that auto-injectable epinephrine be co-prescribed with all asthma biologics due to the risk of delayed anaphylaxis. Prior authorization criteria for this class of drugs are outlined in **Appendix 5**. The PDL status for TIMs approved to treat moderate-to-severe asthma and atopic dermatitis is presented in **Appendix 1**. There are no preferred monoclonal antibodies for asthma on the PDL. During the fourth quarter of 2021, asthma biologic agents billed through point of sale pharmacy claims in the fee-for-service (FFS) population included 4 claims for mepolizumab and 28 claims for dupilumab. In the third quarter of 2021, provider-administered claims were submitted for mepolizumab (n=5), benralizuamb (n=2), and omalizumab (n=16).

Background:
Asthma is a heterogeneous disease, characterized by chronic airway inflammation which results in bronchial hyper-responsiveness.[2] It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[2] The Centers for Disease Control and Prevention (CDC) estimates that 25 million Americans, including 5 million children have asthma.[11] In the United States (U.S.), asthma is more than twice as common among Black children as among White children (13.5% and 6.4% respectively), and is somewhat more common among Black adults.[11] It is estimated that severe asthma accounts for about 5 to 10% of the total asthma population, but exact prevalence is unknown due to the heterogeneous presentation of severe asthma.[12] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with management of asthma exacerbations.[13]

The 2021 GINA guidelines introduced definitions of difficult-to-treat and severe asthma which begin with the concept of uncontrolled asthma.[2] Uncontrolled asthma includes: 1) poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or 2) frequent exacerbations (2 or more per year) requiring OCS or serious exacerbations (1 or more per year) requiring hospitalization.[2] Difficult to treat asthma is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller, usually a LABA, or with maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.[2] Severe asthma is a subset of difficult-to-treat asthma.[2] It is defined as asthma that is uncontrolled despite adherence with maximal optimized high-dose ICS-LABA or that requires high-dose ICS-LABA to remain controlled.[2]

Phenotyping severe asthma based on demographic or clinical characteristics may help to effectively target treatment. The underlying pathophysiology of asthma is multi-factorial and includes several phenotypes: eosinophil predominant, neutrophil predominant, and allergic asthma. Allergic asthma is the most common phenotype, describing between 40% and 50% of cases, and can be identified through allergy testing for environmental allergens, blood immunoglobin E (IgE) levels, eosinophilia, and FeNO testing.[14] Patients with eosinophilic asthma have high levels of sputum and blood eosinophils.[2] Type 2 high inflammation asthma is characterized by the release of signature cytokines IL-4, IL-5 and IL-13 from immune system cells which contribute to mucus production, IgE synthesis, subepithelial fibrosis, bronchial remodeling and airway hyperresponsiveness.[15] Severe asthma with T2 inflammation is associated with allergy, higher risk of exacerbations, hospitalization and dependency on OCS, and increased risk of death compared to people with severe asthma without T2 inflammation.[4] The 2021 GINA guideline lists 5 criteria in its definition of severe asthma with T2 inflammation which are prognostic markers: 1) a blood eosinophil count of 150 cells/μL or more; 2) FeNO of 20 ppb or more; 3) sputum eosinophils of 2% or more; 4) asthma that is clinically allergen driven; and 5) the need for maintenance OCS.[2]

The long-term goals of asthma management are to achieve good symptom control, and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side-effects of treatment.[2] The patient's own goals regarding their asthma and its treatment should also be identified.[2] In the 2021 GINA guidelines, the options for ongoing treatment for adults and adolescents 12 years and older have been clarified by delineating 2 treatment "tracks" based on the choice of reliever consisting of 4 steps each. Treatment may be stepped up or down within a track using the same reliever at each step, or treatment may be switched between tracks, according to the individual patient's needs.[2] In Track 1, the preferred approach recommended by GINA, low-dose ICS-formoterol is the symptom reliever.[2] In Track 2, the symptom reliever is a SABA.[2] The GINA guidance recommends Step 1 and Step 2 of asthma treatment begin with as-needed low-dose ICS-formoterol (Track 1).[2] For safety, the GINA guidelines no longer recommend treatment of asthma with a short acting beta-agonist (SABA) alone in adults and adolescents; evidence has shown that using ICS-formoterol as a reliever reduces the risk of exacerbations and asthma-related mortality compared with using a SABA reliever alone.[2] However, if use of an ICS-formoterol inhaler is not possible or not preferred by a patient with no exacerbations on their current therapy, using as-needed SABA and low dose ICS together (in combination, or with the ICS taken right after the SABA) is an alternative approach (Track 2).[2] If asthma remains uncontrolled despite good adherence and proper inhaler technique, therapy can be advanced to Step 3. For adults and adolescents, the preferred Step 3 treatment in Track 1 is low-dose ICS-formoterol as both maintenance and as-needed reliever therapy (MART).[2]

Track 2 recommends a low-dose maintenance ICS-LABA with as needed SABA in Step 3.[2] The preferred Step 4 treatment for asthma varies depending on what has been tried for Step 3, but includes medium-dose ICS-formoterol or ICS-LABA as maintenance with additional controllers, including long-acting muscarinic antagonists (LAMAs) such as tiotropium and leukotriene receptor antagonists (LTRAs) such as montelukast.[2] Preferred treatment in Step 5 is referral for expert assessment, phenotyping, and add-on therapy to high-dose ICS-formoterol or high-dose ICS-LABA depending on which track is being prescribed.[2] Adding a monoclonal antibody for patients with severe asthma unresponsive to controller-drug treatments is also recommended in Step 5.[2] Low-dose azithromycin for patients older than 18 years with severe asthma has also been added to the GINA guidance after referral in Step 5.[2]

In the GINA guidance, treatment steps for children aged 6 to 11 years recommend Step 1 begin with low-dose ICS taken whenever SABA is taken.[2] Taking ICS whenever SABA is taken is preferred over daily ICS, as poor adherence is highly likely.[2] In Step 2 for children, low-dose ICS is administered daily and a daily LTRA may be added while continuing to use as needed SABA.[2] Daily ICS is preferred over taking ICS whenever SABA is taken, as there is much stronger evidence for efficacy and safety.[2] Step 3 includes MART with very-low-dose ICS-formoterol to reduce the risk of severe exacerbations.[2] Other Step 3 options include low-dose ICS-LABA or medium-dose ICS.[2] Step 4 advances therapy to medium-dose ICS-LABA or low-dose ICS-formoterol MART and referral for expert opinion.[2] In Step 5, referral for phenotypic assessment and higher dose ICS-LABA, or add-on IgE, or anti-IL-5 therapy, or low-dose OCS is recommended.[2]

Omalizumab is an anti-IgE monoclonal antibody that has been available for over a decade to manage severe allergic asthma. Three additional monoclonal antibodies; mepolizumab, reslizumab, and benralizumab, mediate the effects of IL-5 and are effective in management of eosinophilic asthma as add-on therapy. Interleukin-5 is critical for eosinophil maturation and activation. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion. The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Dupilumab is an IL-4 receptor antagonist which modulates signaling of both the IL-4 and IL-13 pathways. Dupilumab is also indicated as add-on maintenance therapy for moderate to severe asthma. Omalizumab, dupilumab, and mepolizumab are approved for children as young as 6 years, and benralizumab is approved for people aged 12 years and older. Reslizumab is approved only for people aged 18 years and older.

Monoclonal antibodies targeting IgE or IL-4, IL-5 and IL-13 (i.e. downstream mediators) are highly effective in reducing exacerbations and symptoms in people with severe allergic and eosinophilic asthma, respectively.[16] However, these therapies are not appropriate for 30–50% of patients with severe asthma who present with non-allergic, non-eosinophilic asthma.[16] Inflammation in these patients may be neutrophilic-prominent or present with normal levels of eosinophils and neutrophils. These patients constitute a clinical asthma phenotype, driven by distinct, yet poorly understood pathobiological mechanisms.[16] Recently developed therapies to manage severe asthma are directed at interfering with the cytokines TSLP, IL-25, and IL-33, which are released by airway epithelial cells in response to allergens, air pollutants, and viruses.[17] Thymic stromal lymphopoietin has been shown to drive various elements of asthma pathophysiology, including airway hyperresponsiveness, mucus overproduction and airway remodeling, via effects triggered downstream.[18] It has been hypothesized that interfering upstream in the inflammatory cascade might improve asthma outcomes in a broader patient population with a range of inflammatory phenotypes.[18] The efficacy of an anti-TSLP monoclonal antibody (tezepelumab), an anti-IL-33 monoclonal antibody (itepekimab), and a monoclonal antibody inhibiting the interleukin-33 receptor (astegolimab) in patients with severe asthma has been recently demonstrated in clinical trials.[17] To date, only tezepelumab has received FDA approval and will be discussed in detail later in this class update.

Although the monoclonal antibodies used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab; therefore, the drug carries an FDA boxed warning recommending observation after infusion.[19] Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.[20,21] There are notable

differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration, dosing regimen, and FDA-approved indication. **Table 1** summarizes significant prescribing information for the monoclonal antibodies with FDA approval to treat moderate-to-severe asthma.

Table 1. Targeted Immune Modulators FDA-Approved to Manage Moderate-to-Severe Asthma

Generic Name	Brand Name	Year Approved	Target	Asthma Indication	Administration Route	Administration Age for Asthma	Boxed Warning
Benralizumab[20]	FASENRA	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	SC	≥ 12 yo	No
Dupilumab[22]	DUPIXENT	2017	IL-4 Receptor	Add on maintenance treatment for moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	SC	≥ 6 yo	No
Mepolizumab[21]	NUCALA	2015	IL-5	Severe asthma with an eosinophilic phenotype	SC	≥ 6 yo	No
Omalizumab[23]	XOLAIR	2003	IgE	Moderate-to-severe persistent asthma with positive allergy testing and inadequately controlled with inhaled corticosteroids	SC	≥ 6 yo	Yes: for possible anaphylaxis
Reslizumab[19]	CINQAIR	2016	IL-5	Severe asthma with an eosinophilic phenotype	IV Infusion	≥ 18 yo	Yes: for possible anaphylaxis
Tezepelumab[6]	TEZSPIRE	2021	TSLP	Severe asthma	SC	≥ 12 yo	No

Abbreviations: FDA = Food and Drug Administration; IgE = immunoglobulin E; IL = interleukin; IU = International Units; IV = intravenous; SC = subcutaneous; TSLP = thymic stromal lymphopoietin; YO = years old

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased emergency department (ED) visits or hospitalizations; 2) decreased chronic use of OCS; 3) improved quality of life; or 4) improved symptom management. Several instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The Asthma Control Questionnaire (ACQ-6) is a 5-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[24] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units documented as a minimal clinically important difference (MCID).[25] An ACQ score consistently greater than 1.5 indicates poor symptom control.[25] The Asthma Quality of Life Questionnaire (AQLQ-12) contains 32 items assessing disease-specific, health-related quality-of-life that include domains of activity limitations, symptoms, emotional function, and environmental stimuli in patients aged 12 years and older.[14] The scale ranges from 1 (severely impaired) to 7 (not impaired at all). Total and domain scores are calculated by taking the mean of all questions overall or for each domain.[14] The MCID for this tool is 0.5 points for each item.[14] The St. George's Respiratory Questionnaire (SGRQ) was developed to measure health in chronic health airflow limitation.[26] The questionnaire is a 50 or 76 item assessment (depending on version) that includes 2 domains: frequency and severity of symptoms and impact on activities, which can be used with a 1-month, 3-month, or 12-month recall.[14] The scale ranges from 0 (no symptoms/limitations) to 100 (severe symptoms/ limitations).[14] Scoring varies by item and item scores are converted into a domain score and an overall score, both reported on the same scale.[14] The

MCID for the SGRQ is 4 points.[14] The Asthma Control Test (ACT) contains 5 self-reported items related to symptoms and daily functioning over past 4 weeks used in patients aged 12 years and older.[14] Assessments include shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control.[14] The scale ranges from 5 (poor control) to 25 (complete control) with scores of 19 and greater indicating well-controlled asthma.[14] Each item is scored on 5-point Likert scale and the sum of scores across all items yields the total score.[14] The MCID for the ACT is 3 points.[14] A summary of the outcomes commonly used in clinical trials is presented in **Table 2.** Change from baseline in forced expiratory volume is a common surrogate endpoint used in asthma treatment trials since it is highly reproducible. A decline in lung function is observed when forced expiratory volume in 1 second (FEV_1) is 60% or less of predicted values or peak expiratory flow shows a 30% or greater decrease from baseline.[14]

Table 2. Summary of Outcome Measures for Asthma Symptoms[14]

Measure	Scale	Minimal Clinically Important Difference (MCID)
Asthma Control Questionnaire (ACQ-6)	0 (totally controlled) to 6 (severely uncontrolled)	0.5
Asthma Control Test (ACT)	5 (poor control) to 25 (complete control)	3
Asthma Quality of Life Questionnaire (AQLQ-12)	1 (severely impaired) to 7 (not impaired at all)	0.5
Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	1 (severely impaired) to 7 (not impaired at all)	0.5
St. George's Respiratory Questionnaire (SGRQ)	0 (no symptoms/limitations) to 100 (severe symptoms/limitations)	4

Methods:

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

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

New Systematic Reviews:

Cochrane: Monoclonal Antibodies for Chronic Rhinosinusitis

A 2021 Cochrane Review assessed the effects of 3 monoclonal antibodies; dupilumab, mepolizumab, and omalizumab, for the treatment of chronic rhinosinusitis.[1] Literature was searched through September 2020. Ten studies with an overall low risk-of-bias met inclusion criteria.[1] All of the studies were sponsored or supported by industry.[1] Of 1,262 adult participants, 1,260 had severe CRSwNP and were using topical nasal steroids to manage symptoms; 43% to 100% also had asthma.[1] Primary outcomes were disease-specific HRQoL, disease severity and serious adverse events (SAEs).[1]

Three RCTs evaluated dupilumab versus placebo (n=784).[1] Disease-specific HRQoL was measured with the Sino-Nasal Outcome Test-22 (SNOT-22), a 22-item questionnaire, with a score range of 0 to 110; MCID 8.9 points.[1] At 24 weeks, dupilumab results in a large reduction (improvement) in the SNOT-22 score (mean difference [MD] -19.61, 95% CI -22.54 to -16.69; 3 studies; high certainty).[1] At between 16 and 52 weeks of follow-up, dupilumab probably results in a large reduction in disease severity, as measured by a 0- to 10-point visual analog scale (MD -3.00, 95% CI -3.47 to -2.53; 3 studies; moderate certainty).[1] This is a global symptom score, including all aspects of chronic rhinosinusitis symptoms. At 16 and 52 weeks of follow-up, dupilumab may result in a reduction in SAEs compared to placebo (5.9% versus 12.5%, risk ratio (RR) 0.47, 95% CI 0.29 to 0.76; 3 studies, 782 participants; low certainty).[1]

Two RCTs evaluated mepolizumab versus placebo (n=135).[1] Disease-specific HRQoL was measured with the SNOT-22. At 25 weeks, the SNOT-22 score may be reduced (improved) in participants receiving mepolizumab (MD -13.26 points, 95% CI -22.08 to -4.44; 1 study; 105 participants; low certainty; MCID 8.9).[1] It is very uncertain whether there is a difference in disease severity at 25 weeks: on a 0- to 10-point VAS, disease severity was -2.03 lower in those receiving mepolizumab (95% CI -3.65 to -0.41; 1 study; 72 participants; very low certainty).[1] It is very uncertain if there is a difference in the number of SAEs between mepolizumab and placebo at 25 to 40 weeks (1.4% versus 0%; RR 1.57, 95% CI 0.07 to 35.46; 2 studies; 135 participants, very low certainty).[1]

Five studies compared omalizumab to placebo (n=329).[1] Disease-specific HRQL was measured with the SNOT-22. At 24 weeks omalizumab probably results in a large reduction in SNOT-22 score (MD -15.62, 95% CI -19.79 to -11.45; 2 studies; 265 participants; moderate certainty; MCID 8.9).[1] No evidence was identified for overall disease severity.[1] It is very uncertain whether omalizumab affects the number of SEAs compared to placebo, with follow-up between 20 and 26 weeks (0.8% versus 2.5%, RR 0.32, 95% CI 0.05 to 2.00; 5 studies; 329 participants; very low certainty).[1]

In summary, in patients with chronic rhinosinusitis, dupilumab improves disease-specific HRQoL and may reduce disease severity compared to placebo.[1] At 16 and 52 weeks of follow-up, dupilumab may result in a reduction in SAEs compared to placebo.[1] Mepolizumab may improve disease-related HRQoL, it is uncertain if there is a difference in disease severity or the number of SAEs, compared with placebo.[1] Omalizuamb may improve disease-related HRQoL, but it is uncertain if there is a difference in the number of SAEs compared with placebo.[1] There is no evidence regarding the effect of omalizumab on disease severity.[1] Cochrane reviewers identified the following limitations to the data: 1) all studies were in adults, there are no data for children; 2) there is a lack of long-term evidence, and only one study had a 52-week follow-up; 3) sample sizes were insufficient and length of follow-up too short to comprehensively and adequately assess the risk of adverse effects.[1]

After review, 4 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).[27-30]

New Guidelines:

High Quality Guidelines:

<u>Global Initiative for Asthma: Difficult-to-Treat and Severe Asthma</u>

The April 2021 GINA guidance provides recommendations for management for difficult-to-treat and severe asthma in adolescent and adult patients.[2] For patients with exacerbations or poor symptom control on high-dose ICS-LABA who have eosinophilic or allergic biomarkers, consider adding a monoclonal antibody or maintenance OCS.[2] Targeted treatment should be considered using the parameters described below.

A. Anti-IgE for severe allergic asthma:
    i. Sensitization on skin prick testing or specific IgE challenge
    ii. Total serum IgE and weight

iii. Number of exacerbations in the past year
iv. Factors that may predict good asthma response to anti-IgE monoclonal antibody treatment include: blood eosinophils ≥ 260 cells/µL, FeNO ≥ 20 ppb, allergen-driven symptoms, and childhood-onset asthma.[2]

B. Anti-IL-5/Anti-IL-5 Receptors for severe eosinophilic asthma:
   i. Number of exacerbations in the last year
   ii. Blood eosinophils (e.g. ≥ 150 cells/µL or ≥ 300 cells/µL: depending on which medication is selected)
   iii. Factors that may predict good asthma response to anti-IL5 monoclonal antibody treatment include: higher blood eosinophils, more exacerbations in previous year, adult-onset asthma, and nasal polyposis.[2]

C. Anti-IL-4 Receptors for severe eosinophilic or T2 asthma:
   i. Number of exacerbations in the last year
   ii. Blood eosinophils ≥ 150 cells/µL or FeNO ≥ 25 ppb
   iii. Need for maintenance OCS
   iv. Factors that may predict good asthma response to anti-IL-4 monoclonal antibody treatment include: higher blood eosinophils and higher FeNO.[2]

Choose one agent if patient meets eligibility and trial for at least 4 months and assess response.[31] If good response, continue targeted therapy and re-evaluate every 3 to 6 months.[2] If response is unclear, extend trial 6 to 12 months.[2] If no response, consider switching to a different targeted therapy, if patient meets eligibility parameters.[2]

<u>Canadian Agency for Drugs and Technologies in Health: Dupilumab for Type 2 or Eosinophilic Asthma</u>

A clinical review of dupilumab for severe asthma was published August 2021 by CADTH.[3] The review summarized data from 3 RCTs that compared dupilumab to placebo in patients with moderate-to-severe asthma who were already receiving standard of care treatment.[3] Both the 200 mg and 300 mg doses of dupilumab reduced the annualized rate of severe asthma exacerbations compared to placebo.[3] In a population with severe OCS-dependent asthma, dupilumab 300 mg every 2 weeks reduced the daily OCS dose requirement versus placebo.[3] There was no clear or consistent indication of serious safety or tolerability issues with dupilumab in the included studies.[3] None of the included studies had an active comparator and only 1 trial was 52 weeks in duration.[3] Overall, the studies were unlikely to be of sufficient duration to assess the longer term safety and efficacy of dupilumab.[3] Based on a review of the evidence, CADTH implemented the following conditions for dupilumab utilization:

1. Patient is inadequately controlled with high-dose ICS, defined as at least 500 mcg of fluticasone propionate or equivalent daily, and 1 or more additional asthma controller(s) (e.g., LABAs).[3]
2. Patient must have an eosinophil count ≥ 150 cells/µL or have OCS-dependent asthma.[3]
3. A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed prior to initiation of dupilumab treatment.[3]
4. Dupilumab should not be used in combination with other biologics used to treat asthma.[3]
5. Patients should be managed by a physician with expertise in treating asthma.[3]
6. The effects of treatment should be assessed every 12 months to determine whether reimbursement should continue.[3] Dupilumab should be discontinued if any of the following occur:
   a. the 12-month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment or
   b. the asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently or
   c. the number of clinically significant asthma exacerbations has increased within the previous 12 months or

d. in patients on maintenance treatment with OCS, there has been no decrease in the OCS dose in the first 12 months of treatment or
e. in patients on maintenance treatment with OCS, the reduction in the dose of OCS achieved after the first 12 months of treatment is not maintained or improved subsequently.[3]

National Institute for Health and Care Excellence: Mepolizumab For Treating Severe Eosinophilic Asthma

In February 2021, NICE published guidance for the use of mepolizumab in treating severe eosinophilic asthma.[5] There is no evidence directly comparing mepolizumab with benralizumab and reslizumab.[5] However, an indirect comparison suggests that it works as well as benralizumab and reslizumab for people with a blood eosinophil count of 400 cells/µL or more.[5] Mepolizumab, as an add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if it is used for adults who have agreed to and followed the optimized standard treatment plan **and** the patient meets at least one of the following criteria:

- the blood eosinophil count has been recorded as 300 cells/µL or more and the person has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, **or**
- the patient has had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months **or**
- the blood eosinophil count has been recorded as 400 cells/µL or more and the person has had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months.[5]

At 12 months mepolizumab should be discontinued if asthma has not responded adequately.[5] An adequate response is defined as: a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or a clinically significant reduction in continuous OCS use while maintaining or improving asthma control.[5]

National Institute for Health and Care Excellence: Dupilumab For Treating Severe Asthma

In December 2021, NICE published guidance for the use of dupilumab for treating severe asthma with T2 inflammmation.[4] Some aspects of the guidance were based on proprietary real-world observational evidence submitted by the manufacturer and responses from stakeholders.[4] Clinical trial results show that adding dupilumab to standard asthma treatment is more effective than placebo plus standard treatment at reducing the frequency of severe exacerbations, and the use of OCS in people with severe asthma with T2 inflammation.[4] Dupilumab as add-on maintenance therapy is recommended as an option for treating severe asthma with T2 inflammation that is inadequately controlled in people 12 years and older, despite maintenance therapy with high-dose ICS and another maintenance treatment, only if:

- the dosage used is 400 mg initially and then 200 mg subcutaneously every other week **and**
- the person has agreed to and follows an optimized standard treatment plan **and**
- the person has a blood eosinophil count of 150 cells/µL or more and FeNO of 25 ppb or more, and has had at least 4 or more exacerbations in the previous 12 months **and**
- the person is not eligible for mepolizumab, reslizumab or benralizumab (IL-5 inhibitors are the standard of care for severe asthma in the UK), or has asthma that has not responded adequately to these biological therapies).[4]

Stop dupilumab if the rate of severe asthma exacerbations has not been reduced by at least 50% after 12 months.[4]

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

Randomized Controlled Trials:
A total of 189 citations were manually reviewed from the initial literature search. After further review, 189 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts[32]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Dupilumab	DUPIXENT	10/2021	Warnings and Precautions	Hypersensitivity reactions including erythema multiforme were reported in less than 1% of subjects who received dupilumab in clinical trials. Adverse reactions of helminth infections (5 cases of enterobiasis and 1 case of ascariasis) were reported in pediatric patients 6 to 11 years old who participated in the pediatric asthma development program.
Dupilumab	DUPIXENT	12/2021	Adverse Reactions: Postmarketing Experience	Immune system disorders: angioedema Skin and subcutaneous tissue disorders: Facial skin reactions, including erythema, rash, scaling, edema, papules, pruritus, burning, and pain

NEW DRUG EVALUATION: Tezepelumab
See **Appendix 4** 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.

Tezepelumab is FDA-approved as add-on maintenance treatment for patients aged 12 years and older with severe asthma.[6] Tezepelumab binds to TSLP in the upstream inflammatory cascade.[6] FDA granted tezepelumab "breakthrough therapy designation" for the treatment of severe asthma without an eosinophilic phenotype.[7] Tezepelumab is administered by a healthcare provider via subcutaneous injection every 4 weeks.[6]

Clinical Efficacy:
Clinical data from 2 studies (NAVIGATOR and PATHWAY) were submitted to the FDA to support the licensing application for tezepelumab.[7] The PATHWAY trial was a dose-finding, placebo-controlled, phase 2 trial which evaluated 3 doses (70 mg every 4 weeks, 210 mg every 4 weeks, and 280 mg every 2 weeks) of tezepelumab on asthma exacerbation rates in adults (n=550) with inadequately controlled, severe asthma.[8] Patients had documented history of at least 2 asthma exacerbation events or at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) within the 12 months prior to study enrollment.[8] The primary efficacy end point was the AAER (events per patient-year) at week 52.[8] An asthma exacerbation was defined as a worsening of asthma symptoms that led to any of the following: the use of systemic glucocorticoids (oral or injectable) or, in the case of a stable maintenance regimen of oral glucocorticoids, a doubling of the dose for 3 or more days; an emergency department visit due to asthma that led to systemic glucocorticoid

treatment; or an inpatient hospitalization due to asthma[8] Secondary end points included the changes from baseline in the pre-bronchodilator FEV_1, ACQ-6 score, and AQLQ score.[8] The efficacy analyses were based on the intention-to-treat (ITT) population, which consisted of patients who underwent randomization and received at least one dose of tezepelumab or placebo.[8]

The use of tezepelumab at a dose of 70 mg every 4 weeks (low-dose), 210 mg every 4 weeks (medium-dose) or 280 mg every 2 weeks (high-dose), resulted in AAER at week 52 of 0.27, 0.20, and 0.23 per patient-year, respectively, as compared with 0.72 per patient-year in the placebo group.[8] Asthma exacerbation rates were lower in the respective tezepelumab groups than in the placebo group by 62% (90% CI, 42 to 75; P<0.001), 71% (90% CI, 54 to 82; P<0.001), and 66% (90% CI, 47 to 79; P<0.001).[8] The change from baseline at week 52 in the prebronchodilator FEV_1 was greater in the low-dose, medium-dose, and high-dose tezepelumab groups than in the placebo group by 0.12 liters (95% CI, 0.02 to 0.22; P = 0.015), 0.13 liters (95% CI, 0.03 to 0.23; P=0.009), and 0.15 liters (95% CI, 0.05 to 0.25; P = 0.002).[8]

The NAVIGATOR trial enrolled adults and adolescents aged 12 to 80 years old with severe, uncontrolled asthma in a phase 3, multi-center, double-blind, randomized study.[9] A total of 1061 patients were randomized from 294 study sites in 18 countries; 82 (8%) of these patients were adolescents.[9] The proportion of participants who were enrolled in the U.S. (18%) was higher than those in any of the other international study sites. To be eligible for the study, patients must have been receiving medium- to high-dose ICS for at least 3 months before screening, and must have been taking at least one additional controller medication with or without OCS in the 3 months before the date of informed consent.[9] In addition, subjects must have had at least 2 asthma exacerbations during the 12 months prior to study enrollment.[9] The adult study population included similar proportions of patients with an eosinophil count of less than 300 cells/µL and patients with at least 300 cells/µL. Approximately 25% of patients had an eosinophil count of less than 150 cells/µL or of greater than 450 cells/µL.[9] Adolescents were excluded from assessing target eosinophil counts. Add-on therapy with tezepelumab, at a dose of 210 mg administered subcutaneously every 4 weeks, was compared to placebo administered via the same route and dosing interval. During the trial, all the patients continued to receive their previously prescribed ICS plus additional controller medications, with or without OCS, without change. Patients were permitted to use SABAs for symptom relief as needed.

The primary objective of the NAVIGATOR study was to assess the effect of tezepelumab compared with placebo on AAER (events per patient-year) over the 52-week treatment period.[9] Prior to enrollment, 60% of subjects experienced 2 asthma exacerbations in the previous 12 months, while 40% of subjects experienced more than 2 asthma exacerbations. The definition of an asthma exacerbation was a worsening of asthma that led to any of the following: 1) use of systemic corticosteroids for at least 3 consecutive days; 2) an emergency room or urgent care visit that required systemic corticosteroids for at least 3 days; or 3) an inpatient hospitalization due to asthma. For patients receiving maintenance oral glucocorticoids, a temporary doubling of the stable existing maintenance dose for at least three days qualified for the definition of asthma exacerbation. In addition to the overall population, the primary objective was assessed a priori in a subgroup of patients with blood eosinophil counts less than 300 cells/µL. Key secondary objectives included assessment of the effect of tezepelumab compared with placebo on pulmonary function (pre-bronchodilator FEV_1) and on patient-reported outcomes, including health-related quality of life (HRQoL) using the AQLQ-12 and asthma control (using the ACQ-6).[9]

The annualized rate of asthma exacerbations was lower with tezepelumab than with placebo among adults and adolescents with severe, uncontrolled asthma, including those with low blood eosinophil counts at baseline.[9] Moderate-quality evidence showed that for the overall population, AAER was 0.93 events per patient year with tezepelumab and 2.10 events per patient year with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001).[9] In patients with a blood eosinophil count of less than 300 cells/µL, the AAER was 1.02 events per patient year with tezepelumab and 1.73 events per patient year with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P<0.001).[9] At week 52, improvements were greater with tezepelumab than with placebo with respect to the prebronchodilator FEV_1 (0.23 vs. 0.09 liters; difference, 0.13 liters; 95% CI, 0.08 to 0.18; P<0.001) and scores on the ACQ-6 (−1.55 vs. −1.22; difference, −0.33; 95% CI, −0.46 to

−0.20; P<0.001; MCID = 0.5), and AQLQ-12 (1.49 vs. 1.15; difference, 0.34; 95% CI, 0.20 to 0.47; P<0.001; MCID = 0.5).[9] Although symptom scores on the ACQ-6 and AQLQ-12 improved, they did not meet the MICD of 0.5. Additional safety and efficacy data from the PATHWAY and NAVIGATOR trials are described and evaluated in **Table 6**.

A randomized, double-blind trial (SOURCE) was conducted in 150 adults with severe asthma who were receiving OCS, in addition to standard treatment.[33] The primary objective for this RCT was to evaluate the efficacy of tezepelumab in reducing OCS use in adults with OCS-dependent asthma.[33] Data from this trial has not yet been published. The FDA analysis indicated in this trial, subcutaneous administration of tezepelumab 210 mg every 4 weeks did not result in a statistically significant reduction in the maintenance dose of OCS at 48 weeks compared to placebo.[7]

Trial Limitations:
The phase 2 PATHWAY trial was conducted in primarily white, female adults, which limits extrapolation of data to ethnically diverse populations.[8] In the NAVIGATOR trial, although the adolescent subpopulation was not powered to demonstrate statistical significance, numerical reductions in asthma exacerbations and improvements in lung function were observed compared to placebo.[7] Partial extrapolation of efficacy in adults was used to support FDA approval in the adolescent subgroup, as the pathophysiology of asthma is similar in adults and adolescents.[7] All of the subjects met the criteria of severe asthma but some sub-populations including smokers were excluded from the clinical trial. Long-term safety data is not available, although a long-term extension study is currently underway.

Clinical Safety:
In the NAVIGATOR trial, the frequencies and types of AEs did not differ meaningfully between tezepelumab and placebo.[9] The most frequently reported AEs with tezepelumab compared with placebo in the NAVIGATOR trial included nasopharyngitis (21.4% vs. 21.5%); upper respiratory tract infection (11.2% vs. 16.4%); headache (8.1% vs. 8.5%); bronchitis (4.7% vs. 6.2%); back pain (4.0% vs. 2.8%); and arthralgia (3.8% vs. 2.4%).[9] In the pooled safety population from the PATHWAY, NAVIGATOR and SOURCE trials, the most common adverse effects observed with tezepelumab were pharyngitis, arthralgia, and back pain.[6] The incidence rates of adverse effects observed with tezepelumab compared with placebo in the pooled safety population are presented in **Table 4**. Thymic stromal lymphopoietin may be involved in the immunological response to some parasitic infections; such infections should be treated before starting tezepelumab.[6] No episodes of anaphylaxis or increases in serious infections were reported during clinical trials.[7]

Table 4. Adverse Reactions With Tezepelumab With Incidence Greater Than 3% And More Common Than Placebo In Pooled Safety Population[6]

Adverse Reaction	Tezepelumab (n=665)	Placebo (n=669)
Pharyngitis	4%	3%
Arthralgia	4%	3%
Back Pain	4%	3%

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Annualized rate of asthma exacerbations
2) Improved pulmonary function
3) Asthma control and symptoms
4) Health related quality of life
5) Asthma-related morbidity or mortality
6) Serious AEs
7) Study withdrawal due to an AE

Primary Study Endpoint:
1) Annualized rate of asthma exacerbations

Table 5. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Blocks thymic stromal lymphopoietin, an upstream modulator of inflammation
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Volume of Distribution: 3.9 liters; No data on protein binding
Elimination	Tezepelumab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance.
Half-Life	26 days
Metabolism	Tezepelumab is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic enzymes.

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
Corren J. et al[8] PATHWAY Phase 2, MC, DB, PC, PG, RCT	1. Tezepelumab 70 mg SC every 4 weeks 2. Tezepelumab 210 mg SC every 4 weeks 3. Tezepelumab 280 mg SC every 2 weeks 4. Placebo SC every 2 weeks 52 weeks	Demographics: 1. Mean age: 50 yo 2. Male: 35% 3. Race - White: 90% Asian: 3% Black: 3% 4. Baseline ACQ-6 score: 2.7 5. Baseline AQLQ score: 4 6. Mean baseline eosinophil level ≤ 250 cells/µL: 56% 7. Baseline exacerbations in previous 12 months: 1 or 2 exacerbations: 80% More than 2 exacerbations: 20% Key Inclusion Criteria: 1.Aged 18-75 yo 2. Severe, uncontrolled asthma 3. Medium- or high-dose ICS use 4. ACQ-6 ≥ 1.5 5. History of ≥ 2 asthma exacerbations leading to OCS treatment or 1 exacerbation leading to hospitalization in previous 12 mos 6. Mean baseline FEV_1 40-80% Key Exclusion Criteria: 1. Any pulmonary disease associated with high eosinophil counts, excluding asthma 2. Any significant infection requiring antibiotic or antiviral treatment 2 weeks prior to randomization 3. History of HIV, cancer, or hepatitis B or C 4. Current smoker or smoking history ≥ 10 pack years 5. Use of biologic agent 30 days prior to randomization or	ITT: 1. 138 2. 137 3. 137 4. 138 Attrition: 1. 8 (5.7%) 2. 11 (8%) 3. 15 (11%) 4. 22 (16%)	Primary Endpoint: AAER over 52 weeks 1. 0.27 events per patient-year 2. 0.20 events per patient-year 3. 0.23 events per patient-year 4. 0.72 events per patient-year **1 vs. 4**: Relative reduction: 62% 90% CI 42 to 75 P<0.001 **2 vs. 4**: Relative reduction: 71% 90% CI 54 to 82 P<0.001 **3 vs. 4:** Relative reduction: 66% 90% CI 47 to 79 P<0.001 Secondary Endpoints: LS mean change from baseline in pre-bronchodilator FEV_1 at week 52 1. 0.07 L 2. 0.08 L 3. 0.10 L 4. -0.06 L **1 vs. 4:** Difference: 0.12 L 95% CI 0.02 to 0.22 P=0.015 **2 vs. 4**: Difference: 0.13 L 95% CI 0.03 to 0.23 P=0.009 **3 vs. 4**: Difference: 0.15 L 95% CI 0.05 to 0.25 P=0.002 LS mean change from baseline in ACQ-6 at week 52 1. -1.17 2. -1.20 3. -1.22 4. -0.91 **1 vs. 4**: Difference: -0.26 95% CI -0.52 to 0.01	NA NA NA NA	AEs 1. 67.4% (n=93) 2. 65.7% (n=90) 3. 65% (n=89) 4. 65.9% (n=91) SAEs 1. 12.3% (n=17) 2. 9.5% (n=13) 3. 13.1% (n=18) 4. 13% (n=18) Discontinuation due to AE 1. 0% 2. 1.5% (n=2) 3. 2.2% (n=3) 4. 0.7% (n=1)	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1:1 via IVRS. Patients stratified by geographic region, blood eosinophil count (≥ 250 cells/µL or < 250 cells/µL), and ICS dose (medium vs. high). Baseline characteristics balanced between groups. Performance Bias: Low. Trial agents were similar in appearance. Injections administered by staff at study site who were unaware of trial-group assignments. Detection Bias: Low. Patients and providers blinded to treatment. Patients recorded ACQ-6 and AQLQ scores in an electronic device. Attrition Bias: Low. Higher attrition in the placebo arm, primarily due to withdrawal by the patient (16%). Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Funded by MedImmune (a member of the AstraZeneca group) and Amgen. Sponsors developed the protocol and conducted data analysis. **Applicability**: Patient: Higher proportion of females compared to males (65% vs. 35%) and White (90%) subjects compared to Black (3%) and Asian races (3%) were enrolled. Intervention: Dose finding Phase 2 trial. Comparator: Placebo comparator is appropriate. Outcomes: Annualized rates of asthma exacerbations were used in other monoclonal antibody trials for severe asthma. Setting: 108 sites in 12 countries.

		immunosuppressive drug 12 weeks prior to randomization		P=0.059 **2 vs. 4:** Difference: -0.29 95% CI -0.56 to -0.01 P=0.039 **3 vs. 4**: Difference: -0.31 95% CI -0.58 to -0.04 P=0.024 LS mean change from baseline in AQLQ-12 at week 52 1. 1.12 2. 1.17 3. 1.32 4. 0.97 **1 vs. 4**: Difference: 0.14 95% CI -0.13 to 0.42 P=.309 **2 vs. 4:** Difference: 0.20 95% CI -0.09 to 0.48 P=0.185 **3 vs. 4**: Difference: 0.34 95% CI 0.06 to 0.63 P=0.017	NA			
1. Menzie-Gow A., et al[9] NAVIGATOR Phase 3, MC, DB, PC, PG, RCT	1. Tezepelumab 210 mg SC every 4 weeks 2. Placebo SC every 4 weeks 52 weeks	<u>Demographics</u>: 1. Mean age: 49 yo 2. Male: 37% 3. Race - White: 63% Asian: 28% Black: 6% 4. Baseline high-dose ICS use:75% 5. Baseline OCS use: 9% 6. Mean baseline FEV_1 : 63% 7. Mean baseline ACQ-6 score: 2.8 8. Mean baseline AQLQ score: 4 9. Mean baseline eosinophil level ≤ 300 cells/µL: 58.4% 10. Baseline exacerbations in previous 12 months: 2 exacerbations: 60% More than 2 exacerbations: 40% <u>Key Inclusion Criteria</u>: 1. Age 12-80 yo	<u>ITT</u>: 1. 528 2. 531 <u>Attrition</u>: 1. 36 (6.8%) 2. 57 (10.7%)	<u>Primary Endpoint</u>: AAER over 52 weeks for overall population 1. 0.93 events per patient-year 2. 2.10 events per patient-year Rate ratio: 0.44 95% CI 0.37 to 0.53 P<0.0001 AAER over 52 weeks in patients with eosinophil < 300 cells/µL 1. 1.02 events per patient-year (n=309) 2. 1.73 events per patient-year (n=309) Rate ratio: 0.59 95% CI 0.46 to 0.75 P<0.001 <u>Secondary Endpoints</u>: LS mean change from baseline in pre-bronchodilator FEV_1 at week 52	NA NA NA	<u>AEs</u> 1. 77.1% (n=407) 2. 80.8% (n=429) <u>SAEs</u> 1. 9.8% (n=52) 2. 13.7% (n=73) <u>Discontinuation due to AE</u> 1. 2.1% (n=11) 2. 3.6% (n=19)	NA NA NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Randomized 1:1 via IVRS. Patients stratified by geographic region and age. Baseline characteristics balanced between groups. <u>Performance Bias</u>: Low. Placebo was matched to active drug in volume, appearance, and packaging. Injections administered by HCP at study site. <u>Detection Bias</u>: Low. Patients and providers blinded to treatment. Independent adjudication committee assessed blinded data. Asthma exacerbation defined in study protocol (use of OCS, ER admit, or inpatient admission). <u>Attrition Bias</u>: Low. Higher attrition in the placebo arm, primarily due to withdrawal by the patient (4.9%). Data post-withdrawal from the study were assumed to be missing at random and were not imputed into the primary analysis. <u>Reporting Bias</u>: Low. Protocol available online. According to FDA, 195 subjects had 1 important protocol deviation, but none of the deviations impacted the study quality or overall interpretation of the results.

		2. Severe, uncontrolled asthma 3. Medium- or high-dose ICS use plus 1 additional controller (LABA, LAMA, theophylline, LTRA) with or without OCS 4. ACQ-6 ≥ 1.5 5. History of ≥ 2 asthma exacerbations in previous 12 mos Key Exclusion Criteria: 1. Any pulmonary disease associated with high eosinophil counts, excluding asthma 2. Any significant infection requiring antibiotic or antiviral treatment 2 weeks prior to randomization 3. Helminth or parasitic infection diagnosed 6 mos before randomization that had been treated or was unresponsive to SOC treatment 4. History of HIV, cancer, or hepatitis B or C 5. Current smoker or smoking history ≥ 10 pack years 6. Use of biologic agent 4 mos prior to randomization or immunosuppressive drug 12 weeks prior to randomization		1. 0.23 L 2. 0.09 L LS mean difference: 0.13 L 95% CI 0.08 to 0.18 P<0.001 LS mean change from baseline in ACQ-6 at week 52 1. -1.55 2. -1.22 LS mean difference: -0.33 95% CI -0.46 to -0.20 P<0.001 LS mean change from baseline in AQLQ-12 at week 52 1. 1.49 2. 1.15 LS mean difference: 0.34 95% CI 0.20 to 0.47 P<0.001	NA NA			Other Bias: Unclear. Sponsored by AstraZeneca and Amgen. Five investigators reported conflict of interest due to support from various manufacturers including AstraZeneca and Amgen. **Applicability**: Patient: Relevant patient groups (e.g. smokers) were excluded and percentage of included adolescents was small (8%). Higher proportion of females compared to males (63% vs. 37%) and White subjects (63%) compared to Asian (28%) Black (6%) races were enrolled. All patients met GINA criteria for severe asthma and had at least 2 exacerbations in the prior 12 months. Intervention: Dosing evaluated in a phase 2 RCT and showed reduction in AAER. Comparator: Placebo comparator is appropriate. Outcomes: Annualized rates of asthma exacerbations were used in other monoclonal antibody trials for severe asthma. Setting: 294 sites in 18 countries. 18% of sites were in the US, which was the highest percentage of all participating countries.

Abbreviations : ACQ = Asthma Control Questionnaire; AAER = annualized asthma exacerbation rate; AQLQ = Asthma Quality of Life Questionnaire; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; ER = Emergency Room; FDA = Food and Drug Administration; FEV_1 = forced expiratory volume in 1 second; GINA = Global Initiative for Asthma; HCP = health care professional; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICS = inhaled corticosteroid; ITT = intention to treat; IVRS = interactive voice response system; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic agent; L = liters; LS = least squares; LTRA = leukotriene receptor antagonist; MC = multi-center; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OCS = oral corticosteroids; PC = placebo-controlled; PG = parallel-group; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous; SOC = standard of care; US = United States; yo = years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL	Atopic Dermatitis Indication
abrocitinib	CIBINQO	TABLET	ORAL	N	Y
benralizumab	FASENRA PEN	AUTO INJCT	SUBCUT	N	
benralizumab	FASENRA	SYRINGE	SUBCUT	N	
dupilumab	DUPIXENT PEN	PEN INJCTR	SUBCUT	N	Y
dupilumab	DUPIXENT SYRINGE	SYRINGE	SUBCUT	N	Y
mepolizumab	NUCALA	AUTO INJCT	SUBCUT	N	
mepolizumab	NUCALA	SYRINGE	SUBCUT	N	
mepolizumab	NUCALA	VIAL	SUBCUT	N	
omalizumab	XOLAIR	SYRINGE	SUBCUT	N	
omalizumab	XOLAIR	VIAL	SUBCUT	N	
reslizumab	CINQAIR	VIAL	INTRAVEN	N	
tezepelumab-ekko	TEZSPIRE	SYRINGE	SUBCUT	N	
tralokinumab-ldrm	ADBRY	SYRINGE	SUBCUT	N	Y

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1946 to February Week 3, 2022, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 03, 2022

1.	benralizumab.mp	538
2.	mepolizumab.mp	1064
3.	exp Omalizumab/	2078
4.	reslizumab.mp	335
5.	dupilumab.mp	1521
6.	tezpelumab.mp	76
7.	anti-asthmatic agents	12512
8.	severe asthma.mp	9053
9.	1 or 2 or 3 or 4 or 5 or 6 or 7	16030
10.	8 and 9	1923
11.	limit 10 to (english language and humans and yr=”2021-current”)	189

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TEZSPIRE™ (tezepelumab-ekko) injection, for subcutaneous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

TEZSPIRE is a thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody (IgG2λ), indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. (1)

Limitations of Use:

- Not for relief of acute bronchospasm or status asthmaticus. (1)

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection. (2)
- Recommended dosage is 210 mg administered once every 4 weeks. (2)

DOSAGE FORMS AND STRENGTHS

Injection:

- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose glass vial. (3)
- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled syringe. (3)

CONTRAINDICATIONS

Known hypersensitivity to tezepelumab-ekko or excipients. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Hypersensitivity reactions (e.g., rash, allergic conjunctivitis) can occur after administration of TEZSPIRE. Initiate appropriate treatment as clinically indicated in the event of a hypersensitivity reaction. (5.1)
- Risk Associated with Abrupt Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Decrease corticosteroids gradually, if appropriate. (5.3)
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with TEZSPIRE. If patients become infected while receiving TEZSPIRE and do not respond to anti-helminth treatment, discontinue TEZSPIRE until the parasitic infection resolves. (5.4)
- Vaccination: Avoid use of live attenuated vaccines. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 3%) are pharyngitis, arthralgia, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 12/2021

Appendix 4: Key Inclusion Criteria

Population	Adults and children with asthma or chronic rhinosinusitis
Intervention	Biological maintenance treatments for asthma or chronic rhinosinusitis
Comparator	Placebo or active therapies
Outcomes	Mortality, exacerbations, hospitalizations
Timing	As needed
Setting	Outpatient

Targeted Immune Modulators for Severe Asthma and Severe Atopic Dermatitis

Goal(s):

- Restrict use of targeted immune modulators to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required an Emergency Department visit or hospitalization or for patients with severe atopic dermatitis.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria, mild-to-moderate atopic dermatitis).

Length of Authorization:

- Up to 12 months

Requires PA:

- Targeted immune modulators with indications for severe asthma or severe atopic dermatitis (see **Table 2** below) (pharmacy and provider-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)	Atopic Dermatitis (AD)
Abrocitinib CIBINQO							≥18 years
Benralizumab FASENRA	≥12 years						
Dupilumab DUPIXENT	≥6 years (or with oral corticosteroid dependent asthma)					≥18 years	≥6 years
Mepolizumab NUCALA	≥6 years			≥ 12 years	≥18 years	≥18 years	
Omalizumab XOLAIR		≥6 years				≥18 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)							

Table 3. FDA-Approved Abrocitinib Dosing for Atopic Dermatitis

Assessment	Recommended Dose
CYP2C19 Poor Metabolizer	50 mg once daily
GFR 30 to 60 mL/min	50 mg once daily
GFR < 30 mL/min	Use is not recommended
Severe hepatic impairment (Child-Pugh Class C)	Use is not recommended
Abbreviations: GFR=glomerular filtration rate; mL=milliliters; min=minutes	

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 (ages 6 – 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				

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

Approval Criteria		
3. Is the request for an FDA-approved indication and age (**Table 2**)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a concurrent prescription for EpiPen® or equivalent to enable management of possible delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. 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 #7	**No:** Go to #14
7. 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 #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for abrocitinib?	**Yes:** Go to #9	**No:** Go to # 13

Approval Criteria		
9. Are baseline labs (platelets, lymphocytes, lipids) documented? *Note: Abrocitinib therapy should not be initiated if platelet count is < 50,000/mm^3, absolute lymphocyte count is < 500/mm^3, absolute neutrophil count (ANC) is < 1,000/mm^3, or hemoglobin is < 8 g/dL	**Yes:** Go to # 10 Document Lab and Date Obtained: Platelets:_____ Lymphocytes:_____ Lipids:_____ Hemoglobin:	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient currently taking other targeted immune modulators or oral immunosuppressants?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. If the patient has renal or hepatic impairment has the dose been adjusted as described in Table 3?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the patient 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? *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:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13

Approval Criteria		
13. 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
14. 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 #15
15. 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 #16
16. Is the request for treatment of nasal polyps?	**Yes:** Go to # 17	**No:** Go to #19
17. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to # 18	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
18. 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
19. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. 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 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 #21 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.
~~20.~~21. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.
~~21.~~22. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, or tezepelumab, etc.)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #23
~~22.~~23. Is the request for tezepelumab?	**Yes:** Approve for up to 12 months.	No: Go to # 24

Approval Criteria		
~~23.~~24. 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 #25
25. 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.

Renewal Criteria		
1. Is the request to renew therapy for EGPA, nasal polyps, or HES?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #4	**No:** Go to #5

Renewal Criteria		
4. 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.
5. 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.
6. Has the number of ED visits, hospitalizations, or asthma exacerbations requiring oral corticosteroids 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.

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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
~~1.~~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

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

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Drug Class Literature Scan: Medications for Vitiligo

Date of Review: June 2022

Date of Last Review: N/A
Literature Search: 1946 - 03/21/2022

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

Conclusions:

- The objective of a 2015 Cochrane review was to update a 2010 review that assessed the effects of therapeutic interventions used in the management of vitiligo.[1] This review identified evidence from individual studies to support existing therapies for vitiligo, but the usefulness of the findings is limited by the different designs, outcome measurements and lack of quality of life measures.[1] There is moderate evidence for the use of topical corticosteroids (TCS), although long-term use is likely to lead to adverse effects.[1] When used as monotherapy, it may be preferable to use super potent TCS preparations to give a better chance of therapeutic response, but close monitoring for adverse effects is necessary.[1] The topical calcineurin inhibitor (TCI), tacrolimus, seems to be a reasonable alternative to topical corticosteroids, particularly on anatomical sites where there may be a higher risk of adverse effects with TCS.[1]
- In 2021, the British Association of Dermatologists (BAD) updated a 2008 guideline for the management of vitiligo for implementation in the United Kingdom National Health Service.[2] First-line treatments consist of topical treatments TCS and TCI.[2] Commonly prescribed TCS include betamethasone dipropionate, clobetasol dipropionate and fluticasone.[2] Tacrolimus, as monotherapy or in combination with phototherapy, is just as effective as TCS therapy but has a safer side-effect profile.[2] Second-line treatments consist of phototherapy (narrow band ultra violet B rays [NB-UVB] or psoralen and UVA [PUVA]) and systemic steroid treatment.[2] Third-line treatments consist of surgical grafting techniques.[2] Despite the autoimmune nature of vitiligo, there is insufficient evidence to support the use of immunosuppressive therapies in managing vitiligo.[2]
- In January 2022, the Oregon HERC revised Guideline Note 21 to broaden coverage of severe inflammatory skin disease.[3] Inflammatory skin conditions in this guideline include: psoriasis, atopic dermatitis, lichen planus, darier disease, pityriasis ruba pilaris, discoid lupus, and vitiligo. Severe forms of these conditions are funded on line 426 and are defined as having functional impairment AND one or more of the following:
    A) At least 10% of body surface area (BSA) involved
    B) Hand, foot, face, or mucous membrane involvement

Recommendations:

- Revise prior authorization (PA) criteria for “Topical Agents for Inflammatory Skin Diseases” to reflect most recent Oregon Health Effectiveness Review Committee (HERC) guidance described in Guideline Note 21.
- Review costs of topical steroids in Executive Session.

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Summary of Current Policy

- In January 2022, the Oregon HERC revised Guideline Note 21 to broaden coverage of severe inflammatory skin disease.[3] Inflammatory skin conditions in this guideline include: psoriasis, atopic dermatitis, lichen planus, darier disease, pityriasis ruba pilaris, discoid lupus, and vitiligo. Severe forms of these conditions are funded on line 426 and are defined as having functional impairment AND one or more of the following:
    - At least 10% of body surface area (BSA) involved
    - Hand, foot, face, or mucous membrane involvement

  The definition of functional impairment, is defined as an assessment of severe disease using the Dermatology Life Quality Index (DLQI) (score $\geq$ 11), Children's Dermatology Life Quality Index (CDLQI) (score $\geq$ 13), or severe score on another validated tool.[3] If inflammatory skin conditions do not meet the criteria stipulated in Guideline Note 21, they are not funded by HERC and are included on lines 482, 504, 532, 541, and 656. The revised 2022 Guideline Note 21 is included in **Appendix 4.**
- Topical calcineurin inhibitors, tacrolimus 0.03% ointment, tacrolimus 0.1% ointment, and pimecrolimus 1% cream are designated as preferred agents on the Preferred Drug List (PDL). The Pharmacy and Therapeutics Committee reviewed topical steroids at the July 2017 meeting. No new comparative evidence was identified since the last review to support a difference in safety or efficacy among equipotent topical corticosteroids. At least one agent in each of the potency categories is designated as preferred on the PDL. A list of preferred topical agents for inflammatory skin conditions is included in **Appendix 1**.

Background:

Vitiligo, a chronic autoimmune skin disorder disease, is the most frequent cause of depigmentation worldwide, with an estimated prevalence of 1%.[4] It usually begins after birth and, although it can develop in childhood, the average age of onset is about 20 years.[5] This disorder can be psychologically devastating and stigmatizing, especially in dark skinned individuals.[4] Vitiligo is clinically characterised by the development of white macules due to the loss of functioning melanocytes in the skin or hair, or both.[4] Two forms of the disease are recognized: segmental vitiligo (SV) and non-segmental vitiligo (NSV).[6] Non-segmental vitiligo, the most common form of vitiligo, is characterized by symmetrical and bilateral white patches.[4] Non-segmental vitiligo develops at all ages, but usually occurs in young people between the ages of 10 years and 30 years.[4] The most commonly affected sites are the fingers, wrists, axillae, groin, mouth, eyes and genitalia.[7] Different NSV clinical subtypes have been described, including generalized, mucosal, acrofacial, and universal, all with a bilateral distribution.[4] In contrast, SV is less common than NSV and usually has asymmetrical, one-sided or band-shaped distribution.[4] Segmental vitiligo accounts for 5–16% of overall vitiligo cases.[4] Segmental vitiligo tends to occur at a young age, before age 30 years in 87% of cases and before age 10 years in 41% of cases.[4]

Vitiligo is classified as an autoimmune disease.[8] Recent evidence points towards an overlapping inflammatory pathogenesis for both SV and NSV.[8] Both types seem to involve a multistep process, which involves initial release of proinflammatory cytokines and neuropeptides elicited by external or internal injury, with subsequent vascular dilatation and immune response.[8] Many studies support the association of vitiligo with thyroid disorders and other associated autoimmune diseases, such as rheumatoid arthritis, psoriasis, adult-onset diabetes mellitus, Addison's disease, pernicious anemia, alopecia areata, and systemic lupus erythematosus.[4] Almost one-third of people with vitiligo have a positive family history of the disease.[4] Several corresponding relevant genes associated with both vitiligo and other pigmentary, autoimmune and autoinflammatory disorders have now been identified.[8] They are involved in immune regulation, melanogenesis and apoptosis.[8]

The diagnosis of vitiligo is generally straightforward, made clinically based upon the finding of acquired, amelanotic, nonscaly, chalky-white macules with distinct margins in a typical distribution: periorificial, lips and tips of distal extremities, penis, segmental and areas of friction.[8] The diagnosis of vitiligo does not usually require confirmatory laboratory tests.[8] A skin biopsy or other tests are not necessary except to exclude other disorders.[8] The diagnosis of vitiligo may be

facilitated by the use of a Wood's lamp, a hand-held ultraviolet (UV) irradiation device that emits ultraviolet A rays (UVA).[8] It helps identify focal melanocyte loss and detect areas of depigmentation that may not be visible to the naked eye, particularly in pale skin.[8] Under the Wood's light, the vitiligo lesions emit a bright blue-white fluorescence and appear sharply demarcated.[8]

Treatment of vitiligo aims to halt disease spread and facilitate repigmentation.[9] Choice of treatment depends on several factors including: the subtype of the disease, the extent, distribution and activity of disease as well as the patient's age, phototype, effect on quality of life and motivation for treatment.[8] The face, neck, trunk and mid-extremities respond best to therapy, while the lips and distal extremities are more resistant.[8] The 2021 BAD Guidelines recommend that first-line treatment consist of high potency or very high potency TCS or topical tacrolimus.[2] Commonly prescribed TCS include betamethasone dipropionate, betamethasone valerate, clobetasol dipropionate and fluticasone propionate.[2] Use of the TCS or tacrolimus ointment, to treat vitiligo is off-label.[10] Topical tacrolimus, as monotherapy or in combination with phototherapy, is just as effective as TCS therapy but has a safer side-effect profile.[2] Second-line treatments consist of phototherapy NB-UVB or psoralen PUVA and systemic steroid treatment.[2] Third-line treatment consists of surgical grafting techniques.[2] Despite the autoimmune nature of vitiligo, there is insufficient evidence to support the use of immunosuppressive therapies in managing vitiligo.[2] Phototherapy has been a mainstay of treatment for vitiligo for several years.[5] Phototherapy is typically administered three times per week and is more effective if commenced early on in the disease.[11] It is used as first-line therapy in extensive disease. It can be used in combination with TCS or topical tacrolimus.[2]

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

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

New Systematic Reviews:
<u>2015 Cochrane: Interventions for Vitiligo</u>
The objective of a 2015 Cochrane review was to update a 2010 review that assessed the effects of therapeutic interventions used in the management of vitiligo.[1] The literature search was conducted through October 2013.[1] The 2015 update identified 39 new randomized controlled trials (RCTs) which added to the 57 RCTs in the previous review makes a total of 96 studies, totaling 4512 participants.[1] Most of the studies (72%) were small and had fewer than 50 participants.[1] Narrowband UVB light was used in 35 RCTs, either alone or in combination with other therapies.[1] Eighteen studies evaluated surgical management and 31 studies compared active treatment versus placebo.[1] Half of the studies lasted longer than six months.[1] Only 7 studies assessed children.[1] Most of the studies included subjects with NSV, only 1 RCT included participants with SV.[1] Most of the studies were conducted in Asia or Australia (n=49) followed by Europe (n=27), the Americas (n=14), and Africa (n=6).[1] Only 5 studies met the criteria for a well-designed trial.[1] Poor design, the number and complexity of the treatments and the fact that many of the studies assessed individual vitiligo patches in the same participant, made comparison of the studies difficult.[1]

Primary outcomes included: quality of life using a validated tool (e.g. DLQI), percentage of repigmentation (success rate defined as 75% or greater repigmentation), and adverse effects.[1] Nine studies assessed quality of life and showed no significant improvement between comparators.[1] Approximately half of the studies assessed repigmentation.[1] Only 3 RCTs reported a statistically significant result for 75% or greater repigmentation with the following results: topical corticosteroids were better than PUVA-sol (psoralen with sunlight) (RR 4.70, 95% CI 1.14 to 19.39, one study, N = 45); hydrocortisone plus laser light was better than laser light alone (RR 2.57, 95% CI 1.20 to 5.50, one study, N = 84); and oral minipulse of prednisolone (OMP) plus NB-UVB was better than OMP alone (RR 7.41, 95% CI 1.03 to 53.26, one study, N = 47).[1] None of the studies reported the long-term benefit of the treatment (i.e. two years sustained repigmentation).[1] The maximum follow-up time, reported in only one study, was one year post-treatment.[1]

Studies assessing topical preparations, in particular TCS, reported the most adverse effects.[1] Most studies examining TCS reported adverse effects including folliculitis, burning, mild pruritus, dryness, mild erythema, atrophy, telangiectasia and acneiform lesions.[1] In studies combining phototherapy and TCS, it was difficult to ascertain which treatment caused these effects.[1] In a meta-analysis comparing NB-UVB to PUVA, the NB-UVB group reported less observations of nausea in three studies (RR 0.13, 95% CI 0.02 to 0.69; I^2 = 0% three studies, N = 156) and erythema in two studies (RR 0.73, 95% CI 0.55 to 0.98; I^2 = 0%, two studies, N = 106), but no itching in two studies (RR 0.57, 95% CI 0.20 to 1.60; I^2 = 0%, two studies, N = 106).[1]

This review identified evidence from individual studies to support existing therapies for vitiligo, but the usefulness of the findings is limited by the different study designs, outcome measurements, and lack of quality of life measures.[1] There is moderate evidence for the use of TCS, although long-term use is likely to lead to adverse effects.[1] When used as monotherapy, it may be preferable to use super potent TCS preparations to provide optimal therapeutic response, but close monitoring for adverse effects is necessary.[1] The TCI, tacrolimus ointment, seems to be a reasonable alternative to TCS, particularly on anatomical sites where there may be a higher risk of adverse effects with TCS.[1] There is a need for follow-up studies to assess permanence of repigmentation as well as high-quality randomized trials using standardized measures and which also address quality of life.[1]

After review, 5 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[12-16]

New Guidelines:

British Association of Dermatologists

In 2021, BAD updated a 2008 guideline for the management of vitiligo for implementation in the United Kingdom National Health Service.[2] The National Institute for Health and Care Excellence (NICE) accredited the process used by BAD to produce the clinical guidelines.[2] A literature search was conducted through May 2019 to identify key articles on vitiligo.[2] Nearly all the evidence supporting BAD recommendations relate to studies in adults.[2] There is very little published evidence for treatment interventions in children aged under 12 years.[2] Young children are more at risk from skin atrophy from TCS treatment, especially on delicate areas such as the face.[2] Nonsteroid options such as tacrolimus should be considered first line alongside potent TCS in children.[2] Topical potent and very potent steroids are more likely to have a systemic effect due to the increased surface-area-to-volume ratio in young children, and caution should be exercised regarding their use, especially in generalized widespread disease.[2]

Treatment recommendations for adults with vitiligo are as follows:

Topical Therapies

- Offer a potent or very potent TCS once daily, to minimize potential side-effects, to people with vitiligo as the first-line treatment, avoiding the periocular area. (Strong Recommendation)[2]

- Consider topical tacrolimus 0.1% ointment twice daily in people with facial vitiligo as an alternative to potent or very potent topical corticosteroids. (Weak Recommendation)[2]
- Consider topical tacrolimus 0.1% ointment twice daily under occlusion on photoexposed areas only in people with nonfacial vitiligo as an alternative to potent or very potent TCS. (Weak Recommendation)[2]
- There is insufficient evidence to recommend topical vitamin D analogs (i.e. calcipotriene) in people with vitiligo.[2]

Systemic Therapies

- Consider oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg per month for a further 3 months in combination with NB-UVB in people with rapidly progressive vitiligo to arrest activity of the disease, after careful consideration of the risks and benefits. (Weak Recommendation)[2]
- Do not offer azathioprine in combination with PUVA (or NB-UVB) to people with vitiligo, due to the risk of malignancy. (Strong Recommendation)[2]
- There is insufficient evidence to recommend any currently available systemic treatments as monotherapy for people with stable vitiligo.[2]
- There is insufficient evidence to recommend minocycline, methotrexate or tofacitinib for people with vitiligo.[2]

Light and Laser Therapy

- Offer NB-UVB (whole body or localized, e.g. home based handheld) as first-line phototherapy to people with vitiligo who have an inadequate response to topical therapy and/or who have extensive or progressive disease. (Strong Recommendation)[2]
- Consider excimer laser or light in people with localized vitiligo in combination with TCIs (more evidence for tacrolimus). (Weak Recommendation)[2]
- There is insufficient evidence to recommend combination treatment of potent or very potent TCS with NB-UVB plus CO_2 laser for people with vitiligo.[2]

A patient management algorithm was developed to be used in conjunction with the summary of recommendations and supporting information provided in the BAD publication.[2]

First line treatment:

- Offer a potent or very potent TCS once daily.[2]
- Consider topical tacrolimus 0.1% ointment twice daily in people with facial vitiligo especially the periocular region.[2]
- Consider topical tacrolimus 0.1% ointment twice daily under occlusion on photoexposed areas only in people with nonfacial vitiligo.[2]
- Consider an intermittent regimen, e.g. alternating weeks of once-daily application of potent or very potent TCS with or without topical tacrolimus for areas with thinner skin.[2]

Second line treatment:

- Offer NB-UVB (whole-body or localized) with or without TCS or topical calcineurin inhibitors.[2]
- For rapidly progressing disease, consider oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg per month for a further 3 months in combination with NB-UVB.[2]

Third line treatment:

- Consider excimer laser/light with TCIs for localized vitiligo.[2]
- Consider cellular grafting for stable segmental or nonsegmental vitiligo.[2]

After review, 3 guidelines were excluded due to poor quality.[17-19]

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Topical Products for Atopic Dermatitis

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

Topical Steroids

Generic	Brand	Route	Form	PDL
alclometasone dipropionate	ALCLOMETASONE DIPROPIONATE	TOPICAL	CREAM (G)	Y
alclometasone dipropionate	ALCLOMETASONE DIPROPIONATE	TOPICAL	OINT. (G)	Y
betamethasone dipropionate	BETAMETHASONE DIPROPIONATE	TOPICAL	CREAM (G)	Y
betamethasone dipropionate	ALPHATREX	TOPICAL	LOTION	Y
betamethasone dipropionate	BETAMETHASONE DIPROPIONATE	TOPICAL	LOTION	Y
betamethasone dipropionate	ALPHATREX	TOPICAL	OINT. (G)	Y
betamethasone dipropionate	BETAMETHASONE DIPROPIONATE	TOPICAL	OINT. (G)	Y
betamethasone valerate	BETAMETHASONE VALERATE	TOPICAL	CREAM (G)	Y
betamethasone valerate	BETATREX	TOPICAL	CREAM (G)	Y
betamethasone valerate	BETAMETHASONE VALERATE	TOPICAL	OINT. (G)	Y
betamethasone valerate	BETATREX	TOPICAL	OINT. (G)	Y
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	CREAM (G)	Y
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	OINT. (G)	Y
desonide	DESONIDE	TOPICAL	CREAM (G)	Y
desonide	DESOWEN	TOPICAL	CREAM (G)	Y
desonide	TRIDESILON	TOPICAL	CREAM (G)	Y
desonide	DESONIDE	TOPICAL	OINT. (G)	Y
desonide	TRIDESILON	TOPICAL	OINT. (G)	Y
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	TOPICAL	CREAM (G)	Y
fluocinolone acetonide	SYNALAR	TOPICAL	CREAM (G)	Y
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	TOPICAL	SOLUTION	Y
fluocinolone acetonide	SYNALAR	TOPICAL	SOLUTION	Y
fluocinonide	FLUOCINONIDE	TOPICAL	CREAM (G)	Y

fluocinonide	VANOS	TOPICAL	CREAM (G)	Y
fluocinonide	FLUOCINONIDE	TOPICAL	SOLUTION	Y
fluocinonide/emollient base	FLUOCINONIDE-E	TOPICAL	CREAM (G)	Y
hydrocortisone	ANTI-ITCH	TOPICAL	CREAM (G)	Y
hydrocortisone	HYDROCORTISONE	TOPICAL	CREAM (G)	Y
hydrocortisone	HYDROCORTISONE	TOPICAL	CREAM (G)	Y
hydrocortisone	HYCORT	TOPICAL	OINT. (G)	Y
hydrocortisone	HYDROCORTISONE	TOPICAL	OINT. (G)	Y
hydrocortisone	HYDROCORTISONE	TOPICAL	OINT. (G)	Y
hydrocortisone acetate	HYDROCORTISONE ACETATE	TOPICAL	CREAM (G)	Y
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	TOPICAL	SOLUTION	Y
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	TOPICAL	CREAM (G)	Y
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	TOPICAL	OINT. (G)	Y
triamcinolone acetonide	TRIANEX	TOPICAL	OINT. (G)	Y
amcinonide	AMCINONIDE	TOPICAL	CREAM (G)	N
betamethasone dipropionate	DIPROSONE	TOPICAL	AEROSOL	N
betamethasone dipropionate	BETAMETHASONE DIPROP AUGMENTED	TOPICAL	GEL (GRAM)	N
betamethasone valerate	BETAMETHASONE VALERATE	TOPICAL	FOAM	N
betamethasone valerate	LUXIQ	TOPICAL	FOAM	N
betamethasone valerate	BETAMETHASONE VALERATE	TOPICAL	LOTION	N
betamethasone/propylene glyc	BETAMETHASONE DIPROP AUGMENTED	TOPICAL	CREAM (G)	N
betamethasone/propylene glyc	BETAMETHASONE DIPROP AUGMENTED	TOPICAL	LOTION	N
betamethasone/propylene glyc	BETAMETHASONE DIPROP AUGMENTED	TOPICAL	OINT. (G)	N
betamethasone/propylene glyc	DIPROLENE	TOPICAL	OINT. (G)	N
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	FOAM	N
clobetasol propionate	OLUX	TOPICAL	FOAM	N
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	GEL (GRAM)	N
clobetasol propionate	IMPEKLO	TOPICAL	LOT MD PMP	N
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	LOTION	N
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	SHAMPOO	N
clobetasol propionate	CLOBEX	TOPICAL	SHAMPOO	N
clobetasol propionate	CLODAN	TOPICAL	SHAMPOO	N
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	SOLUTION	N
clobetasol propionate	CLOBETASOL PROPIONATE	TOPICAL	SPRAY	N
clobetasol propionate	CLOBEX	TOPICAL	SPRAY	N
clobetasol propionate/emoll	CLOBETASOL EMOLLIENT	TOPICAL	CREAM (G)	N
clobetasol propionate/emoll	CLOBETASOL EMOLLIENT	TOPICAL	FOAM	N
clobetasol propionate/emoll	CLOBETASOL EMULSION	TOPICAL	FOAM	N
clobetasol propionate/emoll	OLUX-E	TOPICAL	FOAM	N

clobetasol propionate/emoll	TOVET EMOLLIENT	TOPICAL	FOAM	N
clobetasol/emollient no.65	TOVET KIT	TOPICAL	COMBO. PKG	N
clobetasol/skin cleanser no.28	CLODAN	TOPICAL	KT SHM CLN	N
clocortolone pivalate	CLOCORTOLONE PIVALATE	TOPICAL	CREAM (G)	N
clocortolone pivalate	CLODERM	TOPICAL	CREAM (G)	N
desonide	DESONIDE	TOPICAL	LOTION	N
desoximetasone	DESOXIMETASONE	TOPICAL	CREAM (G)	N
desoximetasone	TOPICORT	TOPICAL	CREAM (G)	N
desoximetasone	DESOXIMETASONE	TOPICAL	GEL (GRAM)	N
desoximetasone	TOPICORT	TOPICAL	GEL (GRAM)	N
desoximetasone	DESOXIMETASONE	TOPICAL	OINT. (G)	N
desoximetasone	TOPICORT	TOPICAL	OINT. (G)	N
desoximetasone	DESOXIMETASONE	TOPICAL	SPRAY	N
desoximetasone	TOPICORT	TOPICAL	SPRAY	N
diflorasone diacet/emollient	APEXICON E	TOPICAL	CREAM (G)	N
diflorasone diacetate	DIFLORASONE DIACETATE	TOPICAL	CREAM (G)	N
diflorasone diacetate	PSORCON	TOPICAL	CREAM (G)	N
diflorasone diacetate	DIFLORASONE DIACETATE	TOPICAL	OINT. (G)	N
fluocinolone acetonide	DERMA-SMOOTHE-FS	TOPICAL	OIL	N
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	TOPICAL	OIL	N
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	TOPICAL	OINT. (G)	N
fluocinolone acetonide	SYNALAR	TOPICAL	OINT. (G)	N
fluocinolone acetonide	CAPEX SHAMPOO	TOPICAL	SHAMPOO	N
fluocinolone/emol comb no.65	SYNALAR	TOPICAL	CMB ONT CR	N
fluocinolone/emol comb no.65	SYNALAR	TOPICAL	CREAM (G)	N
fluocinolone/shower cap	DERMA-SMOOTHE-FS	TOPICAL	OIL	N
fluocinolone/shower cap	FLUOCINOLONE ACETONIDE	TOPICAL	OIL	N
fluocinolone/skin clnsr28	SYNALAR TS	TOPICAL	KIT	N
fluocinonide	FLUOCINONIDE	TOPICAL	GEL (GRAM)	N
fluocinonide	FLUOCINONIDE	TOPICAL	OINT. (G)	N
flurandrenolide	FLURANDRENOLIDE	TOPICAL	CREAM (G)	N
flurandrenolide	FLURANDRENOLIDE	TOPICAL	LOTION	N
flurandrenolide	CORDRAN	TOPICAL	MED. TAPE	N
flurandrenolide	FLURANDRENOLIDE	TOPICAL	OINT. (G)	N
fluticasone propionate	FLUTICASONE PROPIONATE	TOPICAL	CREAM (G)	N
fluticasone propionate	BESER	TOPICAL	LOTION	N
fluticasone propionate	FLUTICASONE PROPIONATE	TOPICAL	LOTION	N
fluticasone propionate	FLUTICASONE PROPIONATE	TOPICAL	OINT. (G)	N
fluticasone/emollient no.65	BESER KIT	TOPICAL	KT LOTN CE	N

halcinonide	HALCINONIDE	TOPICAL	CREAM (G)	N
halcinonide	HALOG	TOPICAL	CREAM (G)	N
halcinonide	HALOG	TOPICAL	OINT. (G)	N
halcinonide	HALOG	TOPICAL	SOLUTION	N
halobetasol propionate	HALOBETASOL PROPIONATE	TOPICAL	CREAM (G)	N
halobetasol propionate	ULTRAVATE	TOPICAL	CREAM (G)	N
halobetasol propionate	HALOBETASOL PROPIONATE	TOPICAL	FOAM	N
halobetasol propionate	LEXETTE	TOPICAL	FOAM	N
halobetasol propionate	BRYHALI	TOPICAL	LOTION	N
halobetasol propionate	ULTRAVATE	TOPICAL	LOTION	N
halobetasol propionate	HALOBETASOL PROPIONATE	TOPICAL	OINT. (G)	N
halobetasol propionate	ULTRAVATE	TOPICAL	OINT. (G)	N
halobetasol/lactic acid	ULTRAVATE X	TOPICAL	CMB ONT CR	N
halobetasol/lactic acid	ULTRAVATE X	TOPICAL	COMBO. PKG	N
hydrocortisone	HYDROCORTISONE	TOPICAL	CREAM (G)	N
hydrocortisone	HYDROCORTISONE	TOPICAL	CREAM PACK	N
hydrocortisone	CETACORT	TOPICAL	LOTION	N
hydrocortisone	HYDROCORTISONE	TOPICAL	LOTION	N
hydrocortisone	HYDROCORTISONE	TOPICAL	LOTION	N
hydrocortisone	SCALP CORT	TOPICAL	LOTION	N
hydrocortisone	SCALP	TOPICAL	SOLUTION	N
hydrocortisone	SCALPICIN	TOPICAL	SOLUTION	N
hydrocortisone	TEXACORT	TOPICAL	SOLUTION	N
hydrocortisone	HYDROCORTISONE	TOPICAL	SPRAY	N
hydrocortisone acet/aloe vera	HYDROCORTISONE ACETATE W/ALOE	TOPICAL	CREAM (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE W/ALOE	TOPICAL	CREAM (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE ACETATE W/ALOE	TOPICAL	OINT. (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE W/ALOE	TOPICAL	OINT. (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE W/ALOE	TOPICAL	PACKET	N
hydrocortisone acetate	MICORT-HC	TOPICAL	CRM/PE APP	N
hydrocortisone acetate	HYDROCORTISONE	TOPICAL	OINT. (G)	N
hydrocortisone acetate	HYDROCORTISONE ACETATE	TOPICAL	OINT. (G)	N
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	TOPICAL	CREAM (G)	N
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	TOPICAL	LOTION	N
hydrocortisone butyrate	LOCOID	TOPICAL	LOTION	N
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	TOPICAL	OINT. (G)	N
hydrocortisone butyrate/emoll	HYDROCORTISONE BUTYRATE	TOPICAL	CREAM (G)	N
hydrocortisone butyrate/emoll	LOCOID LIPOCREAM	TOPICAL	CREAM (G)	N
hydrocortisone probutate	PANDEL	TOPICAL	CREAM (G)	N

hydrocortisone valerate	HYDROCORTISONE VALERATE	TOPICAL	CREAM (G)	N
hydrocortisone valerate	HYDROCORTISONE VALERATE	TOPICAL	OINT. (G)	N
hydrocortisone/aloe vera	ANTI-ITCH WITH ALOE	TOPICAL	CREAM (G)	N
hydrocortisone/aloe vera	HYDROCORTISONE PLUS	TOPICAL	CREAM (G)	N
hydrocortisone/aloe vera	HYDROCORTISONE W/ALOE	TOPICAL	CREAM (G)	N
hydrocortisone/aloe vera	HYDROCORTISONE-ALOE	TOPICAL	CREAM (G)	N
hydrocortisone/aloe vera	HYDROCORTISONE W/ALOE	TOPICAL	OINT. (G)	N
hydrocortisone/skin cleanser25	AQUA GLYCOLIC HC	TOPICAL	COMBO. PKG	N
mometasone furoate	MOMETASONE FUROATE	TOPICAL	CREAM (G)	N
mometasone furoate	MOMETASONE FUROATE	TOPICAL	OINT. (G)	N
mometasone furoate	MOMETASONE FUROATE	TOPICAL	SOLUTION	N
neomycin sulfate/fluocinolone	NEO-SYNALAR	TOPICAL	CREAM (G)	N
neomycin/fluocinolone/emoll 65	NEO-SYNALAR	TOPICAL	CREAM (G)	N
prednicarbate	PREDNICARBATE	TOPICAL	CREAM (G)	N
prednicarbate	PREDNICARBATE	TOPICAL	OINT. (G)	N
triamcinolone acetonide	KENALOG	TOPICAL	AEROSOL	N
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	TOPICAL	AEROSOL	N
triamcinolone acetonide	KENALOG	TOPICAL	LOTION	N
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	TOPICAL	LOTION	N
hydrocortisone	ANUSOL-HC	TOPICAL	CRM/PE APP	
hydrocortisone	HYDROCORTISONE	TOPICAL	CRM/PE APP	
hydrocortisone	PROCTO-MED HC	TOPICAL	CRM/PE APP	
hydrocortisone	PROCTOSOL-HC	TOPICAL	CRM/PE APP	
hydrocortisone	PROCTOZONE-HC	TOPICAL	CRM/PE APP	
neomycin sulfate/hydrocort	NEOMYCIN W/HYDROCORTISONE	TOPICAL	OINT. (G)	

Appendix 2: New Comparative Clinical Trials

A total of 44 citations were manually reviewed from the initial literature search. After further review, 43 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 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Abdel L, et al[20] DB, RCT	1. Topical calcipotriol and betamethasone ointment once daily 2. Monochromatic excimer light twice weekly Duration: 12 weeks	Subjects aged 6 to 64 yo with NSV Mean age: 35 yo N=44	Repigmentation grade after 12 weeks of treatment of 2 stable vitiligo lesions	Percentage of repigmentation 1. 63.75% 2. 65% Difference between treatments: P = 0.23 (NS)	• Small sample size • Method of randomization not described • 18% of patients (n=8) did not complete all treatment sessions for unknown reasons • Repigmentation assessment conducted via visual analysis by 2 independent clinicians
Abbreviations: CI = confidence interval; DB = double blind; N = number; NB-UVB = narrow band ultra violet B; NSV = non-segmental vitiligo; NR = not reported; RCT = randomized clinical trial; VASI = vitiligo and activity scoring index; yo = years old					

Appendix 3: Abstracts of Comparative Clinical Trials

Monochromatic Excimer Light Versus Combination Of Topical Steroid With Vitamin D3 Analogue In The Treatment Of Nonsegmental Vitiligo: A Randomized Blinded Comparative Study[20]

Vitiligo is a difficult disease to treat, socially stigmatizing its patients. Monochromatic excimer light (MEL) was developed for use in dermatology and adapted for the treatment of vitiligo. Comparing the efficacy of MEL versus topical combination therapy of vitamin D3 analogue and steroid in the treatment of nonsegmental vitiligo. Forty-four patients with localized and stable nonsegmental vitiligo participated in the present study. In each patient, two lesions were selected and divided randomly into two groups, group A was treated with daily topical combination of calcipotriol and betamethasone and group B was treated with biweekly sessions of MEL for 3 months. Efficacy based on repigmentation percentages were blindly evaluated by two independent physicians and patient's satisfaction. There was significant improvement in both treatment modalities at the end of the study, but without significant differences in both groups. There was a significant difference between both groups regarding the onset of repigmentation (p-value < 0.05), whereas group B showed early sign of repigmentation in first 4 weeks of treatment in 16 patients versus 7 patients in group A. Both treatment modalities offered encouraging results and both are promising lines for the treatment of vitiligo.

Appendix 4: Prioritized List Guideline Note

Extracted from the January 1, 2022 Prioritized List
Searchable Prioritized List 2022

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE
Lines 426,482,504,532,541,656

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus
G) Vitiligo

The conditions above are included on Line 426 if severe, defined as having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:

C) At least 10% of body surface area involved
D) Hand, foot, face, or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 482, 504, 532, 541 and 656.
For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.

For severe atopic dermatitis/eczema, first-line agents include topical moderate- to high- potency corticosteroids and narrowband UVB. Second line agents include topical calcineurin inhibitors (e.g. pimecrolimus, tacrolimus), topical phosphodiesterase (PDE)-4 inhibitors (e.g. crisaborole), and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids). Use of the topical second line agents (e.g. calcineurin inhibitors and phosphodiesterase (PDE)-4 inhibitors) should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to at least one agent from each of the following three classes: 1) moderate to high potency topical corticosteroids, 2) topical calcineurin inhibitors or topical phosphodiesterase (PDE)-4 inhibitors, and 3) oral immunomodulator therapy.

ICD-10-CM Q82.8 (Other specified congenital malformations of skin) is included on Line 426 only for Darier disease.

Appendix 5: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1946 to March Week 2 2022, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to March 18, 2022

1	exp Vitiligo/cl, dt, ep, ge, pp, th [Classification, Drug Therapy, Epidemiology, Genetics, Physiopathology, Therapy]	2853
2	Glucocorticoids/ or Dermatitis, Atopic/ or topical glucocorticoids.mp. or Anti-Inflammatory Agents/	173169
3	Calcineurin Inhibitors/tu [Therapeutic Use]	650
4	2 or 3	173687
5	1 and 4	179
6	limit 5 to (english language and humans)	165
7	limit 6 to (clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	44

Appendix 6: Key Inclusion Criteria

Population	Adults and Children
Intervention	Topical corticosteroids and topical calcineurin inhibitors
Comparator	Placebo
Outcomes	Extent of repigmentation
Timing	2-3 months
Setting	Outpatient

Topical Agents for Inflammatory Skin Diseases

Goal(s):

- Restrict dermatological drugs only for funded OHP diagnoses. 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, lichen planus, Darier disease, pityriasis rubra pilaris, discoid lupus and vitiligo seborrheic dermatitis, keratoderma and other hypertrophic and atrophic conditions of skin are not funded.

Length of Authorization:

- From 6 to 12 months

Requires PA:

- Non-preferred antipsoriatics
- All atopic dermatitis drugs
- STC = 92 and HIC = L1A, L5F, L9D, T0A
- This PA does not apply to 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 for atopic dermatitis drugs

Drug	Minimum Age
Crisaborole	3 months
Pimecrolimus	2 years
Ruxolitinib	12 years
Tacrolimus 0.03%	2 years
Tacrolimus 0.1%	16 years

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for mild or moderate inflammatory skin conditions?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the request for treatment of severe inflammatory skin disease? 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: 1. At least 10% body surface area involved OR 2. Hand, foot, face, or mucous membrane involvement	**Yes:** Go to #4	**No:** Pass to RPh; deny, not funded by the OHP
4. Is the diagnosis psoriasis?	**Yes:** Go to #8	**No:** Go to #5
5. Is the diagnosis atopic dermatitis?	**Yes:** Go to #6	**No:** Go to #10
6. Does the patient meet the age requirements per the FDA label (Table 1)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 first line agents (i.e. topical corticosteroids, tacrolimus) indicated for the treatment of severe AD? *Note ruxolitinib, pimecrolimus and crisaborole are FDA approved to manage mild to moderate AD, while tacrolimus is FDA approved to manage moderate to severe AD.	**Yes:** Document drug and dates trialed, and intolerances or contraindications (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested product preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #9
9. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Approve for length of treatment; maximum 1 year.
10. 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:** Deny, not funded by the OHP.

P&T/DUR Review: *6/22 (DM); 12/20 (DM); 10/20; 7/19 (DM); 5/19 (DM) 3/18 (DM); 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 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, face or mucous membranes.*
Reference:
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.

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Drug Class Review: Mycobacterium Drugs

Date of Review: June 2022 **Literature Search:** 01/01/2015-01/19/2022
Generic Name: See **Appendix 1**

Purpose for Class Review:
To review evidence related to agents targeting mycobacteria and identify appropriate utilization management strategies.

Research Questions:

1. What is the comparative efficacy and effectiveness of mycobacterial agents for the management of diseases caused by mycobacteria infections?
2. What are the comparative harms of antimicrobials used for the management of diseases caused by mycobacteria infections?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, prior anti-mycobacterial treatment experience, or co-morbidities for which one mycobacteria agent is more effective or associated with fewer adverse events?

Conclusions:

- Evidence was summarized from 3 systematic reviews, 10 high-quality guidelines, and 1 randomized controlled trial (RCT).
- For treatment of brucellosis infection, there was increased risk of treatment failure (relative risk [RR] 2.36; 95% confidence interval [CI] 1.72 to 3.23; P<0.001; I^2=0.0%) and higher risk of relapse (RR 2.74; 95% CI 1.80 to 4.19; I^2=0.0%) with rifampin compared to streptomycin, when given in conjunction with doxycycline background therapy. The subpopulation analysis when the mean population age was over 40 years did not show a difference in treatment failure between rifampin versus streptomycin (RR 1.92; 95% CI 0.93 to 3.97; P=0.078). Differences in safety between the two therapies were not assessed.[1]
- Treatment of non-tubercular pulmonary mycobacteria infections should include multi-drug therapy with the components and length of therapy tailored to the causative organism, susceptibility profile, and severity of illness. If susceptible, most commonly recommended agents are macrolides (clarithromycin, azithromycin), rifampin, isoniazid, ethambutol, fluoroquinolones (FQ) (levofloxacin, moxifloxacin), and aminoglycosides (amikacin, streptomycin).[2,3] Certainty of evidence is generally low.[2,3]
- For all patients with latent TB regardless of human immunodeficiency virus (HIV) status or tuberculosis (TB) prevalence, the World Health Organization (WHO) recommends 6 or 9 months of daily isoniazid, or 3 months of weekly rifapentine plus isoniazid, or 3 months of daily isoniazid plus rifampin as preferred regimens (strong recommendation, moderate to high certainty).[4,5]
- For latent TB, the Centers for Disease Control (CDC) recommend 3 months of weekly isoniazid plus rifapentine (strong recommendation; Adults and children aged >2 years, including HIV-positive persons [as drug interactions allow]), 4 months of daily rifampin (strong recommendation; HIV-negative adults and

children of all ages), and 3 months of daily isoniazid plus rifampin (conditional recommendation; Adults and children of all ages and for HIV-positive persons [as drug interactions allow]) as preferred regimens.[6]

- The preferred regimen for treatment of drug-susceptible TB is 8 weeks of daily isoniazid, rifampin, pyrazinamide, and ethambutol followed by 18 weeks of isoniazid plus rifampin.[7-9]
- Based on evidence from single, open-label RCT, a 4 month regimen consisting of 8 weeks of rifapentine, moxifloxacin, isoniazid, and pyrazinamide followed by 9 weeks of rifapentine, moxifloxacin, and isoniazid, is non-inferior compared to the standard 6 month treatment for the primary endpoint of TB free survival at 12 months for patients with pulmonary TB in those 12 years and older who met other specific inclusion criteria. There were no significant differences in grade 3 or higher adverse reactions.[10] This regimen may be considered as a possible alternative to the standard 6 month regimen in certain patients, particularly those who may be unlikely to complete the longer regimen.[11,12]
- For drug-resistant TB, the WHO recommends the shorter duration all-oral bedaquiline-containing regimen for eligible people who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to FQs has been excluded (conditional recommendation, very low certainly evidence). Bedaquiline, linezolid, and a FQ should be included in treatment of multi-drug resistant (MDR) or rifampin-resistant TB in patients on longer regimens (strong recommendation, moderate certainty evidence for bedaquiline 18 years and over, linezolid, and FQs; conditional recommendation with very low certainty evidence for bedaquiline in people aged 6 to 17 years).[13]
- For drug-resistant TB, the CDC recommends individualized therapy with at least 5 drugs during the intensive phase and 4 drugs during the continuation phase (conditional recommendation, very low certainty evidence). Bedaquiline, moxifloxacin, and levofloxacin all have strong recommendations for inclusion if microbe is susceptible (only one FQ agent in regimen) based on very low certainty evidence. [14]
- In children 3 months to 16 years with non-severe TB without drug resistance, a 4 month treatment regimen of 2 months isoniazid/rifampin/pyrazinamide +/- ethambutol, then 2 months isoniazid/rifampin is preferred (strong recommendation, moderate certainty of evidence).[15]
- Agents in this class have a variety of contraindications, adverse reactions, and drug interactions which are more likely to affect those with certain comorbidities, especially those with hepatic dysfunction and HIV patients taking certain medications. Treatment of mycobacterial infections should be individualized and monitored closely, particularly in at-risk subgroups.

Recommendations:

- Create New Preferred Drug List (PDL) class of oral drug therapies called Mycobacterium Agents as listed in **Appendix 1**
- Change bedaquiline PDL status to preferred given strong recommendations for use in drug-resistant TB.
- Make rifampin and isoniazid preferred based on clinical data as components of first-line treatment regimens for both drug-susceptible TB and latent TB.
- Make pyrazinamide and ethambutol preferred based on clinical data as components of first-line treatment regimens for drug-susceptible TB.
- Make rifapentine preferred based on clinical data as a component of a first-line treatment regimen for latent TB and an alternative regimen for drug-susceptible pulmonary TB.
- Consider making all other agents preferred to prevent barriers to care.
- Review costs in executive session.
- Any new drug or formulations assigned to class will become PDL non-preferred until reviewed.

Background:

Mycobacteria are aerobic, non-motile bacteria which are identified in the laboratory by positive acid-fast alcohol stains.[16] Those responsible for human disease are generally categorized as tubercular (TB), caused by *Mycobacterium tuberculosis*, and nontuberculosis mycobacteria (NTM), such as *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus*, and *Mycobacterium kansasii*.[16] Growth rates are further used to classify NTM as slowly growing (e.g. MAC) and rapidly growing (e.g. *M. abscessus*). Both *M. tuberculosis* and NTM are primarily associated with pulmonary infections, though both can affect other organ systems.[16]

M. tuberculosis exposure, via aerosol droplets, results in one of several outcomes. Exposed persons may immediately clear the organism, immediately develop active disease (primary disease), develop a latent infection, or experience active disease after latent infection (reactivation disease).[17] Reactivation occurs in 5 to 10% of healthy individuals. However, reactivation is markedly higher in those who are immunocompromised, especially those with uncontrolled HIV.[17] Young children are more likely to develop active TB disease, and severe forms of disease after exposure.[15] Most infections in low-burden countries like the United States are categorized as reactivation after exposure 2 years or earlier in foreign-born residents coming from countries with high endemic rates (subgroup case rate 11.5 per 100,000 in 2020).[18] In the United States in 2020, the total TB case rate was 2.2 per 100,000 persons with the highest rates (>2.8 per 100,000) in Hawaii, New York City, California, Washington DC, and Texas; Oregon TB case rates are estimated between 1.4 and 2.8 per 100,000 persons.[18] Testing for HIV should occur at TB diagnosis. Those at highest risk of new HIV diagnosis are people who inject drugs, persons experiencing homelessness, inmates, and those with alcohol use disorder.[18] The risk of TB acquisition after exposure or reactivation of latent disease is more likely with comorbid HIV, and simultaneously, the progression of HIV may be accelerated by concomitant TB.[18]

Public health reporting in Oregon is required for TB, *M. bovis*, and non-respiratory NTM infections.[19] Disease prevalence and laboratory isolation of NTM seem to be increasing with improved culture techniques.[16] Nontubercular mycobacteria are commonly found in the water and soil; water systems in hospitals, hemodialysis centers, and dental centers often have high rates of colonization, due to biofilm formation.[16] Most people have been exposed to NTM; however, disseminated disease is more common in those with significant immunosuppression, such as individuals with structural lung diseases and untreated HIV. Patients with cystic fibrosis (CF) or a history of lung transplantation are at particular risk of pulmonary NTM infections.[16] Patients with more common chronic lung conditions such as asthma or chronic obstructive pulmonary disease are also at higher risk, as the chronic epithelial cell inflammation and impaired mucociliary clearance may predispose patients to infection.[2] Nontubercular mycobacteria can reside in the lungs of exposed individuals transiently, intermittently, and permanently; differentiation of asymptomatic NTM pulmonary infection and active disease requiring treatment can be problematic.[2] Tuberculosis is the leading cause of death from infectious diseases worldwide, while NTM may also be fatal and is a common cause of lung disease.[16,20] Clinical trial outcomes vary based on organism (e.g. TB vs NTM, etc.), disease location, and active versus latent infection. Common outcomes of interest are cure, treatment completion, treatment failure, disease relapse, time to sputum culture or smear conversion (time to change from positive to negative status during treatment), clinical or radiological improvement at 8 weeks and at the end of treatment, mortality, and serious adverse events or adverse events requirement treatment alteration.[8]

The standard treatment for active pulmonary TB generally consists of an 8 week intensive phase followed by a continuation phase, usually for 18 additional weeks.[7-9] Fixed-dose combination products are sometimes available to simplify administration, though this is more common outside of the United States. First-line treatment includes isoniazid (with concomitant pyridoxine for individuals at higher risk peripheral neuropathy), rifampin (synonymous with official International and British nomenclature name of rifampicin), pyrazinamide, and ethambutol for the intensive phase and isoniazid plus rifampin for the continuation phase. Other medications can be considered based on resistance and drug intolerance for second-line therapy. If drug sensitivity is known and both isoniazid and rifampin are sensitive, then ethambutol can be omitted from the intensive phase.[9] Isoniazid causes a rapid drop in multiplying bacteria, ethambutol has early bactericidal activity, while both pyrazinamide and rifamycins have a sterilizing effect to prevent relapses. Rifamycin-type agents include rifampin,

rifabutin, and rifapentine, all used for mycobacteria, as well as rifamycin and rifaximin, which have non-mycobacterial indications. Rifabutin has a niche in first-line therapy to minimize drug interactions, as other rifamycins cause more pronounced hepatic enzyme induction which may result in problematic drug-drug interactions, particularly in certain antiretroviral (ART) regimens.[9] Rifapentine and rifampin are not interchangeable.[6] Rifamycins, specifically rifampin and rifapentine, have been plagued by drug shortages since at least 2020 when one manufacturer discontinued making rifampin and several rifampin-containing fixed-dose combination products, while simultaneously the FDA implemented new testing for nitrosamines, resulting some product shipments being held.[21-24]

Many different treatment dosing intervals have been studied for TB. For active disease, daily dosing remains preferred for the intensive phase and continuation phase, though in certain circumstances thrice-weekly regimens may also be preferred or a reasonable option in the continuation phase.[9] Recommendations can vary in certain clinical circumstances, such as latent infection, age, extrapulmonary or disseminated disease, previous treatment (1 month or more of anti-TB agents in past) and with comorbidities such as HIV.[9,13]

Concerns about drug resistance, specifically MDR-TB (resistant against at least rifampin and isoniazid) and extensively drug-resistant (XDR)-TB (resistant to rifampin, isoniazid, at least one injectable agent [amikacin, kanamycin, or capreomycin], and any of the FQs) are increasing.[14,25] The term "pre-XDR" TB is entering the lexicon as MDR-TB with FQ resistance.[13] Less than 5% of cases worldwide are considered MDR-TB, though this can be over 25% in some areas, specifically many former Soviet countries.[25] Resistance complicates treatment and often requires longer treatment durations.[25] Shorter MDR-TB regimens are defined as 9-12 months and is usually standardized, while longer MDR-TB regimens last 18 months or more and may be standardized or individualized.[13] Treatment of NTM disease includes multi-drug regimens with a duration of several months to greater than 1 year and varies widely by specific organism, site of infection, patient comorbidities, and susceptibility testing.[2,3] Other antimicrobial classes of medications, including FQs, aminoglycosides, and macrolides, can be used in the treatment of NTM and TB in specific treatment situations. Previous guidelines from WHO for treatment of MDR-TB have categorized medications in groups (e.g. group A/fluoroquinolones, group B/second-line injectable agents)[26], though classifications and nomenclature are being adjusted as recommendations change.[13] Rifampin and other rifamycins may also be used, usually in conjunction with other antimicrobials, to treat infections not caused by mycobacteria.

Table 1. World Health Organization Grouping of Medicines for longer MDR-TB regimens[27]

Medication Group	Medications*
Group A • Considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.	• Levofloxacin *or* Moxifloxacin • Bedaquiline • Linezolid
Group B • Conditionally recommended as agents of second choice.	• Clofazimine • Cycloserine *or* Terizidone
Group C • All other medicines that can be used when a regimen cannot be composed with Group A and B agents.	• Ethambutol • Delamanid • Pyrazinamide • Imipenem-cilastatin *or* Meropenem

• Ranked by the relative balance of benefit to harm usually expected of each agent.	• Amikacin *or* streptomycin (only if amikacin cannot be used because of availability or documented resistance) • Ethionamide *or* Prothionamide • *p*-aminosalicylic acid
Not included in Groups A through C: • Kanamycin and capreomycin are associated with poorer outcomes • Gatifloxacin and high-dose isoniazid were used in very few patients and thioacetazone was not used at all. Gatifloxacin and thioacetazone are not currently available in quality-assured formulations. High-dose isoniazid may have a role in patients with confirmed susceptibility to isoniazid. • Clavulanic acid should be included only as a companion agent to the carbapenems and should not be counted as an additional effective agent. *Not all agents currently marketed in the United States Note: Pretomanid is absent from table as current place in therapy is as a component of shorter MDR-TB regimens.[13]	

The medications specific to mycobacterial infections (**Appendix 1**) have not been previously reviewed for the Oregon Health Plan (OHP) Fee-for-Service (FFS) PDL, with the exception of bedaquiline, which was reviewed in 2014 after its Food and Drug Administration (FDA) approval using phase 2 studies. It was made non-preferred given insufficient evidence to support efficacy and a black box warning for increased risk of death. Pyridoxine, used as ancillary therapy to reduce the risk of peripheral neuropathy secondary to isoniazid, is a preferred agent on the OHP PDL. Other rifamycin type drugs (e.g. rifamycin, rifaximin) are FDA approved for *E. coli* related traveler's diarrhea and hepatic encephalopathy and are not part of the proposed Mycobacterium Drugs PDL class. Moxifloxacin was moved to preferred status on the PDL at the April 2022 Pharmacy and Therapeutics committee meeting, while levofloxacin was already a preferred agent. Linezolid, azithromycin, and immediate-release clarithromycin tablets are also preferred agents in the oxazolidinones and macrolide PDL classes. Based on 2019 medical claims, the Fee-For-Service (FFS) Medicaid population had fewer than 200 TB cases in adults and children (all anatomic locations). Only one TB patient was coded as having drug resistance and few individuals had concomitant HIV. There were fewer than 150 NTM cases with about 10% having HIV, while ~90 additional patients had ICD-10 codes consistent with latent TB infection. Given length of time in treatment, most patients with mycobacterial infections would be enrolled in a coordinated care organization (CCO) for the duration of therapy. Due to limitations of medical claims, this data may not accurately reflect all new or recent infections and numbers likely overestimate frequency of these infections in the FFS population.

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

Table 2. Indications and Dosing.[28]

Drug Name	Indication(s)*	Strength/Route	Dose and Frequency
Bedaquiline	• MDR TB, in combination with at least 3 other agents	Oral tablet: 20 mg, 100 mg	• 400 mg daily x2 weeks, then 200 mg 3 times weekly x 22 weeks
Aminosalicylic acid	• Active TB	Oral Powder for Suspension, Extended Release: 4 g/1 Packet	• 4 g orally 2 or 3 times/day
Cycloserine	• Active TB • Urinary tract infection (only when more conventional therapy has failed and organism has been demonstrated to be susceptible)	Oral Capsule: 250 mg	• Initial, 250 mg orally every 12 hours for 2 weeks • Then, 500 to 1000 mg/day given in divided doses • MAX dose, 1 g/day
Ethambutol	• Adjunct for pulmonary TB	Oral Tablet: 100 mg, 400 mg	• Varies by weight
Ethionamide	• Active TB	Oral Tablet: 250 mg	• Initial: 250 mg orally once daily for 1 or 2 days • Titration: increase to 250 mg twice daily for 1 or 2 days, then 1 g daily in 3 to 4 divided doses. • Usual dose is 15 to 20 mg/kg/day administered once daily if tolerated or in divided doses if necessary. A daily dosage of 0.5 g to 1 g may reduce resistance • MAX 1 g daily
Isoniazid	• Active TB (with and without concomitant HIV) • Latent TB (with and without concomitant HIV)	• Intramuscular Solution: 100 mg/1 mL • Oral Solution: 50 mg/5 mL • Oral Tablet: 100 mg, 300 mg	• Varies by indication
Pretomanid	• MDR TB, in combination bedaquiline and linezolid	Oral Tablet: 200 mg	• 200 mg once daily in combination with bedaquiline and linezolid for 26 weeks or longer if necessary
Pyrazinamide	• Active TB (with and without concomitant HIV)	Oral Tablet: 500 mg	• Varies, weight based
Rifabutin	• Disseminated infection due to MAC • Prophylaxis of MAC in patients with advanced HIV	Oral Capsule: 150 mg	• 300 mg once daily
Rifampin	• Active TB (with and without concomitant HIV) • Latent TB (with and without concomitant HIV) • Reactivation TB • Extrapulmonary TB • Asymptomatic carriers of *N. meningitidis*	IV Powder for Solution: 600 mg Oral Capsule: 150 mg, 300 mg	• Varies by indication
Rifapentine	• Active TB • Latent TB	Oral Tablet: 150 mg	• Varies by indication and weight

Abbreviations: g = gram; HIV = Human Immunodeficiency Virus; IV = intravenous; MAC = Mycobacterium avium complex; MAX = maximum; MDR = multidrug resistant; mg = milligram; mL = milliliter; TB = tuberculosis
*See current package inserts for age and weight restrictions

Methods:

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

The 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:

Six-Month Therapy for Abdominal Tuberculosis[29]

A 2016 Cochrane review evaluated evidence related to 6-month therapy compared to longer courses for abdominal TB, defined as TB of the gastrointestinal tract or other organ of the abdominal cavity.[29] Three RCTs of children and adults (n=328) were included in this review comparing the standard 6-month regimen of isoniazid, rifampin, pyrazinamide, and ethambutol to longer regimens containing the same medications. Medications were given daily or thrice-weekly using a directly observed therapy (DOT) protocol.[29] All trials were done in Asia and excluded HIV positive individuals and those with anti-TB treatment in the previous 5 years.[29] Primary outcomes of interest were relapse occurring at least 6 months after therapy completion (median 12-39 months), and clinical cure at end of TB treatment.

Relapse was observed in 2 of 140 patients with 6 months of therapy and 0 of 129 who received 9 months of therapy.[29] Statistical comparison was unable to be performed due to low event rate, and there is likely no difference in relapse with the shorter therapy (very low quality evidence).[29] All deaths which occurred were during first 4 months of therapy, and therefore, unrelated to duration of treatment.[29] There is likely no difference in clinical cure between 6 months and 9 months of therapy (RR 1.02, 95% CI 0.97 to 1.08; 294 participants, moderate quality of evidence).[29]

Antibiotic Treatment for Nontuberculous Mycobacteria Lung Infection in People with Cystic Fibrosis[30]

A 2020 Cochrane review attempted to review antibiotic therapy for NTM in patients with CF to compare drug therapy to no treatment or combinations therapy.[30] However, only a single RCT meeting search criteria was identified, and it included individuals with and without CF. The trial sponsor did not provide the review authors with trial data which would allow for analysis of drug therapy in CF patients.[30]

Brucellosis Treatment in Humans[1]

A 2018 meta-analysis compared the use of rifampin versus streptomycin for brucellosis treatment in humans. Brucellosis is an infection caused by *Brucella*, and is endemic to many developing countries. However, it is also seen in developed countries, particularly related to contaminated food imports. Treatment usually involves doxycycline in combination with either rifampin or streptomycin. Fourteen RCTs (N=1383 patients) were included to compare risk of treatment failure; 11 trials were conducted in Europe and 3 were in Asia. The population had doxycycline background therapy included in all regimens, had a mean or median age ranging from 26.4 to 46.0 years, and had 37.0 to 82.0% of patients identified as male.[1] Pooled results showed an increased risk of treatment failure with rifampin

when compared with streptomycin (RR 2.36; 95% CI 1.72 to 3.23; P<0.001; I^2=0.0%) and higher risk of relapse (RR 2.74; 95% CI 1.80 to 4.19; I^2=0.0%).[1] Sensitivity analysis for both outcomes concluded no effect on the data by excluding each specific study.[1] The subpopulation analysis when the mean population age was over 40 years did not show a difference in treatment failure between rifampin versus streptomycin (RR 1.92; 95% CI 0.93 to 3.97; P=0.078).[1] Differences in safety between the two therapies were not assessed.[1]

After review, 93 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), type of infection (e.g., rare infections non-endemic to the Pacific Northwest), or duplicate data (e.g., data assimilated into multiple high-quality guidelines reviewed below).

Guidelines:
High Quality Guidelines:

Management of Non-tuberculous Mycobacterial Pulmonary Disease (NTM-PD)[2]

The British Thoracic Society published a NICE-accredited, 2017 guideline related to clinical considerations for the care of patients with NTM-PD disease.[2] The scope of the document does not include extrapulmonary NTM, neonates and infants (up to 12 months of age), or patients with concomitant HIV infection. A high quality framework was used and recommendations were graded as A through D, with grade A being of high quality while grade D recommendations are based on non-analytic studies such as case reports, expert opinion, or extrapolation of evidence from well-done case-control or cohort studies. Additionally, the guideline committee included clinical practice points, in topic areas where no research evidence is available or likely to become available. Drug therapy recommendations were all grade D due to lack of high-quality data.[2] Treatment recommendations differentiated by organism are listed in **Table 3.**[2]

Table 3. Non-tubercular Pulmonary Mycobacteria Treatment Recommendation[2]

Recommendation
***Mycobacterium avium* complex (MAC)**
Clarithromycin-sensitive MAC-pulmonary disease should be treated with rifampicin, ethambutol and clarithromycin or azithromycin using an intermittent (three times per week) or daily oral regimen. The choice of regimen should be based on the severity of disease and treatment tolerance.
An intermittent (three times per week) oral antibiotic regimen should not be used in individuals with severe MAC-pulmonary disease or in individuals with a history of treatment failure.
An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe MAC-pulmonary disease.
Clarithromycin-resistant MAC-pulmonary disease should be treated with rifampicin, ethambutol and isoniazid or a quinolone, and inclusion of an injectable aminoglycoside (amikacin or streptomycin) should be considered.
Nebulized amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or when longer term treatment with an aminoglycoside is required for the treatment of MAC-pulmonary disease.
Macrolide monotherapy or macrolide/quinolone dual therapy regimens should not be used for the treatment of MAC-pulmonary disease.

Antibiotic treatment for MAC-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium kansasii
Rifampicin-sensitive *M. kansasii*-pulmonary disease should be treated with rifampicin, ethambutol and isoniazid or a macrolide (clarithromycin or azithromycin) using a daily oral regimen.
Rifampicin-resistant *M. kansasii*-pulmonary disease should be treated with a three-drug regimen guided, but not dictated by, drug susceptibility test results using a daily oral regimen.
Antibiotic treatment for *M. kansasii*-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium malmoense
M. malmoense-pulmonary disease should be treated with rifampicin, ethambutol and a macrolide (clarithromycin or azithromycin) using a daily oral regimen.
An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe *M. malmoense*-pulmonary disease.
Nebulized amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or when longer term treatment with an aminoglycoside is required in the treatment of *M. malmoense*-pulmonary disease.
Antibiotic treatment for *M. malmoense*-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium xenopi
M. xenopi-pulmonary disease should be treated with a four-drug regimen (where tolerated) comprising rifampicin, ethambutol and a macrolide (clarithromycin or azithromycin), with either a quinolone (ciprofloxacin or moxifloxacin) or isoniazid.
An injectable aminoglycoside (amikacin or streptomycin) should be considered in individuals with severe *M. xenopi*-pulmonary disease.
Nebulized amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or longer term treatment with an aminoglycoside is required in the treatment of *M. xenopi*-pulmonary disease.
Antibiotic treatment for *M. xenopi*-pulmonary disease should continue for a minimum of 12 months after culture conversion.
Mycobacterium abscessus-Initial Phase
M. abscessus-pulmonary disease treatment should comprise an initial phase antibiotic regimen (including intravenous and oral antibiotics) followed by a continuation phase antibiotic regimen (including inhaled and/or oral antibiotics).
For individuals with *M. abscessus* isolates that are clarithromycin sensitive or demonstrate inducible macrolide resistance, the initial phase antibiotic regimen should include at least a 4-week course of intravenous amikacin, intravenous tigecycline, and (where tolerated) intravenous imipenem, and (where tolerated) oral clarithromycin or oral azithromycin.
For individuals with *M. abscessus* complex isolates that demonstrate constitutive macrolide resistance, the initial phase antibiotic regimen should include a minimum 4-week course of intravenous amikacin, intravenous tigecycline and (where tolerated) intravenous imipenem.

The duration of intravenous treatment should be influenced by the severity of infection, treatment response and tolerance of the regimen.
To reduce the likelihood of treatment-related nausea and vomiting, antiemetic medication such as ondansetron (note potential for QT interval prolongation) and/or aprepitant should be prescribed to individuals receiving tigecycline and/ or imipenem.
Nebulized amikacin may be considered in place of intravenous amikacin when intravenous administration is impractical, contraindicated or longer term treatment with an aminoglycoside is required in individuals with *M. abscessus*-pulmonary disease.
In the context of amikacin-resistant *M. abscessus*, intravenous/nebulized amikacin should be substituted with an alternative intravenous/oral antibiotic.
Mycobacterium abscessus-Continuation Phase
For individuals with *M. abscessus* isolates that are clarithromycin-sensitive or demonstrate inducible macrolide resistance, the continuation phase antibiotic regimen should include nebulized amikacin and a macrolide (oral azithromycin or clarithromycin), in combination with one to three of the following oral antibiotics guided by drug susceptibility and patient tolerance: clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin, and co-trimoxazole.
For individuals with *M. abscessus* complex isolates that demonstrate constitutive macrolide resistance, the continuation phase antibiotic regimen should include nebulized amikacin in combination with two to four of the following oral antibiotics guided by drug susceptibility and patient tolerance: clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin, and co-trimoxazole.
In the context of amikacin-resistant *M. abscessus* nebulized amikacin should be substituted with an alternative oral antibiotic.
Antibiotic treatment for *M. abscessus*-pulmonary disease should continue for a minimum of 12 months after culture conversion. However, individuals who fail to culture-convert may benefit from a long-term suppressive antibiotic regimen.

Treatment of Nontuberculous Mycobacterial Pulmonary Disease[3]

A 2020 guideline jointly sponsored by the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Infectious Diseases Society of American (IDSA) updated treatment recommendations for NTM pulmonary diseases in adults without CF or HIV.[3] The task force conducted literature reviews around 22 different PICO (Population, Intervention, Comparator, and Outcome) questions and created 31 recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. A selection relevant to this class review is included in **Table 4**.[3]

Drug resistance testing should routinely be conducted, particularly for bacteria and treatment combinations where *in vitro* activity is shown to correlate to *in vivo* treatment outcomes.[3] While additional testing can reveal other sensitivities and opportunities for synergy, key combinations to test are MAC to macrolides, *M. kansasii* to both rifampicin and clarithromycin, and *M. abscessus* to both macrolides and amikacin.[3]

Table 4. Non-tubercular Pulmonary Mycobacteria Treatment Recommendations[3]

Question	Clinical Recommendation	Recommendation/Evidence Rating
***Mycobacterium avium* complex**		
Should patients with macrolide-susceptible MAC pulmonary disease be treated with a three-drug regimen with a macrolide or without a macrolide?	Recommend a three-drug regimen that includes a macrolide over a three-drug regimen without a macrolide	Strong recommendation, very low certainty in estimates of effect.
In patients with newly diagnosed macrolide-susceptible MAC pulmonary disease, should an azithromycin-based regimen or a clarithromycin-based regimen be used?	Suggest azithromycin-based treatment regimens rather than clarithromycin-based regimens.	Conditional recommendation, very low certainty in estimates of effect.
Should patients with MAC pulmonary disease be treated with or without a parenteral amikacin or streptomycin-containing regimen?	Suggest that parenteral amikacin or streptomycin be included in the initial treatment regimen for patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease.	Conditional recommendation, moderate certainty in estimates of effect.
In patients with macrolide-susceptible MAC pulmonary disease, should regimens include inhaled amikacin?	Suggest neither inhaled amikacin (parenteral formulation) nor amikacin liposome inhalation suspension be used as part of the initial treatment regimen in patients with newly diagnosed MAC pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
	Recommend addition of amikacin liposome inhalation suspension (ALIS) to the treatment regimen rather than a standard oral regimen, only in patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy.	Strong recommendation, moderate certainty in estimates of effect.
In patients with macrolide-susceptible MAC pulmonary disease, should a three-drug or a two-drug macrolide-containing regimen be used for treatment?	Suggest a treatment regimen with at least three drugs (including a macrolide and ethambutol) over a regimen with two drugs (a macrolide and ethambutol alone).	Conditional recommendation, very low certainty in estimates of effect.
In patients with macrolide susceptible MAC pulmonary disease, should a daily or a three-times weekly macrolide-based regimen be used for treatment?	Suggest a three times per week macrolide-based regimen rather than a daily macrolide-based regimen in patients with noncavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.

	Suggest a daily macrolide-based regimen rather than three times per week macrolide-based regimen in patients with cavitary or severe/advanced nodular bronchiectatic macrolide-susceptible MAC pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
In patients with macrolide-susceptible MAC pulmonary disease, should patients be treated with less than 12 months of treatment after culture negativity or 12 or more months of treatment after culture negativity?	Suggest that patients with macrolide-susceptible MAC pulmonary disease receive treatment for at least 12 months after culture conversion.	Conditional recommendation, very low certainty in estimates of effect.
Mycobacterium kansasii		
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should an isoniazid-containing regimen or a macrolide-containing regimen be used for treatment?	Suggest a regimen of rifampicin, ethambutol, and either isoniazid or macrolide.	Conditional recommendation, very low certainty in estimates of effect.
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should parenteral amikacin or streptomycin be included in the treatment regimen?	Suggest that neither parenteral amikacin nor streptomycin be used routinely for treating patients with *M. kansasii* pulmonary disease.	Strong recommendation, very low certainty in estimates of effect.
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?	Suggest using a regimen of rifampicin, ethambutol, and either isoniazid or macrolide instead of a fluoroquinolone in patients with rifampin-susceptible *M. kansasii* pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
	Suggest a fluoroquinolone (e.g., moxifloxacin) be used as part of a second-line regimen in patients with rifampicin-resistant *M. kansasii* or intolerance to one of the first line antibiotics.	Conditional recommendation, very low certainty in estimates of effect.
In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should a three times per week or daily treatment regimen be used?	Suggest either daily or three times weekly treatment in patients with noncavitary nodular/bronchiectatic *M. kansasii* pulmonary disease treated with a rifampicin, ethambutol and macrolide regimen.	Conditional recommendation, very low certainty in estimates of effect.
	Suggest daily treatment instead of three times weekly treatment in patients with cavitary *M. kansasii*	Conditional recommendation, very low certainty in estimates of effect.

	pulmonary disease treated with a rifampicin, ethambutol and macrolide-based regimen.	
In patients with rifampicin susceptible *M. kansasii* pulmonary disease, should treatment be continued for less than 12 months or 12 or more months?	Suggest that patients with rifampin susceptible *M. kansasii* pulmonary disease be treated for at least 12 months.	Conditional recommendation, very low certainty in estimates of effect.
Mycobacterium xenopi		
In patients with *M. xenopi* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?	Suggest using a multidrug treatment regimen that includes moxifloxacin or macrolide.	Conditional recommendation, low certainty in estimates of effect.
In patients with *M. xenopi* pulmonary disease, should a two, three or four-drug regimen be used for treatment?	Suggest a daily regimen that includes at least three drugs: rifampicin, ethambutol, and either a macrolide and/or a fluoroquinolone (e.g. moxifloxacin).	Conditional recommendation, very low certainty in estimates of effect.
In patients with *M. xenopi* pulmonary disease, should parenteral amikacin or streptomycin be included in the treatment regimen?	Suggest adding parenteral amikacin to the treatment regimen and obtaining expert consultation in patients with cavitary or advanced/severe bronchiectatic *M. xenopi* pulmonary disease.	Conditional recommendation, very low certainty in estimates of effect.
In patients with *M. xenopi* pulmonary disease, should treatment be continued for less than 12 months or 12 or more months after culture conversion?	Suggest that treatment be continued for at least 12 months beyond culture conversion.	Conditional recommendation, very low certainty in estimates of effect.

WHO Prevention of Tuberculosis[4]

In 2020, the Global TB Programme of the WHO began combining recommendations from various TB guidelines it had previously published into a consolidated guideline of current recommendations.[4] These consolidated guidelines are divided into modules, each to address a different area of programmatic management of TB. Module 1 is focused on prevention, including tuberculosis preventive treatment.[4] Latent TB is considered a persistent immune response to *M. tuberculosis* antigens with no evidence of clinically active TB. Most people exposed to TB have no signs or symptoms, but are at risk for active TB. Those who should be screened and treated for latent TB infection varies based on patient age, immune risk factors, exposure history, and a country's TB incidence.[5] This module builds on the 2018 guidelines to reflect newer evidence and simplify recommendations.[4,5] Based on 2018 recommendations, those requiring treatment as a high-risk contact of a patient with known MDR-TB, "preventative treatment may be considered based on individualized risk assessment and sound clinical judgement" (conditional recommendation, very low-quality evidence).[5] This area is identified as an area of opportunity for future research.[4] Updated recommended options for treatment of latent TB are[4]:

- Recommended regimens (strong recommendation; moderate to high certainty in the estimates of effect):
    - 6 or 9 months of daily isoniazid
    - 3 months of weekly rifapentine plus isoniazid
    - 3 months of daily isoniazid plus rifampicin
- Alternative regimens (conditional recommendation; low to moderate certainty in the estimates of effect):
    - 1 month of daily rifapentine plus isoniazid
    - 4 months of daily rifampicin

One additional recommendation, applicable only to settings with high TB transmission as defined by national authorities, is for adults and adolescents living with HIV who have latent TB, a positive skin test or status is unknown but are unlikely to have active TB, should receive at least 36 months of daily isoniazid preventive treatment (IPT). This recommendation applies regardless of ART use, immunosuppression, history of previous TB treatment, and pregnancy. (Conditional recommendation, low certainty in the estimates of effect)

Guidelines for the Treatment of Latent Tuberculosis Infection[6]

In 2020, the CDC and National Tuberculosis Controllers Association updated previous 2000 guidance for the treatment of latent TB in the US.[6] Recommended regimens are intended for persons who are presumed to be infected with TB that is susceptible to isoniazid or rifampin, but are not appropriate if exposure is likely from MDR-TB strains.[6] These recommendations are in **Table 5**. Preference was determined by balance of desirable and undesirable consequences of the intervention, quality of evidence, patient values, patient preferences, and regimen feasibility. Preference in priority rank for preferred versus alternative regimens was given for shorter duration given efficacy compared to 6 to 9 months of isoniazid, tolerability, and completion rates.[6] The authors note that 6 and 9 month treatment regimens of daily monotherapy isoniazid have not been directly compared. Additionally, 2 months of rifampin plus pyrazinamide are not recommended for treatment of latent TB due to hepatotoxicity, but in those treated for active disease with isoniazid, rifampin, and pyrazinamide for 2 months, who are later determined to have had latent disease, the regimen is considered an effective treatment.[6]

Table 5. Treatment Regimens for Latent TB Infection in the United States[6]

Treatment Recommendation	Population	Strength of Recommendation	Place in Therapy
3 months of once-weekly isoniazid plus rifapentine	Adults and children aged >2 years, including HIV-positive persons (as drug interactions allow)	Strong	Preferred
4 months of daily rifampin	HIV-negative adults and children of all ages	Strong	Preferred
3 months of daily isoniazid plus rifampin	Adults and children of all ages and for HIV-positive persons (as drug interactions allow)	Conditional	Preferred
6 months of daily isoniazid	HIV-negative adults and children of all ages	Strong	Alternative
6 months of daily isoniazid	HIV-positive adults and children of all ages	Conditional	Alternative
9 months of daily isoniazid	Adults and children of all ages, both HIV-negative and HIV-positive	Conditional	Alternative

Tuberculosis[7]

Guidelines on tuberculosis were published by NICE in 2016, with the last update in September of 2019.[7] This guidance focused on the prevention, identification, and management of both latent and active TB in children, young people, and adults and is created specifically for the United Kingdom and National Health Service.[7] Treatment related aspects of this guideline were reviewed.

Factors which increase risk for conversion of latent TB to active include: comorbid HIV, age less than 5 years, excessive alcohol intake, injection drug use, history of solid organ transplant, current hematological malignancy, concomitant chemotherapy, history of jejunal-ileal bypass, diabetes mellitus, chronic kidney disease (including dialysis), history of a gastrectomy, silicosis, or administration of anti-tumor necrosis factor-alpha or other therapeutic immune modulators.[7] Regimens recommended latent TB treatment in persons younger than 65 years, including those with HIV, who have evidence of latent TB or have been in close contact with a suspected or confirmed infectious contact are found in **Table 6**. Adults aged 35 to 65 years without other risk factors should be offered treatment only if hepatotoxicity is not a concern.[7] Testing for HIV, hepatitis B, and hepatitis C should be offered before starting latent TB treatment.[7]

Table 6. Latent Tuberculosis Treatment Regimens[7]

Agents	Duration	Preferred Circumstances
Isoniazid (with pyridoxine) plus rifampin	3 months	• Younger than 35 years • Concern for hepatotoxicity • Other risk factors
Isoniazid (with pyridoxine)	6 months	• Situations where drug-drug interactions from rifamycins are a concern (e.g. HIV, organ transplant)

The preferred regimen for active TB without suspected drug-resistance is isoniazid, rifampin, pyrazinamide, and ethambutol for a 2 month intensive phase followed by isoniazid plus rifampin for a 4 month continuation phase, with modifications as needed based on drug susceptibility testing.[7] People with active TB in the central nervous system should receive the standard intensive phase with a prolonged, 10 month, continuation phase.[7] Spinal TB without central nervous system involvement, as well as active TB of the lymph nodes should not be routinely extended beyond 6 months.[7] Dosing should be daily for extrapulmonary TB and is preferred for pulmonary TB.[7] Thrice-weekly may be considered if there is need for DOT and daily DOT is not possible.[7]

The use of rapid drug susceptibility testing for rifampin resistance should be performed in patients with the following risk factors: history of previous TB treatment, known contact with a case of MDR-TB, or birth/residence in a country identified by WHO with a high proportion (5% or greater) of new MDR-TB cases.[7] Identification of rifampin resistance should prompt additional drug-susceptibility testing and treatment with a regimen involving at least 6 active agents.[7] This guideline did not include specific treatments for MDR-TB.

Treatment of Drug-susceptible Tuberculosis[9]

A 2016 guideline, jointly sponsored by the ATS, CDC, and IDSA, provides recommendations for the treatment of drug-susceptible tuberculosis in children and adults in high-resource settings.[9] These are endorsed by ERS and the US National Tuberculosis Controllers Association. Additional American, Canadian, and International society representatives, including those from the WHO participated in guideline creation. The expert committee conducted literature reviews and created recommendations using the GRADE approach with the focus of cure for the individual patient while also preventing drug resistance and minimization of transmission to other exposed persons.

The PICO questions included in this guideline were primarily focused on treatment intervals and duration over specific medication choices, as the preferred regimen had not changed. Drug treatment can be done using DOT or self-administered therapy (SAT). Directly observed therapy has been associated with improved treatment success, and it is suggested over SAT for routine treatment of patients with all forms of tuberculosis (conditional recommendation; low certainty in the evidence).[9] The preferred regimen for microbiologically confirmed, drug-susceptible pulmonary TB is an intensive phase of isoniazid, rifampin, pyrazinamide, and ethambutol daily for 8 weeks followed by isoniazid plus rifampin daily for 18 weeks.[9] Alternatives for 5 days/week dosing are included, but only in the setting of DOT.[9] Use of daily dosing is preferred over intermittent dosing (thrice-weekly, twice-weekly, weekly) in the intensive phase (strong recommendation; moderate certainty in the evidence), while daily or thrice-weekly is preferred for the continuation phase over less frequent intermittent dosing (strong recommendation; moderate certainty in the evidence).[9] The 6-month preferred regimen is recommended in coinfected HIV patients who are receiving ART over treatment beyond 6 months (conditional recommendation; very low certainty in the evidence).[9] Pyridoxine should be included in all patients at risk of neuropathy while taking concomitant isoniazid.[9]

Treatment of Drug-susceptible Tuberculosis and Patient Care[8]

The World Health Organization published a 2017 update to previous 2010 guidelines focused on the treatment of drug-susceptible TB, with the aim to provide evidence across a variety of geographical, economic, and social settings.[8] Recommendations were created by the guideline development group (GDG) and received funding from the United States Agency for International Development (USAID). Members of the GDG followed the WHO policy on conflict of interest and used the GRADE approach. The ATS/CDC/IDSA guideline update on this topic was in process during preparation for the WHO update and information was shared between the two groups. The group provided recommendations in response to evidence for previously used and new PICO questions. Applicable treatment recommendations are located in **Table 7**.

Table 7. Treatment of Drug-susceptible Tuberculosis[8]

Clinical Recommendation	Recommendation/Evidence Rating
In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone containing regimens should not be used and the 6-month rifampicin-based 2HRZE/4H remains the recommended regimen. *Note: New evidence available for one specific regimen.*[10] *See June 2021 WHO rapid communication.*[11]	Strong recommendation Moderate certainty
The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB.	Conditional recommendation Low certainty
In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and daily dosing remains the recommended dosing frequency.	Conditional recommendation Very low certainty
ART should be started in all TB patients living with HIV regardless of their CD4 cell count.	Strong recommendation High certainty
TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment. HIV-positive patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm^3) should receive ART within the first 2 weeks of initiating TB treatment.	Strong recommendation High certainty
In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-month standard treatment regimen is recommended over an extended treatment for 8 months or more.	Conditional recommendation Very low certainty
In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used.	Strong recommendation Moderate certainty
In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.	Conditional recommendation Very low certainty
In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug susceptibility testing should be conducted to inform the choice of treatment regimen.	Good practice statement*
Abbreviations: ART = antiretroviral treatment; HIV = human immunodeficiency virus; TB = tuberculosis; 2HRZE/4HR = 2-month isoniazid/rifampin/pyrazinamide/ethambutol intensive phase then 4-month isoniazid/rifampin continuation phase * No randomized controlled trials or direct comparative evidence available for category II regimen vs. another regimen	

Treatment of Drug-Susceptible Tuberculosis: Rapid Communication[11]

The WHO issued a rapid communication for the treatment of drug-susceptible TB in June 2021.[11] The Global TB Programme received data from Study 31[10] and convened a guideline development group to review the results. This open-label, non-inferiority RCT included 2516 patients at 34 clinical sites in 13 countries.[10] Results indicate that a 4 month treatment regimen containing rifapentine, moxifloxacin, isoniazid, and pyrazinamide (intensive phase: daily dosing of all 4 agents for 8 weeks; continuation phase: discontinue pyrazinamide and continue remaining 3 agents daily for an additional 9 weeks) was as effective as the 6 month standard TB regimen at meeting the primary endpoint of tuberculosis disease-free survival at 12 months after randomization.[10] The other regimen studied, rifapentine, isoniazid, ethambutol, and pyrazinamide did not meet non-inferiority criteria.[10] The WHO guideline development group supports the 4 month rifapentine/moxifloxacin/isoniazid/pyrazinamide regimen as a possible alternative to the standard 6 months traditional regimen. Incorporation and grading of this data is planned for next drug-susceptible TB module update.[11]

Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis-Interim Guidance[12]

In 2022, the CDC issued interim guidance related to the results of a CDC and National Institutes of Health sponsored RCT (Study 31[10]/A5349).[12] The CDC recommends this regimen be considered a treatment option in patients 12 years and older, weighing 40 kg or more, with drug-susceptible TB and who are not pregnant or breastfeeding.[12] It can be used in those with concomitant HIV and CD4 counts ≥ 100 cells/mcg/L and who are on or plan to receive an efavirenz based ART regimen.[12] This regimen has not been compared in other studies. Given recent availability of the data, this guidance is not graded within the normal guideline creation process and is based on expert opinion with comments from external subject matter experts.[12]

Treatment of Drug-Resistant Tuberculosis[14]

In 2019 the ATS, CDC, ERS, and IDSA jointly sponsored a new practice guideline on the treatment of MDR-TB. Aspects of this document were previously reviewed by DURM in April 2022 in the fluoroquinolone class update. Methodology used matched the drug-sensitive TB guidelines previously described by these societies. The scope of this document included MDR-TB and isoniazid-resistant, rifampin-sensitive TB.[14]

Treatment of active MDR-TB is recommended to include at least 5 drugs during the intensive phase and 4 drugs during the continuation phase (conditional recommendation, very low certainty in the evidence).[14] The intensive phase is suggested to continue for 5 to 7 months beyond culture conversion (conditional recommendation, very low certainty in the evidence), with a total treatment duration of 15 to 21 months after culture conversion (conditional recommendation, very low certainty in the evidence).[14] Total duration is suggested as 15 to 24 months after culture conversion in pre-XDR TB and XDR-TB (conditional recommendation, very low certainty in the evidence).[14] Drug selection should be guided by susceptibility testing (*in-vitro* growth based or molecular resistance testing) and only include agents with documented or high likelihood of susceptibility (ungraded good practice statement).[14] Agent specific recommendations are included in **Table 8**, adjusted odds ratio and 95% confidence intervals for death or treatment success are included in full guideline.[14] For persons exposed to an MDR-TB contact, it is suggested to offer treatment for latent TB rather than observation (conditional recommendation, very low certainty of evidence).[14] For treatment of presumed MDR latent TB, it is suggested to treat with 6 to 12 months with a later generation FQ alone or with a second agent based on the susceptibility of the source-case of MDR-TB.[14] Pyrazinamide should not be generally used as the second agent due to increased toxicity, adverse events, and discontinuations.[14]

Table 8. Individual Drug Recommendations for Use in MDR-TB[14]

Drug or Drug Class	Recommendation		Certainty of the Evidence
	FOR	AGAINST	
Bedaquiline	Strong		Very Low
Fluoroquinolone: Moxifloxacin	Strong		Very Low
Fluoroquinolone: Levofloxacin	Strong		Very Low
Linezolid	Conditional		Very Low
Clofazimine	Conditional		Very Low
Cycloserine	Conditional		Very Low
Injectables: Amikacin	Conditional		Very Low
Injectables: Streptomycin	Conditional		Very Low
Ethambutol	Conditional		Very Low
Pyrazinamide Injectables:	Conditional		Very Low
Carbapenems w/ clavulanic acid	Conditional		Very Low
Delamanid	No recommendation for or against due to absence of data, committee concurs with 2019 WHO conditional recommendation that it may be included for treatment of MDR-TB or rifampin-resistant TB in longer regimens in individuals aged 3 years and older.		Very Low
Ethionamide		Conditional	Very Low
Prothionamide		Conditional	Very Low
Injectables: Kanamycin		Conditional	Very Low
P-Aminosalicylic Acid		Conditional	Very Low
Injectables: Capreomycin		Conditional	Very Low
Macrolides: Azithromycin		Strong	Very Low
Macrolides: Clarithromycin		Strong	Very Low
Amoxicillin-clavulanate		Strong	Very Low

Drug-resistant Tuberculosis Treatment[13]

The WHO published module 4 of its consolidated TB guidelines in 2020. Module 4 focuses on treatment of MDR-TB and rifampin-resistant TB, with a focus on providing evidence-based information to inform use of novel all-oral regimens and potential label expansion of new TB medications. The process and methods to develop recommendations complied with WHO standards for guideline development.[13] Drug therapy recommendations are included in **Table 9**.

Table 9. Drug Recommendations for Use in Drug-resistant TB[13]

Clinical Recommendation	Recommendation/Evidence Rating
In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.	Conditional/very low certainty
In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.	Conditional/very low certainty
A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.	Conditional/very low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.	Conditional/very low certainty
Kanamycin and capreomycin are not to be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Levofloxacin or moxifloxacin should be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Strong/moderate certainty
Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more.	Strong/moderate certainty
Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.	Conditional/very low certainty
Linezolid should be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Strong/moderate certainty
Clofazimine and cycloserine or terizidone may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Ethambutol may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty

Delamanid may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients aged 3 years or more on longer regimens.	Conditional/moderate certainty
Pyrazinamide may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Imipenem–cilastatin or meropenem may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Conditional/very low certainty
Amikacin may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.	Conditional/very low certainty
Ethionamide or prothionamide may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.	Conditional against use/very low certainty
P-aminosalicylic acid may be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.	Conditional against use/very low certainty
Clavulanic acid should not be included in the treatment of multidrug- or rifampicin-resistant tuberculosis patients on longer regimens.	Strong against use/low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.	Conditional/very low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.	Conditional/very low certainty
In multidrug- or rifampicin-resistant tuberculosis patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.	Conditional/very low certainty
A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid, may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.	Conditional/very low certainty

Management of Tuberculosis in Children and Adolescents[15]

In 2022, the Global TB Programme of the WHO published Module 5 of consolidated guidelines on the management of tuberculosis in children and adolescents, which is primarily an update from previous 2014 guidelines.[15] These recommendations apply to children under 10 years of age and adolescents aged 10 through 19 years with various types of TB. Treatment recommendations for preventative treatment options mirror those described previously in Module 4, with the 3 month regimen of weekly rifapentine plus isoniazid restricted to those age 2 years and above, while the 1 month regimen of daily rifapentine plus isoniazid is reserved for the aged 13 years and older.[15] Additional treatment recommendations are contained in **Table 10**. Multiple recommendations were carried over from the 2014 guidelines for various extrapulmonary TB infections.[15] The treatment recommendations are all variations of the traditional 4-drug regimen with differences in duration and frequency of dosing during the intensive and continuation phase.[15] Other recommended regimens align with recommendations already described in the other WHO TB consolidated guideline modules.[15]

Table 10. Drug Recommendations for Children and Adolescents with Tuberculosis[15]

Clinical Recommendation	**Recommendation/Evidence Rating**
In children and adolescents between 3 months and 16 years of age with non-severe TB and without suspicion/evidence of MDR or rifampin-resistant TB, a 4-month treatment regimen (2 months isoniazid/rifampin/pyrazinamide +/- ethambutol, then 2 months isoniazid/rifampin) should be used. *Ethambutol should be included during intensive phase in settings with high HIV prevalence or of isoniazid resistance.*	Strong/moderate certainty
In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis without suspicion/evidence of MDR or rifampin-resistant TB, a 6-month intensive regimen (isoniazid/rifampin at higher doses with pyrazinamide and ethionamide) may be used as an alternative option to the 12-month regimen (2 months isoniazid/rifampin/pyrazinamide/ethambutol, 10 months isoniazid/rifampin).	Conditional/very low certainty
In children with MDR or rifampin-resistant TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used.	Conditional/very low certainty
Bedaquiline may be included in longer MDR-TB regimens for patients aged 6–17 years.	Conditional/very low certainty
In children with MDR or rifampin-resistant TB aged below 3 years, delamanid may be used as part of longer regimens.	Conditional/very low certainty
Patients aged 12 years and older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide.	Conditional/moderate certainty

After review, 13 guidelines were excluded due to poor quality or obsolescence.

Randomized Controlled Trials:

A total of 18 citations were manually reviewed from the initial literature search. After further review, 17 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 trial is summarized in the table below. Full abstract is included in **Appendix 4**.

Table 11. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Dorman et al.[10] Study 31	1. Study regimen 1 <u>8 week</u> rifapentine isoniazid moxifloxacin pyrazinamide <u>9 week</u> rifapentine isoniazid moxifloxacin 2. Study regimen 2 <u>8 week</u> rifapentine isoniazid pyrazinamide ethambutol <u>9 week</u> rifapentine isoniazid 3. Control <u>8 week</u> rifampin isoniazid pyrazinamide ethambutol <u>18 week</u> rifampin isoniazid 1:1:1 randomization	N=2343 71% male Median age (years) 31.0 (range 13.7-81.4) 3% 12-17 years 11% Asian 72% Black 2 % White 15% Multiracial 8% HIV+ Mean weight 53.1 kg 24% smoker 11% treatment-experienced Inclusion -12 years and older -Newly diagnosed pulmonary TB -susceptibility to isoniazid, rifampin, and fluoroquinolones confirmed by culture -If HIV+, CD4 count at least 100 cells/mcgL	Efficacy: Survival free of TB at 12 months after randomization as favorable, unfavorable, not-assessable Non-inferiority assessment, 6.6% or less in upper boundary of 95% confidence interval Total follow up 18 months-secondary endpoint of survival at 18 months not yet performed Safety: Adverse event grade 3 or higher with onset during treatment and up to 14 days after last dose	<u>Efficacy 12 months:</u> 1. 15.5% unfavorable 1.0% difference (95% CI -2.6% to 4.5%) Met non-inferiority criteria 2. 17.7% unfavorable 3.0% difference (95% CI -0.6% to 6.6%) Did NOT meet non-inferiority criteria 3. 14.6% unfavorable <u>Safety 12 months:</u> 1. 18.8% Adjusted difference -0.6% (95% CI -4.3% to 3.2%) 2. 14.3% Adjusted difference -5.1% (95% CI -8.7% to -1.5%) 3. 19.3%	Open-label Randomization stratified site, presence of baseline cavitation, and HIV status.

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Appendix 1: Specific Drug Information

Generic	Brand	Route	Form	PDL
bedaquiline fumarate	SIRTURO	ORAL	TABLET	N
aminosalicylic acid	PASER	ORAL	GRANPKT DR	
cycloserine	CYCLOSERINE	ORAL	CAPSULE	
ethambutol HCl	ETHAMBUTOL HCL	ORAL	TABLET	
ethambutol HCl	MYAMBUTOL	ORAL	TABLET	
ethionamide	TRECATOR	ORAL	TABLET	
isoniazid	ISONIAZID	ORAL	SOLUTION	
isoniazid	ISONIAZID	ORAL	TABLET	
pretomanid	PRETOMANID	ORAL	TABLET	
pyrazinamide	PYRAZINAMIDE	ORAL	TABLET	
rifabutin	MYCOBUTIN	ORAL	CAPSULE	
rifabutin	RIFABUTIN	ORAL	CAPSULE	
rifampin	RIFAMPIN	ORAL	CAPSULE	
rifapentine	PRIFTIN	ORAL	TABLET	

Table 12. Clinical Pharmacology and Pharmacokinetics [28]

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
bedaquiline	• Inhibits mycobacterial adenosine 5'-triphosphate (ATP) synthase	• Tmax, oral: 4 to 5 hours • Effects of food: Bioavailability increased by 2-fold	• Substrate of CYP3A4 • Renal excretion: 0.001% or less • Fecal excretion: Extensive • Dialyzable: No (hemodialysis); no (peritoneal dialysis)	• Half-life: 5.5 months (parent drug and M2 metabolite) • Vd: 164 L
aminosalicylic acid	• Inhibits folic acid and cell wall synthesis that leads to reduced iron uptake	• Oral: time to peak concentration, 5 h (1.5 to 24 h) • Effect of food: decreases time to peak to 2 h (45 min to 24 h)	• Acetylation • Renal (glomerular filtration): 80%, 50% or more as metabolites • Dialyzable: no	• Half-life: 26.4 min, Renal disease 30.8 min
cycloserine	• Inhibiting cell-wall synthesis	• Tmax: 3 to 4 hours Bioavailability: 70 to 90% • Effect of food: Reduced Cmax, Prolonged Tmax (high-fat meals)	• Hepatic: 35% • Fecal: minimal • Renal: 50% to 70% • Renal Clearance: 0.11 to 0.013 L/hour/kg • Dialyzable: yes (hemodialysis)	• Half-life: 10 to 25 hours • Vd: 0.11 to 0.26 L/kg
ethambutol	• Inhibits the synthesis of metabolites, subsequently impairing cell metabolism and cell multiplication eventually leading to cell death	• Tmax: 2 to 4 hours • Effect of food: not significant	• Liver: 10% to 20% via oxidation • Major metabolite: aldehydic intermediate, inactive • Dicarboxylic acid: inactive • Fecal: 20% to 22% unchanged • Renal: approximately 50% unchanged, 8% to 15% changed	• Half-life: 2.5 to 4 hours
ethionamide	• Unknown, appears to inhibit peptide synthesis	• Tmax, oral (film-coated tablet): 1.02 hours	• Hepatic: extensive • Ethionamide-sulphoxide: active against *M. tuberculosis*	• Half-life: 1.92 hours (film-coated tablet)

		• Bioavailability, oral: nearly 100%	• Renal: Less than 1% unchanged • Dialyzable: No; 2.1% removed	• Ethionamide-sulphoxide: 1.68 to 2.25 hours
isoniazid	• Unknown, may relate to inhibition of mycolic acid synthesis and disruption of the cell wall	• Systemic: Readily absorbed: food reduces bioavailability	• Systemic: Hepatic • Fecal: small amounts • Renal: 75–95%	• Half-life: Fast acetylators: 0.5 to 1.6 h Adults (including elderly patients) Slow acetylators: 2 to 5 h Adults (including elderly patients); 2.3 to 4.9 h Children (1.5 to 15 y); 7.8 to 19.8 h Neonates • Vd: 0.57 to 0.76 L/kg
pretomanid	Inhibits mycolic acid biosynthesis to block cell wall production	• Tmax, oral: 4 to 5 hours • Effects of food: Increased Cmax by 76%; increased AUC by 88%	• Metabolized via reduction and oxidation • Substrate of CYP3A4 • Inhibitor of OAT3 • Renal excretion: 53% as changed drug; 1% unchanged • Fecal excretion: 38% as changed drug • Total body clearance: 3.9 L/hr (fed); 7.6 L/hr (fasted)	• Half-time: 16 to 17.4 hrs • Vd: 97 L (fed), 180 L (fasted)
pyrazinamide	Unknown	• Tmax, Oral: 0.75 to 4 hours • Bioavailability, Oral: rapidly and almost completely absorbed • Effect of food: Cmax decreased by 17%, Tmax increased 80%	• Liver: primary site via hydrolysis • Pyrazinoic acid: active • Renal: approximately 70%, 1% to 14% unchanged • Dialyzable: yes (hemodialysis), 45% removed	• Half-life: adults 12.3 hours • Vd: 0.75 to 1.65 L/kg
rifabutin	Inhibition of DNA-dependent RNA polymerase resulting in the inhibition of protein synthesis	• Systemic: Readily absorbed; high fat food slows absorption	• Systemic: Hepatic • Systemic: 30% fecal; 5% unchanged in the urine; 5% unchanged in the bile; 53% in urine as metabolites	• 45 h (range 16 to 69) • Vd: 9.3 ± 1.5 L/kg

			• In dialysis—Hemodialysis is not expected to enhance elimination • Systemic: Fecal: 30%, 5% unchanged; Renal: 53% metabolites, 5% unchanged	
rifampin	Inhibition of DNA-dependent RNA polymerase resulting in the inhibition of protein synthesis	• Oral: Rapidly absorbed • Tmax, oral: 1 to 4 hours • Tmax, IV: 30 minutes • Effects of food: Absorption reduced by 30%, Cmax reduced by 36% ,Tmax increased by 103% • Effects of food (patients with tuberculosis): Tmax delayed by 2 hours; decreased Cmax	• 25-desacetyl-rifampin: Microbiologically active • Formylrifampin: Active • Renal excretion Up to 30% • Biliary excretion: Rapidly eliminated in the bile • Total body clearance: 0.19 L/hr/kg (300 mg); 0.14 L/hr/kg (600 mg)	• Half-life: Adults: 3.35 hours (600 mg); 5.08 hours (900 mg), reduced in pediatrics and prolonged in renal or hepatic impairment and biliary obstruction • Vd: 0.66 L/kg (300 mg); 0.64 L/kg (600 mg)
rifapentine	Inhibits bacterial RNA transcription by preventing initiation of RNA chain formation by forming a stable complex with bacterial DNA-dependent RNA polymerase	• Tmax, adult, oral: 4.83 to 6 hours • Tmax, pediatric, oral: 3.2 hours • Bioavailability (relative): 70% • Effects of food: Increases AUC and Cmax by 40% to 50%	• 25-desacetyl rifapentine (major): Active • Inducer of CYP3A4 and CYP2C8/9 • Renal excretion: 17% • Fecal excretion: 70%	• Half-life: Adult: 13.19 hours • Vd (adult): 70.2 L
Abbreviations: AUC=area under the curve; Cmax=maximum concentration; DNA=deoxyribonucleic acid; L=liter; RNA=ribonucleic acid; Tmax=time to maximum concentration; Vd=volume of distribution.				

Drug Safety:

Boxed Warnings:[28]

Bedaquiline: Increased risk of death; QT prolongation

Isoniazid: Severe and sometimes fatal hepatitis

Risk Evaluation Mitigation Strategy Programs:[28]

None

Contraindications:[28]

- General
  - Hypersensitivity: p-aminosalicylic acid, cycloserine, ethambutol, ethionamide, isoniazid, pyrazinamide, rifabutin, rifampin
  - History of severe adverse reactions to isoniazid (e.g. drug fever, chills, arthritis)
- Renal
  - End-Stage renal disease: p-aminosalicylic acid
  - Severe renal insufficiency: cycloserine
- Psychiatric
  - Depression, anxiety, psychosis: cycloserine
  - Alcohol use (excessive): cycloserine
- Neurologic
  - Epilepsy: cycloserine
  - Optic neuritis (clinical judgment of risk/benefit required): ethambutol
  - Inability to appreciate or report visual side effects/vision changes: ethambutol
- Hepatic
  - Severe hepatic impairment/damage: ethionamide, pyrazinamide
  - History of isoniazid associated or other drug induced liver injury: isoniazid
  - Acute liver injury: isoniazid
- Acute gout: pyrazinamide
- Drug Interactions/Place in therapy
  - Use when bedaquiline and/or linezolid are contraindicated: pretomanid (only approval is for use in combination with those agents)
  - Concomitant use of delavirdine, rilpivirine, voriconazole: rifabutin
  - Concomitant use with atazanavir, darunavir, fosamprenavir, saquinavir (unboosted or ritonavir boosted), tipranavir, rilpivirine, elvitegravir/cobicistat, or praziquantel (within 4 weeks prior to praziquantel use until 1 day after end of praziquantel treatment): rifampin
  - Concomitant rilpivirine: rifapentine

Table 13. Summary of Warnings and Precautions.[28]

Warnings and Precautions	bedaquiline	p-aminosalicylic acid	cycloserine	ethambutol	ethionamide	isoniazid	pretomanid	pyrazinamide	rifabutin	rifampin	rifapentine
Allergic dermatitis			X								
Anemia			X								
Central nervous system toxicity, increased risk with chronic alcoholism			X								
Clostridioides difficile-associated diarrhea									X		X
Drug Interactions	hepatotoxins (drug or alcohol); strong/ moderate CYP3A4 inducers			aluminum containing antacids		Avoid tyramine (e.g. wine, cheese) and histamine (e.g. tuna) containing foods.	strong/ moderate CYP3A4 inducers		Select HIV drugs	cefazolin/ rifampin or pre-existing vitamin K-dependent coagulation disorders in patients at increase bleeding risk; select HIV drugs	Select HIV drugs
Congestive heart failure		X									
Diabetes mellitus (preexisting)								X		X	
B vitamins		Vitamin B12 supplementation recommended	Folic acid and B12 deficiency			Vitamin B6 supplementation recommended					
Gout/hyperuricemia								X			
Hepatotoxicity	X	X		X			X	X		X (sometimes cholestatic or mixed pattern)	X
Hypersensitivity									X	X	X
Myelosuppression							X		X		
Ophthalmic				X		X	X		X		

				(including blindness)							
Paradoxical drug reaction										X	
Peptic ulcer disease		X									
Peripheral neuropathy						X	X				
Porphyria											X
Pulmonary toxicity										X	
QT prolongation	X						X				
Red-orange discoloration of body tissues/fluids.									X	X	X
Relapse, especially with poor adherence, cavitary pulmonary lesions, or bilateral pulmonary disease.											X
Resistance	X				X			X	X		
Severe cutaneous reactions/drug reaction with eosinophilia and systemic symptoms (DRESS)									X	X	X
Severe hepatic impairment (preexisting)	X	X						X			X
Severe Renal Impairment or end stage renal disease (preexisting)	X	X				X			X		

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 19, 2022

# ▲	Searches	Results
1	bedaquiline.mp.	987
2	Aminosalicylic Acid/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	1306
3	Cycloserine/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	721
4	Ethambutol/ae, tu [Adverse Effects, Therapeutic Use]	2538
5	Ethionamide/ae, tu [Adverse Effects, Therapeutic Use]	548
6	Isoniazid/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	7801
7	pretomanid.mp.	253
8	Pyrazinamide/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	1656
9	Rifabutin/ae, tu [Adverse Effects, Therapeutic Use]	521
10	Rifampin/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	8472
11	Rifampin/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	8472
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	17817
13	limit 12 to english language	12788
14	limit 13 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	258
15	limit 14 to yr="2015 -Current"	136

Appendix 3: Key Inclusion Criteria

Population	Adults and children, including special populations such as immunocompromised individuals
Intervention	Medications in Appendix 1
Comparator	Active comparators
Outcomes	Cure, treatment completion, treatment failure, disease relapse, time to sputum culture or smear conversion, clinical or radiological improvement at 8 weeks and at the end of treatment, mortality, and serious adverse events or adverse events requirement treatment alteration
Timing	Treatment of active or latent mycobacterial infections (excluding diseases not generally prevalent in the United States, such as leprosy)
Setting	Outpatient

Appendix 4: Abstracts of Comparative Clinical Trials

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis[10]

BACKGROUND: Rifapentine-based regimens have potent antimycobacterial activity that may allow for a shorter course in patients with drug-susceptible pulmonary tuberculosis.

METHODS: In an open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary tuberculosis from 13 countries, we compared two 4-month rifapentine-based regimens with a standard 6-month regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (control) using a noninferiority margin of 6.6 percentage points. In one 4-month regimen, rifampin was replaced with rifapentine; in the other, rifampin was replaced with rifapentine and ethambutol with moxifloxacin. The primary efficacy outcome was survival free of tuberculosis at 12 months.

RESULTS: Among 2516 participants who had undergone randomization, 2343 had a culture positive for Mycobacterium tuberculosis that was not resistant to isoniazid, rifampin, or fluoroquinolones (microbiologically eligible population; 768 in the control group, 791 in the rifapentine-moxifloxacin group, and 784 in the rifapentine group), of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome (assessable population; 726 in the control group, 756 in the rifapentine-moxifloxacin group, and 752 in the rifapentine group). Rifapentine with moxifloxacin was noninferior to the control in the microbiologically eligible population (15.5% vs. 14.6% had an unfavorable outcome; difference, 1.0 percentage point; 95% confidence interval [CI], -2.6 to 4.5) and in the assessable population (11.6% vs. 9.6%; difference, 2.0 percentage points; 95% CI, -1.1 to 5.1). Noninferiority was shown in the secondary and sensitivity analyses. Rifapentine without moxifloxacin was not shown to be noninferior to the control in either population (17.7% vs. 14.6% with an unfavorable outcome in the microbiologically eligible population; difference, 3.0 percentage points [95% CI, -0.6 to 6.6]; and 14.2% vs. 9.6% in the assessable population; difference, 4.4 percentage points [95% CI, 1.2 to 7.7]). Adverse events of grade 3 or higher occurred during the on-treatment period in 19.3% of participants in the control group, 18.8% in the rifapentine-moxifloxacin group, and 14.3% in the rifapentine group.

CONCLUSIONS: The efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis. (Funded by the Centers for Disease Control and Prevention and others; Study 31/A5349 ClinicalTrials.gov number, NCT02410772.).

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Drug Class Update: Estrogens

Date of Review: June 2022

Date of Last Review: January 2017
Dates of Literature Search: 09/01/2016 - 04/04/2022

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

Purpose for Class Update:
A comprehensive literature search and evaluation on the comparative efficacy and safety of estrogen preparations was performed based on evidence published since the last update in 2017.

Research Questions:
1. Is there new comparative evidence on the effectiveness of estrogen therapies, used as monotherapy or in combination with progestins, for the treatment of menopausal symptoms or prevention of osteoporosis?
2. Is there new comparative evidence on the harms of estrogen products?
3. Are there subpopulations of women in which certain estrogen products have demonstrated superior efficacy or increased risk of harms?

Conclusions:
- There were two systematic reviews, two guidelines, two safety warnings and two safety alerts identified since the last review in January of 2017.
- There is moderate quality evidence from a Cochrane review evaluating long-term hormone therapy (HT) (at least 1 year) for perimenopausal and menopausal women that HT reduces in the risk of fracture.[1] There is moderate quality evidence that combination HT increases the risk of stroke, venous thromboembolism (VTE) and gallbladder disease.[1]
- Hormone therapy for the primary prevention of chronic conditions in postmenopausal women was the focus of a 2017 Agency for Healthcare Research and Quality (AHRQ) review.[2] There is moderate to high quality evidence demonstrating the risk of diabetes and fractures is reduced with the use of estrogen alone. Combination estrogen and progestin therapy was found to decrease the risk of colorectal cancers, diabetes and fractures based on moderate to high quality of evidence. Increased risk of harms associated with estrogen use and combination HT included: gallbladder disease, breast cancer, stroke, VTE and urinary incontinence.[2]
- Guideline updates from National Institute for Health and Care Excellence (NICE) and the European Alliance of Associations for Rheumatology (EULAR) support the current policy on estrogens.[3,4]

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- Two new formulations of estradiol were approved since the last review. Estradiol/progesterone 1 mg/100 mg combination product (Bijuva) capsules were approved for the use of moderate to severe vasomotor symptoms based on one placebo-controlled trial.[5] Estradiol vaginal inserts (Imvexxy) 4 mcg and 10 mcg were approved for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.[6]
- There was insufficient evidence on subgroup populations, such as differences in ethnicities and race, time since onset of menopausal symptoms and women with an intact uterus.

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on evaluation of the clinical evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:
- No changes were made to the estrogen derivatives PDL as a result of the update in 2017.
- Current policy consists of a prior authorization (PA) criteria requiring an Oregon Health Plan (OHP) approved diagnosis.

Background:
Estrogens are part of hormone replacement therapy used for reducing menopausal symptoms.[1] Estrogen is often used in combination with progestin products. The FDA approved uses for HT are for the treatment of menopausal symptoms and prevention of osteoporosis.[2] Estrogen is also used off-label for gender dysphoria disorder and palliative care in metastatic breast and prostate cancer.[7]

Menopause causes decreased estrogen levels with corresponding cessation of menstrual cycle, vasomotor symptoms, musculoskeletal, urogenital and psychological symptoms.[3] Symptoms can be associated with decreased quality of life affecting families and work environments. Menopause alone has been identified as a risk factor for cardiovascular disease (CVD).[2] Approximately 60% to 80% of women experience menopausal symptoms, 20% of them are considered severe symptoms. Prevalence varies between different ethnic groups and cultures, with a higher incidence in Black and Hispanic women.[8]

Treatment recommendations for menopausal symptoms include the use of lubricants and gels as well as lifestyle modifications (e.g., weight loss, smoking cessation). Estrogen products are considered the most effective treatment for vasomotor symptoms and should be considered in women who need additional treatment for menopausal symptoms who do not have contraindications. In women with an intact uterus, estrogen is given in combination with progestins to avoid hyperplasia or carcinoma.[8] A reduction in 50% or more in the frequency and severity of vasomotor symptoms is considered a clinically meaningful effect.[8] Estrogen is available as the following dosage formulations: oral, vaginal, intranasal, transdermal or subcutaneous implant. Estrogen derivatives include estradiol, estradiol valerate synthetic conjugated estrogens, ethinyl estradiol, or conjugated equine estrogen (**Appendix 1**).

Evidence for the long-term benefits and risks of HT has been mixed. Findings from the Women's Health Initiative (WHI) found HT prevented fractures and colon cancer, but noted an increased risk of cardiovascular (CV) events and breast cancer.[9] Mixed evidence has also suggested the use of HT in older women for prevention of CV disease, osteoporosis and cognitive decline. Observational studies of HT have demonstrated a reduced risk of coronary heart disease (CHD); however, findings from randomized controlled trials (RCTs) failed to demonstrate CHD benefits.[2] The United States Preventative Services Task Force (USPSTF) recommends against the use of HT for the primary prevention of chronic conditions.[10]

Oregon Health Plan (OHP) fee-for-service (FFS) population 125 women received oral estrogen products (99% preferred formulations), 35 patients received topical estrogen products (100% preferred formulations) and 22 patients received transdermal estrogen products (49% preferred formulations) based on claims from the first quarter of 2022. The overall cost for the class does not represent a substantial monetary burden to OHP.

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

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

New Systematic Reviews:

Hormone Replacement Therapy

Cochrane – Long-term Hormone Replacement Therapy for Perimenopausal and Postmenopausal Women
A 2017 review evaluated the literature to determine the effects of long-term HT, at least 1 year's timeframe, on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women.[1] The use of HT (e.g., estrogens with or without progestins) were included in the systematic review. Routes of administration included oral, transdermal, subcutaneous, or intranasal. Most studies used moderate doses of estrogen (e.g., conjugated equine estrogens [CEE] 0.625 mg daily, estradiol 1 mg, transdermal estradiol 0.05 mg twice weekly). The dose of progesterone used in continuous combination estrogen and progesterone regimens were the following; medroxyprogesterone acetate (MPA) 2.5 mg daily, MPA 10 mg daily and 1 mg norethindrone daily. Twenty-two studies were included (n=43,637) involving predominately healthy postmenopausal women of whom most were 60 years and older (range of 26 to 91 years).[1] Only 30% of women were 50-59 years, which is the age of women who most often seek the use of estrogen for the management of vasomotor symptoms.[1] Most of the evidence was found to be at low risk of bias.

The use of combined continuous HT, moderate dose estrogen and medroxyprogesterone, was associated with moderate quality of evidence for all of the outcomes studied. Findings are presented in **Table 1**.[1] There were more coronary events, stroke, VTE, breast cancer, gallbladder disease and death from lung cancer with the use of HT compared to placebo. There was a reduction in the risk of clinical fractures with HT versus placebo. The use of estrogen only HT are also presented in **Table 1**. Moderate strength of evidence found an increased the risk of stroke, VTE with follow-up of 1-2 years and gallbladder disease with estrogen compared to placebo.[1] The risk of breast cancer and clinical fractures was reduced with the use of HT compared to placebo. There was no effect on the risk of coronary disease with the use of estrogen only HT.

Table 1. Hormone Therapy in Postmenopausal Women[1]

Outcome	Follow-up	Results	Quality of Evidence
Combined Continuous Hormone Therapy Compared to Placebo			
Coronary events (MI or cardiac death)	Mean/median 1 year	RR 1.89 (95% CI, 1.15 to 3.10)	Moderate
Stroke	Mean 3 years	RR 1.46 (95% CI, 1.02 to 2.09)	Moderate
Venous thromboembolism (DVT or PE)	Mean/median 1 year	RR 4.28 (95% CI, 2.49 to 7.34)	Moderate
Breast cancer	Median 5.6 years	RR 1.27 (95% CI, 1.03 to 1.56)	Moderate
Death from lung cancer	Median 8 years	RR 1.74 (95% CI, 1.18 to 2.55)	Moderate
Gallbladder disease	Mean 5.6 years	RR 1.64 (95% CI, 1.30 to 2.06)	Moderate
All clinical fractures	Mean 5.6 years	RR 0.78 (95% CI, 0.71 to 0.86)	Moderate
Estrogen Only Hormone Therapy compared to Placebo			
Coronary events (MI or cardiac death)	Mean 7.1 years	RR 0.94 (95% CI, 0.78 to 1.13)	Moderate
Stroke	Mean 7.1 years	RR 1.33 (95% CI, 1.06 to 1.67)	Moderate
Venous thromboembolism (DVT or PE)	1-2 years	RR 2.22 (95% CI, 1.12 to 4.39)	Moderate
Venous thromboembolism (DVT or PE)	Mean 7.1 years	RR 1.32 (95% CI, 1.00 to 1.74)	Moderate
Breast cancer	Mean 7.1 years	RR 0.79 (95% CI, 0.61 to 1.01)	Moderate
Gallbladder disease	Mean 7.1 years	RR 1.78 (95% CI, 1.42 to 2.24)	Moderate
All clinical fractures	Mean 7.1 years	RR 0.73 (95% CI, 0.65 to 0.80)	Moderate

Abbreviations: CI – confidence interval; DVT – deep vein thrombosis; MI – myocardial infarction; PE – pulmonary embolism; RR – relative risk.

There is good evidence for the use of HT for relief of menopausal symptoms associated with menopause. Evidence suggests additional benefit for prevention of postmenopausal osteoporosis but is reserved for patients who are unable to take non-estrogen options. Estrogens should not be used for primary or secondary prevention CV disease. Estrogens should be avoided in women who are at high risk of CV disease, thromboembolic disease or certain cancers (e.g., breast, uterine).[1]

AHRQ – Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women

The AHRQ did a systematic review and meta-analysis for the U.S. Preventive Services Task Force in 2017. The objective was to evaluate the benefits and risks of HT for primary prevention of chronic conditions in postmenopausal women.[2] Evidence was searched through August of 2016 and ongoing surveillance of the literature occurred through August 2017. Most studies included healthy women who were perimenopausal or postmenopausal with one year or more of HT. Seventeen fair-quality trials were identified and met eligibility criteria for inclusion into the review.[2] The WHI was the largest contributor to the data. Analyses were divided into those women who used estrogen alone and those who took combination therapy with estrogen and progestin therapy.

There are benefits and risks identified with both estrogen alone and combination estrogen plus progestin therapy (**Tables 2 and 3**).[2] There was no increased risk or benefit of all-cause mortality in women who took estrogen alone or estrogen plus progestin based on moderate to high quality of evidence.

Table 2. Risks and Benefits of Estrogen Monotherapy compared to Placebo[2]

Outcome	Population	Cases/Quality of Evidence
Benefits of Therapy		
Diabetes (new diagnosis requiring medication)	Per 10,0000 women over 6.8 to 7.2 years	137 fewer cases/moderate
Fractures	Per 10,000 women over 6.8 to 7.2 years	382 fewer cases/high
Risks of Therapy		
Gallbladder disease*	Per 10,000 women 5.4 to 7.1 years	213 more cases/moderate
Stroke	Per 10,000 women 5.4 to 7.1 years	79 more cases/moderate
Venous thromboembolism	Per 10,000 women 5.4 to 7.1 years	78 more cases/moderate
Urinary incontinence†	Per 10,000 women during a 1 year follow-up	1,261 more cases/moderate
Key: * Gallbladder disease was defined as cholecystitis and cholelithiasis); † Urinary incontinence was defined as stress, urge and overall		

Table 3. Risks and Benefits of Estrogen Plus Progestin Therapy compared to Placebo[2]

Outcome	Population	Cases/Quality of Evidence
Benefits of Therapy		
Colorectal cancer	Per 10,0000 women over 5.0 to 5.6 years	33 fewer cases/moderate
Diabetes (new diagnosis requiring medication)	Per 10,000 women over 5.0 to 5.6 years	77 fewer cases/moderate
Fractures	Per 10,000 women over 5.0 to 5.6 years	222 fewer cases/high
Risks of Therapy		
Invasive breast cancer	Per 10,000 women 4.0 to 5.6 years	52 more cases/high
Probable dementia	Per 10,000 women 4.0 to 5.6 years	88 more cases/moderate
Gallbladder disease	Per 10,000 women 4.0 to 5.6 years	116 more cases/moderate
Stroke	Per 10,000 women 4.0 to 5.6 years	53 more cases/high
Venous thromboembolism	Per 10,000 women 4.0 to 5.6 years	120 more cases/moderate
Urinary incontinence†	Per 10,000 women follow-up of 1 year	876 more cases/moderate
Key: * Gallbladder disease was defined as cholecystitis and cholelithiasis); † Urinary incontinence was defined as stress, urge and overall		

Limitations to the evidence were lack of comparisons between the different types, doses and delivery routes of HT. Subgroup analyses and trials were not powered to detect differences in preventative outcomes. There was insufficient data on the use of HT in women who were younger and nonwhite ethnicity.

After review, 16 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).[11–26]

New Guidelines:
High Quality Guidelines:

NICE – Menopause: Diagnosis and Management
The National Institute for Health and Care Excellence originally published guidance for the management of menopause in 2015 and has since provided updates in 2019 and 2021.[3] All recommendations include routine assessment of symptoms to tailor therapy to current needs of women experiencing menopause. Treatment recommendations for management of menopausal symptoms are outlined in **Table 4**.[3] Vasomotor symptoms should not be treated with SSRIs, SNRIs, or clonidine as first-line treatment. Isoflavones or black cohosh may relieve vasomotor symptoms; however, preparation may vary, drug interactions have been reported, multiple preparations are available and safety is unknown.

Vaginal estrogens relieved symptoms of urogenital atrophy without the safety risks associated with systemic estrogen products. Oral HT increases the risk of VTE and can present early in treatment and increases with age.[3] The risk of VTE is not significantly increased with the use of transdermal products. After discontinuation of HT the increased risk of VTE is eliminated. Women who are at increased risk of VTE or who have a body mass index greater than 30 kg/m^2 should consider transdermal HT instead of oral therapy.[3] Additional risks with HT include an increased incidence of stroke; however, the evidence is low to very low quality. There was no additional CV risk noted with HT use in women under the age of 60 years and there was no increased risk of CV mortality. Low quality evidence found no increased risk of diabetes with the use of HT. The use of HT had no benefit or risk of developing or preventing dementia based on very low to moderate quality of evidence.[3] There is low to moderate quality of evidence that HT reduces the risk of fragility fracture, even upon HT discontinuation.

Additional safety updates on the increased risk of breast cancer with HT was added to the guidance.[27] The increased risk is with all HT preparations except for vaginal estrogens. The increased risk persists for more than 10 years after the HT is discontinued. The shortest duration and lowest dose of HT should be utilized.

Table 4. NICE Recommendations for Management of Menopausal Symptoms[3]

Symptom	Recommendation	Quality of Evidence
Vasomotor Symptoms	• Offer HT after discussing the short-term (up to 5 years) and longer-term benefits and risks • Options include: - Estrogen and progestin to women with a uterus - Estrogen alone to women without a uterus	• Very low to moderate quality • Limited data beyond 1 year
Urogenital Atrophy	• Vaginal estrogens should be offered (even if taking systemic HT) and continue treatment as long as needed to relieve symptoms • Vagina estrogens should be offered to women in whom HT is contraindicated	• Very low to moderate quality
Psychological Symptoms	• Recommended HT for women with low mood due to menopause • There is no clear evidence for the use of SSRIs or SNRIs to ease low mood in women with menopausal symptoms who have not been diagnosed with depression	• Very low quality of evidence
Altered Sexual Function	• Consider testosterone supplementation for menopausal women with low sexual desire if HT is not effective	• Very low quality of evidence
Abbreviations: HT – hormone therapy; SNRIs- serotonin norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors		

EULAR – Recommendations for Women's Health and the Management of Family Planning, Assisted Reproduction, Pregnancy and Menopause in Patients with Systemic Lupus Erythematosus and/or Antiphospholipid Syndrome

A 2017 guideline completed by EULAR updated the recommendations for the use of HT in women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS).[4] Guideline methodology was well described and authors reported no conflicts of interest. The evidence was graded from level 1 to 3, with level 1 evidence being the highest level, consisting of RCTs or meta-analyses, level 2 is sufficient evidence with questionable confidence in the evidence and level 3 being the lowest level of evidence. Grading of the recommendations ranged from A to D. Grade A is based on high level of evidence, Grade B recommendations are based on level 1 evidence with concerns of validity, Grade C is based on level 1 or 2 evidence and Grade D is based on expert opinion.[4] The focus of this review will be on the recommendations for the use of estrogens in women with SLE and/or APS. Other therapies will be discussed according to their corresponding class update. The use of estrogen products, as part of HT, can be used for women with severe vasomotor menopausal symptoms that have SLE which is stable/inactive based on negative antiphospholipid antibodies (aPL).[4] There is no evidence of severe exacerbations of SLE with the use of HT in RCTs lasting up to 24 months. In women with APS, the benefits of the use of HT should be weighed against the risk of thrombotic and CV risks. Evidence is limited on the optimal duration of HT; however, it is recommended that the shortest duration possible be used.

Additional Guidelines for Clinical Context:

Endocrine Society – Pharmacological Management of Osteoporosis in Postmenopausal Women

The recommendations for the use of HT were included in the guidelines for the management of osteoporosis in postmenopausal women issued by the Endocrine Society.[28] Recommendations were based off a systematic review and meta-analysis; however, specifics of the search were not included. The evidence was graded from very low quality to high quality. The strength of recommendations were designated as "recommended" and "we suggest" based on the evidence. Fifty percent of authors had conflicts of interest and funding was provided by the Endocrine Society, which partners with industry. Recommendations will be included for clinical context but not used for policy decisions.

The use of estrogen only HT is recommended for postmenopausal women with hysterectomy who are at high risk of fracture to prevent all types of fractures with the following patient characteristics; under 60 years of age or < 10 years past menopause; at low risk of deep vein thrombosis, those who are not candidates for the use of bisphosphonates or denosumab, bothersome vasomotor symptoms, climacteric symptoms, without contraindications, no history of stroke or myocardial infarction, without breast cancer, and willing to take HT.[28] This is a suggested recommendation supported by moderate quality of evidence.

After review, 5 guidelines were excluded due to poor quality or insufficient evidence.[29–33]

New Formulations or Indications:

Estradiol and progesterone capsules (Bijuva): In 2018 a new drug approval was granted for the estradiol/progesterone 1 mg/100 mg combination product indicated for women with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.[5] Combination estradiol/progesterone was shown to reduce moderate to severe vasomotor symptoms, frequency and severity, more than placebo in one 12-week, randomized, single-arm study (n=726). At 12 weeks reduction in mean weekly frequency of symptoms were reported as clinically meaningful with a difference from placebo in the estradiol/progesterone arm of -16.58; $p<0.001$.[5] The severity of weekly moderate to severe vasomotor symptoms was reduced with estradiol/progesterone by -0.57 ($p<0.001$) compared to placebo at week 12. Four cases of breast cancer were diagnosed over the year-long safety study, 2 in patients treated with estradiol/progesterone 0.5 mg/100 mg and 2 in the estradiol/progesterone 1 mg/100 mg and none in the placebo group. As with other estrogen products there

is a black box warning for the risk of increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.[5] There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

Estradiol vaginal inserts (Imvexxy): Estradiol vaginal inserts 4 mcg and 10 mcg were approved in 2018 for the treatment of moderate to severe dyspareunia, symptom of vulvar and vaginal atrophy, due to menopause.[6] Evidence for approval was from one 12-week, double-blind, placebo-controlled, study of 574 women who were postmenopausal. For moderate to severe symptoms of dyspareunia associated with postmenopausal vulvar and vaginal atrophy at 12 weeks compared to baseline were associated with reductions; estradiol 4 mcg, estradiol 12 mcg and placebo, -1.52 ($p = 0.0149$ compared to placebo), -1.69 ($p<0.0001$ compared to placebo) and -1.28, respectively.[6] As with other estrogen products there is a black box warning for the risk of increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.[6] There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

New FDA Safety Alerts:

Table 5. 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)
Estradiol Topical[34]	Divigel Vivelle-DOT	December 2019 October 2021	Boxed Warning	The boxed warning was updated to document that the risk of increased adverse CV events and dementia seen with higher CE doses with lower have not been fully studied and these risks can't be excluded with lower CE doses. The risk of CV events, dementia and breast cancer with combination therapy (e.g., low CE with MPA), have also not been studied and therefore, an increased risk cannot be excluded. The risks and benefits should be discussed with the patient.
Estradiol Topical[34]	Climara Alora Estraderm Minivelle Elestrin Estrogel Divigel Menostar	November 2017	Warnings and Precautions	There is evidence for an increased risk of ovarian cancer with the use of HT. The exact duration of HT use associated with an increased risk of ovarian cancer is not known.
Abbreviations: CE – conjugated estrogens; CV – cardiovascular; COC - combination oral contraceptives; HT – hormone therapy; MPA – medroxyprogesterone acetate.				

Randomized Controlled Trials:
No new RCTS were identified. A total of 1,168 citations were manually reviewed from the literature search. Only trials reporting new comparative evidence were considered for inclusion. After manual review RCTs were excluded due to wrong study design, comparator, outcome studied, or lack of reported comparative outcome data.

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Appendix 1: Current Preferred Drug List

Estrogens, Oral

Generic	Brand	Form	PDL
estradiol	ESTRACE	TABLET	Y
estradiol	ESTRADIOL	TABLET	Y
estrogens,conj.,synthetic A	CENESTIN	TABLET	Y
estropipate	ESTROPIPATE	TABLET	Y
estropipate	OGEN	TABLET	Y
drospirenone/estradiol	ANGELIQ	TABLET	N
estradiol/norethindrone acet	ACTIVELLA	TABLET	N
estradiol/norethindrone acet	AMABELZ	TABLET	N
estradiol/norethindrone acet	ESTRADIOL-NORETHINDRNE ACETAT	TABLET	N
estradiol/norethindrone acet	LOPREEZA	TABLET	N
estradiol/norethindrone acet	MIMVEY	TABLET	N
estradiol/norgestimate	PREFEST	TABLET	N
estradiol/progesterone	BIJUVA	CAPSULE	N
estrogen,con/m-progest acet	PREMPHASE	TABLET	N
estrogen,con/m-progest acet	PREMPRO	TABLET	N
estrogen,ester/me-testosterone	ESTRATEST	TABLET	N
estrogen,ester/me-testosterone	ESTRATEST H.S.	TABLET	N
estrogen,ester/me-testosterone	ESTROGEN-METHYLTESTOSTERONE	TABLET	N
estrogen,ester/me-testosterone	SYNTEST D.S.	TABLET	N
estrogens, conjugated	PREMARIN	TABLET	N
estrogens,conj/bazedoxifene	DUAVEE	TABLET	N
estrogens,esterified	ESTRATAB	TABLET	N
estrogens,esterified	MENEST	TABLET	N
norethindrone ac-eth estradiol	FEMHRT	TABLET	N
norethindrone ac-eth estradiol	FYAVOLV	TABLET	N
norethindrone ac-eth estradiol	JINTELI	TABLET	N
norethindrone ac-eth estradiol	NORETHINDRON-ETHINYL ESTRADIOL	TABLET	N

Estrogens, Topical

Generic	Brand	Form	PDL
estradiol	ALORA	PATCH TDSW	Y
estradiol	DOTTI	PATCH TDSW	Y
estradiol	ESTRADERM	PATCH TDSW	Y
estradiol	ESTRADIOL (TWICE WEEKLY)	PATCH TDSW	Y
estradiol	LYLLANA	PATCH TDSW	Y
estradiol	MINIVELLE	PATCH TDSW	Y
estradiol	VIVELLE-DOT	PATCH TDSW	Y

estradiol	CLIMARA	PATCH TDWK	Y
estradiol	ESTRADIOL (ONCE WEEKLY)	PATCH TDWK	Y
estradiol	ELESTRIN	GEL MD PMP	N
estradiol	ESTROGEL	GEL MD PMP	N
estradiol	DIVIGEL	GEL PACKET	N
estradiol	MENOSTAR	PATCH TDWK	N
estradiol	EVAMIST	SPRAY	N
estradiol/levonorgestrel	CLIMARA PRO	PATCH TDWK	N
estradiol/norethindrone acet	COMBIPATCH	PATCH TDSW	N

Estrogens, Vaginal

Generic	Brand	Form	PDL
estradiol	ESTRADIOL	TABLET	Y
estradiol	VAGIFEM	TABLET	Y
estradiol	YUVAFEM	TABLET	Y
estrogens, conjugated	PREMARIN	CREAM/APPL	Y
estradiol	ESTRACE	CREAM/APPL	N
estradiol	ESTRADIOL	CREAM/APPL	N
estradiol	ESTRING	VAG RING	N
estradiol acetate	FEMRING	VAG RING	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 04, 2022
Search Strategy:

#	Searches	Results
1	vasomotor system.mp. or Vasomotor System/	9471
2	Osteoporosis, Postmenopausal/	13826
3	hypoestrogenism.mp.	496
4	vagina atrophy.mp.	3
5	vulva atrophy.mp.	0
6	estrogen replacement therapy.mp. or Estrogen Replacement Therapy/	16825
7	estrogen.mp. or Estrogens/	186764
8	estradiol.mp. or Estradiol/	128143
9	estropipate.mp.	61
10	ethinyl estradiol.mp. or Ethinyl Estradiol/	10611
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	278558
12	limit 11 to (english language and humans and yr="2016 -Current")	26502
13	limit 12 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	1168

Appendix 3: Key Inclusion Criteria

Population	Women with menopausal symptoms, individuals with hypoestrogenism or osteoporosis
Intervention	Estrogen derivatives (monotherapy and with progestins)
Comparator	Placebo or other active treatments for menopausal symptoms, hypoestrogenism, or postmenopausal osteoporosis prevention
Outcomes	Improvement in the frequency or severity of menopausal symptoms, estrogen levels or decreased fracture rates
Timing	Onset of mild to moderate menopausal symptoms or relevant diagnosis
Setting	Outpatient

Estrogen Derivatives

Goal(s):

- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the estrogen requested for a patient ≥18 years old?	**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 a co-pay.~~ Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
4. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #5	**No:** Go to #6

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

P&T / DUR Review: *6/22 (KS), 1/17 (SS); 11/15 (KS)*
Implementation: *4/1/17; 1/1/16*