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, August 7, 2025 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	A. Gibler (OHA)
	E. Legislative Update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Buprenorphine Policy Evaluation	
	B. Quarterly Utilization Report	
	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	
	C. Oregon State Drug Review	D. Engen (OSU)
	1. Off-label uses of GLP-1 Receptor Agonists and Dual GLP-1/GIP Receptor Agonists	K. Sentena (OSU)
	2. Pharmacologic Management of Vasomotor Menopausal Symptoms	
	IV. OLD BUSINESS	
1:40 PM	A. Gene Therapy for Sickle Cell Disease	S. Fletcher (OSU)
	1. Prior Authorization Update	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

V. NEW BUSINESS

1:50 PM	A. P&T Evidence Methods and Procedures for Non-drug Items 1. P&T Policies and Procedures 2. DURM Evidence Summary Methods 3. Public Comment and Discussion	S. Fletcher (OSU)
2:00 PM	B. New Drug Policy Update 1. Prior Authorization Criteria Update 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
2:10 PM	C. Second-generation Antipsychotics Class Update and New Drug Evaluation 1. Major Depressive Disorder DERP Report 2. Psychosis and Bipolar Disorder DERP Report 3. Lybalvi® (olanzapine/samidorphan) New Drug Evaluation 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:35 PM	D. Modafinil and Armodafinil Drug Use Evaluation 1. Drug Use Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
2:50 PM	BREAK	
3:05 PM	E. Hepatitis B Antivirals Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:25 PM	F. New Antibiotics for Urinary Tract Infections 1. Orlynvah™ (sulopenem etzadroxil/probenecid) New Drug Evaluation 2. Blujepa™ (gepotidacin) New Drug Evaluation 3. Pivya™ (pivmecillinam) New Drug Evaluation 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
3:50 PM	G. Vykat™ XR (diazoxide choline) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
4:05 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, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2025
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2025
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2025
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2026
Bridget Bradley, PharmD, BCPP	Pharmacist	Kaiser Northwest Psychiatry	Beaverton	December 2026
Samara Stevens, ND	Public	Mental Health Naturopath	Portland	December 2026
Jeanne Savage, MD	Physician	Medical Director, Trillium	Portland	December 2026
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2027
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2027
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2027
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2027

OREGON HEALTH AUTHORITY

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Health Systems Division
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, June 5th, 2025
1:05 PM - 3:35 PM
Via Zoom webinar

MEETING MINUTES

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

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

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

Audience: Adrian Lau*, J&J; Chad Duncan*, Vertex; Mary Rebar*; Greg Kichens, Artia Solutions; Reya Nematian, Advanced Health; Lewis Backus, OHA; Haylie Utzman, OSU PharmD Candidate; Lisa Pulver; Andy Berg, Audaire Health; Heidi Gullett, MD, OHA-HERC; Divine Marcelo, Amgen; Lynda Finch, Biogen; Tammi Ocumpaugh, Otsuka; Erin Nowak, AbbVie; Gary Parenteau, Dexcom; Mark Kantor, AllCare Health; April Grant, Vertex; Shauna Wick, Trillium; Jill Carroll; Chris Ferrin, IHN; Rosalie Elliott, Umpqua Health; Deron Grothe, Braeburn; Lisa Dunn; Aliethia McLeod, Trillium; T Shriner; Amy Breen, Teva; Brett Freund; Melissa Snider, Gilead; Erika Rosie; Bryan Armstrong, CareOregon; Levi Smith; Chris Johnson; Marissa Dunn; Norm Navarro; Kimberly Keller; Bryan Mauk

(*) Provided verbal testimony

I. CALL TO ORDER

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

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

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

D. Department Update provided by Andrew Gibler, PharmD

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Report

B. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Datroway® (datopotamab deruxtecan-dlnk) to Table 1 in the Oncology Agents PA criteria

C. Orphan Drug Policy Updates
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Niktimvo™ (axatilimab-csfr); Vykat™ XR (diazoxide choline); and Ryoncil® (remestemcel-L-rknd) based on their FDA-approved label

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

III. DUR ACTIVITIES

A. ProDUR Report: Lan Starkweather, PharmD

B. RetroDUR Report: Dave Engen, PharmD

C. Oregon State Drug Review: Kathy Sentena, PharmD

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

2. Update on the Biosimilar Landscape in the United States Market

3. Review of Off-Label Use of Gabapentin and Pregabalin

IV. NEW BUSINESS

A. Actinic Keratosis(AK) Class Review: Deanna Moretz, PharmD
Recommendation:
- Add "Topical Agents for Actinic Keratosis" class to the PDL
- Make preferred at least one topical formulation of 5-FU and imiquimod - indicated to treat basal cell carcinoma and genital warts
- Maintain diclofenac 3% gel as non-preferred and add tirbanibulin 1% ointment and aminolevulinic acid gel as non-preferred
- Implement PA criteria for topical agents used in AK to provide a pathway to coverage for AK in people with the EPSDT benefit.
- Evaluate costs in executive session

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

B. Egrifta SV® (tesamorelin) PA Update: Deanna Moretz, PharmD
Recommendations:
- Revise Tesamorelin PA criteria to define medical necessity and appropriateness for patients eligible for coverage under Early Periodic Screening Diagnostic and Treatment (EPSDT)

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

C. **Drugs for Dry Eye Disease**: Kathy Sentena, PharmD
Recommendations:
- Create a "Drugs for Dry Eye" PDL class
- Make all prescription products for the treatment of dry eye and vernal keratoconjunctivitis non-preferred based on the evidence
- Implement PA criteria to provide a pathway for coverage for therapies for vernal keratoconjunctivitis, for patients with comorbidities which allow for funding of dry eye, or who qualify under EPSTD
- Evaluate comparative costs in executive session
ACTION: Motion to approve, 2nd, all in favor

D. **Spravato® (esketamine) Prior Authorization Update and Drug Use Evaluation:** Sarah Servid, PharmD
Recommendations:
- Update PA criteria to clarify documentation required to support diagnosis and permit monotherapy with esketamine in people with treatment-resistant depression
Public Comment: Adrian Lau, Johnson & Johnson
ACTION: Motion to approve, 2nd, all in favor

E. **Journavx™ (suzetrigine) New Drug Evaluation:** Sara Fletcher, PharmD
Recommendations:
- Implement PA as proposed including use beyond 48 hours and limit use to no more than 14 days
Public Comment: Chad Duncan, Vertex; Mary Rebar
ACTION: Motion to approve, 2nd, all in favor

F. **Topical Drugs for Molluscum Contagiosum:** Dave Engen, PharmD
Recommendations:
- Create a new PDL class for agents to treat molluscum contagiosum
- Add cantharidin topical solution 0.7% (Ycanth®) and berdazimer gel 10.3% (Zelsuvmi™) to the Molluscum Contagiosum Drugs PDL class
- Implement PA criteria for cantharidin and berdazimer to define medical necessity under EPSDT
ACTION: Motion to approve, 2nd, all in favor

G. **Nutritional Supplements PA Update**: Sara Fletcher, PharmD
Recommendations:
- Add coverage for oral solid dosage forms, powders, and concentrated liquids of nutritional supplements for people with inborn errors of metabolism
- implement the proposed Nutritional Supplements as Prescribed Drugs for Special Conditions PA criteria to limit coverage to specific nutritional supplements based on current standards of care for those eligible under EPSDT
ACTION: Motion to approve, 2nd, all in favor

H. Nuedexta® (dextromethorphan/quinidine) New Drug Evaluation: Deanna Moretz, PharmD
Recommendations:
- Implement PA criteria for dextromethorphan/quinidine to define medical necessity under EPSDT
- Maintain dextromethorphan 20 mg/quinidine 10 mg as nonpreferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

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

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

VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. Actinic Keratosis
Recommendation: Make 5% imiquimod cream and 5% 5-FU cream preferred. Make all other product non-preferred
ACTION: Motion to approve, 2nd, all in favor

B. Drugs for Dry Eye Disease
Recommendations: Make all products non-preferred
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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Drug Policy Evaluation (Brief): Buprenorphine

Background:

In August of 2023, the DURM conducted a policy evaluation on quantity limits on buprenorphine products. The policy evaluation recommended raising the quantity limit of 24mg per day on buprenorphine products to 32mg per day. The goal of this change was to provide access to higher dose for members with Opioid Use Disorder (OUD) who might benefit for the higher dose. Those recommendations were implemented in August of 2023.

Research Questions:

1. Was there an increase in the number of members with a single prescription with a daily dose over 24mg
2. Was there an increase in the number of members with multiple prescriptions with a daily dose totally over 24mg
3. Was there an increase in the total units (aka tablets) per day
4. Was there a decrease in the proportion of members with a diagnosis of OUD before or after treatment (i.e., was buprenorphine being used more frequently for the treatment of pain vs. OUD).

Conclusions:

There was a small increase in members receiving over 24mg per day of buprenorphine (12.2%, p=0.0019), suggesting the policy had the desired impact to provide access to higher doses for the minority of members who would benefit from a higher dose. There was a decrease in the proportion of members without an OUD diagnosis during the baseline period, but the small magnitude of this change does not warrant a policy change. No other meaningful changes in healthcare resource utilization were observed. The policy change to raise the daily quantity limit from 24mg to 32 mg per day on buprenorphine products appears to have had the desired outcome without introducing unexpected increases in utilization. There may be dose consolidation opportunities, in particular for claims for 2mg tablets with quantities of 4 units per day and higher.

Recommendations:

No policy changes recommended.

Methods:

Claims were evaluated from 10/21/2020 to 12/31/2024. The index date was defined as the first buprenorphine claim for a member. Members were included in the study if the index date fell within one of 2 distinct periods: before the policy change 1/1/2021-9/30/2022, and after the policy change 10/1/2023-9/30/2024. The baseline period was the 9 months prior to the index date. The follow up period was 90 days beginning at the index date. Members were excluded if they had

other primary insurance coverage, non-continuous Medicaid FFS eligibility during the baseline or the follow up period, or were not between 18 and 65 years old as of the index date.

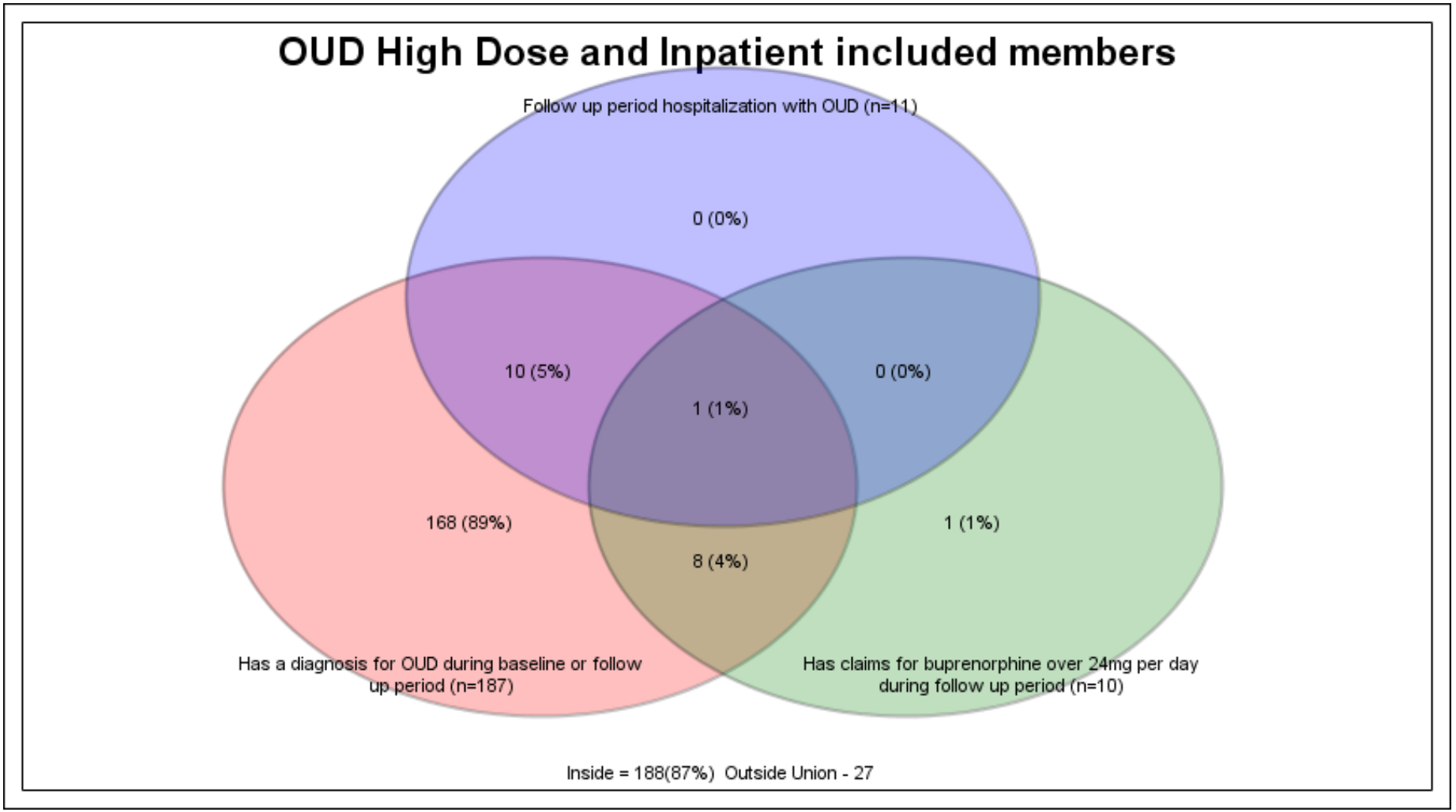
Results:
In total, 215 members were included in the study, with 133 included in the before policy change group and 82 in the after policy change group. There were no significant differences in age or gender between the two groups. A small but significant reduction in the proportion of members with baseline OUD was observed from before to after the policy change (86.47% vs. 75.61%, p = 0.0427). After the policy change, 87.80% of members continued to have claims for 24mg/day or less, while 12.2% of new starts included doses exceeding 24mg per day (p=0.0019). There was no significant difference in the proportion of members with claims for multiple strengths. The average number of units per day remained unchanged. There was no significant difference in the proportion of members with a claim with an OUD diagnosis during the follow-up period.

As part of an *ad hoc* analysis, no differences were observed in the proportion of members receiving buprenorphine in the inpatient setting, receiving naltrexone microspheres, or hospitalizations with a diagnosis of OUD. Additionally, there appears to be opportunities for dose consolidation for several strength and units per day combination:

A. 2mg x 12 units per day => 12mg x 2 units per day
B. 2mg x 8 units per day => 8mg x 2 units per day
C. 2mg x 6 units per day => 6mg x 2 units per day
D. 2mg x 4 units per day => 4mg x 2 units per day or 8mg once daily

Full study results and details are available by request to DURM.

Additional Venn diagram: OUD Hospitalizations, OUD Diagnosis, and buprenorphine claims over 24mg per day


OUD High Dose and Inpatient included members
Follow up period hospitalization with OUD (n=11)
0 (0%)
10 (5%)
1 (1%)
0 (0%)
168 (89%)
8 (4%)
1 (1%)
Has a diagnosis for OUD during baseline or follow up period (n=187)
Has claims for buprenorphine over 24mg per day during follow up period (n=10)
Inside = 188(87%) Outside Union - 27

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Prevent use of high-dose transmucosal buprenorphine products for off-label indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Transmucosal buprenorphine products that exceed an average daily dose of 32 mg per day

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. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 32 mg (e.g., >32 mg/day or >64 mg every other day)?	**Yes:** Go to #3	**No:** Go to #7

Approval Criteria		
3. Is there documentation of inadequate symptom improvement with 32 mg daily?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there recent documentation (within past month) from a urine drug screen indicating that buprenorphine is being taken?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the prescriber evaluated the PDMP in the past 3 months?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the member have access to naloxone?	**Yes:** Approve for 30 days. Subsequent requests for continuation of therapy will require documentation of objective clinical benefit with higher doses (e.g. improved management of OUD), documentation of a comprehensive treatment plan for OUD, and ongoing monitoring plan for safety risks.	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the requested medication a preferred agent?	**Yes:** Approve for 6 months. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #8

Approval Criteria		
8. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for 6 months. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: *10/23; 8/23 (SS); 2/23; 12/22; 12/20;11/19; 1/19; 1/17; 9/16; 1/15; 9/09; 5/09*

Implementation: *9/1/23; 1/1/2020; 3/1/2019; 4/1/2017; 9/1/13; 1/1/10*

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: January 2024 - December 2024

Eligibility	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
Total Members (FFS & Encounter)	1,276,290	1,264,099	1,268,663	1,249,346	1,239,354	1,231,095	1,226,816	1,235,264	1,241,007	1,247,678	1,254,503	1,257,986	1,249,342
FFS Members	118,187	112,962	110,868	105,128	103,204	102,443	98,771	97,509	96,865	99,056	99,856	98,868	103,643
OHP Basic with Medicare	9,270	9,176	9,007	8,737	8,820	8,839	8,606	8,437	8,250	8,222	7,915	7,437	8,560
OHP Basic without Medicare	9,779	9,707	9,663	9,533	9,402	9,417	9,308	9,241	9,221	9,278	9,034	8,899	9,374
ACA	99,138	94,079	92,198	86,858	84,982	84,187	80,857	79,831	79,394	81,556	82,907	82,532	85,710
Encounter Members	1,158,103	1,151,137	1,157,795	1,144,218	1,136,150	1,128,652	1,128,045	1,137,755	1,144,142	1,148,622	1,154,647	1,159,118	1,145,699
OHP Basic with Medicare	104,359	105,114	105,811	106,369	106,771	106,835	107,175	107,413	106,294	103,103	98,130	90,342	103,976
OHP Basic without Medicare	67,029	67,008	67,065	67,120	66,762	66,760	66,835	66,785	66,566	66,469	66,271	65,605	66,690
ACA	986,715	979,015	984,919	970,729	962,617	955,057	954,035	963,557	971,282	979,050	990,246	1,003,171	975,033

Gross Cost Figures for Drugs	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	YTD Sum
Total Amount Paid (FFS & Encounter)	$130,904,250	$122,931,185	$127,451,409	$132,657,913	$138,531,613	$124,908,094	$136,168,038	$134,069,187	$131,881,283	$145,525,838	$130,449,428	$143,010,508	$1,598,488,747
Mental Health Carve-Out Drugs	$11,430,220	$10,630,965	$10,930,213	$11,462,242	$11,667,964	$10,925,916	$11,869,586	$11,597,846	$11,350,042	$12,736,330	$11,548,612	$13,451,291	$139,601,226
OHP Basic with Medicare	$2,241	$126	$7,048	$6,918	$10,164	$13,561	$3,422	$73	$6,729	$10,123	$9,428	$1,297	$71,131
OHP Basic without Medicare	$4,019,549	$3,687,727	$3,666,382	$3,973,994	$3,977,278	$3,776,940	$4,037,639	$4,028,697	$3,783,273	$4,254,794	$3,758,651	$4,342,444	$47,307,367
ACA	$6,927,343	$6,395,533	$6,822,529	$6,964,855	$7,160,202	$6,695,095	$7,326,019	$7,127,251	$7,108,079	$7,940,373	$7,297,380	$8,511,429	$86,276,089
FFS Physical Health Drugs	$6,860,360	$6,167,380	$6,091,146	$6,220,592	$6,147,605	$5,490,283	$6,037,257	$5,565,109	$5,483,445	$5,815,092	$4,940,252	$5,485,970	$70,304,490
OHP Basic with Medicare	$311,240	$285,274	$275,866	$289,710	$315,279	$257,176	$299,686	$293,277	$252,165	$285,468	$207,198	$226,642	$3,298,981
OHP Basic without Medicare	$1,641,197	$1,386,981	$1,362,550	$1,443,649	$1,417,506	$1,267,794	$1,467,730	$1,277,660	$1,233,003	$1,320,302	$1,044,596	$1,186,612	$16,049,578
ACA	$4,503,078	$4,077,447	$4,041,348	$3,997,216	$3,978,027	$3,586,198	$3,926,344	$3,674,829	$3,631,635	$3,841,115	$3,363,507	$3,648,823	$46,269,567
FFS Physician Administered Drugs	$2,130,463	$1,552,483	$1,548,387	$1,415,177	$1,113,626	$1,290,107	$1,288,738	$1,515,368	$919,318	$1,350,561	$1,630,610	$1,231,986	$16,986,824
OHP Basic with Medicare	$204,370	$189,728	$99,263	$150,964	$106,708	$130,433	$126,158	$159,750	$130,964	$130,010	$96,634	$122,821	$1,647,803
OHP Basic without Medicare	$274,176	$337,079	$296,179	$267,064	$215,197	$491,581	$192,566	$295,895	$53,454	$313,577	$432,161	$191,554	$3,360,484
ACA	$964,511	$530,953	$568,577	$383,947	$356,601	$328,039	$409,923	$479,696	$461,097	$498,454	$639,335	$525,008	$6,146,141
Encounter Physical Health Drugs	$83,308,214	$78,117,546	$81,986,708	$86,093,613	$87,952,799	$79,007,250	$88,265,610	$87,050,987	$87,077,763	$94,404,115	$85,488,263	$92,464,168	$1,031,217,037
OHP Basic with Medicare	$401,914	$385,642	$414,946	$387,779	$375,698	$370,301	$390,994	$389,844	$397,940	$429,442	$352,733	$334,826	$4,632,060
OHP Basic without Medicare	$18,432,697	$16,795,453	$17,667,070	$18,648,147	$18,990,087	$17,195,448	$19,373,027	$19,027,214	$18,241,984	$19,933,608	$17,880,322	$19,432,618	$221,617,678
ACA	$55,691,552	$51,227,580	$53,997,853	$56,227,023	$57,482,072	$51,539,343	$57,101,815	$56,617,224	$57,529,797	$61,564,909	$56,136,044	$60,968,623	$676,083,834
Encounter Physician Administered Drugs	$27,174,994	$26,462,811	$26,894,955	$27,466,289	$31,649,620	$28,194,538	$28,706,847	$28,339,877	$27,050,715	$31,219,740	$26,841,691	$30,377,093	$340,379,170
OHP Basic with Medicare	$1,423,784	$1,311,408	$1,150,565	$1,183,245	$1,186,971	$1,032,735	$1,104,072	$1,006,679	$976,441	$1,088,206	$768,425	$767,158	$12,999,689
OHP Basic without Medicare	$5,063,811	$5,564,504	$5,562,490	$5,898,608	$5,710,027	$5,408,303	$6,249,038	$6,147,461	$5,438,721	$6,333,206	$5,315,887	$5,705,962	$68,398,019
ACA	$16,953,983	$16,106,839	$16,338,925	$16,953,271	$21,221,351	$18,771,778	$18,023,185	$17,793,884	$16,931,224	$19,766,288	$17,601,973	$19,606,786	$216,069,485

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: July 18, 2025

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: January 2024 - December 2024

YTD Percent Paid Amounts

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

Last Updated: July 18, 2025

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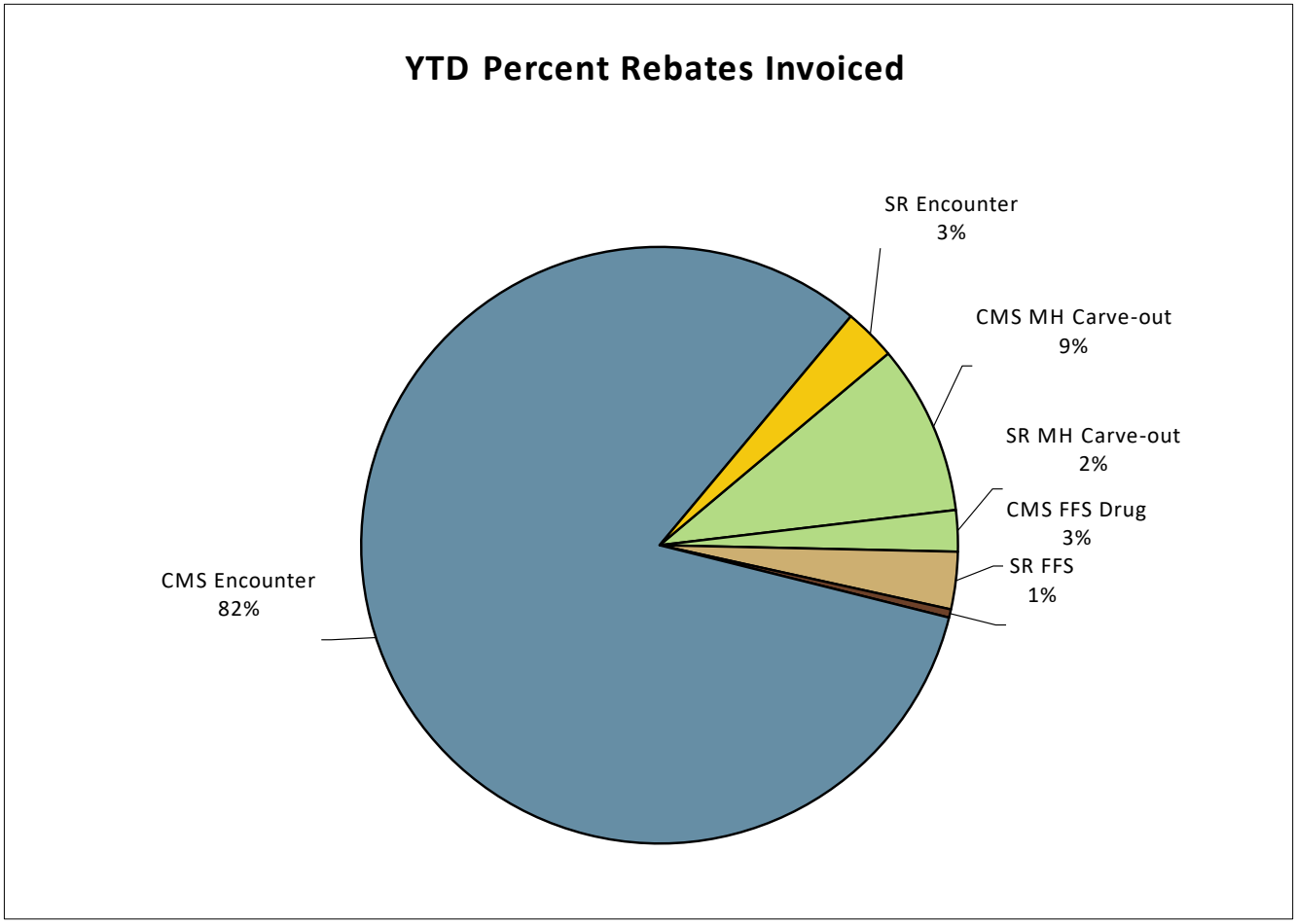
Pharmacy Utilization Summary Report: January 2024 - December 2024

Quarterly Rebates Invoiced	2024-Q1	2024-Q2	2024-Q3	2024-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$131,758,438	$130,969,443	$122,747,785	$129,444,570	$514,920,235
CMS MH Carve-out	$11,879,438	$11,689,044	$11,615,227	$12,313,786	$47,497,494
SR MH Carve-out	$2,369,032	$2,860,832	$2,919,188	$3,356,035	$11,505,087
CMS FFS Drug	$4,828,081	$4,213,833	$3,738,675	$3,214,771	$15,995,360
SR FFS	$679,922	$637,183	$509,682	$481,944	$2,308,732
CMS Encounter	$108,041,277	$108,284,612	$100,748,046	$106,054,276	$423,128,211
SR Encounter	$3,960,688	$3,283,939	$3,216,966	$4,023,758	$14,485,351

Quaterly Net Drug Costs	2024-Q1	2024-Q2	2024-Q3	2024-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$249,528,406	$265,128,178	$279,370,723	$289,541,204	$1,083,568,512
Mental Health Carve-Out Drugs	$18,742,929	$19,506,247	$20,283,058	$22,066,412	$80,598,645
FFS Phys Health + PAD	$18,842,215	$16,826,373	$16,560,878	$16,757,756	$68,987,222
Encounter Phys Health + PAD	$211,943,262	$228,795,558	$242,526,787	$250,717,037	$933,982,645



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

Last Updated: July 18, 2025

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: January 2024 - December 2024

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$102.57	$97.25	$100.46	$106.18	$111.78	$101.46	$110.99	$108.53	$106.27	$116.64	$103.98	$113.68	$106.65
Mental Health Carve-Out Drugs	$8.96	$8.41	$8.62	$9.17	$9.41	$8.87	$9.68	$9.39	$9.15	$10.21	$9.21	$10.69	$9.31
FFS Physical Health Drugs	$58.05	$54.60	$54.94	$59.17	$59.57	$53.59	$61.12	$57.07	$56.61	$58.71	$49.47	$55.49	$56.53
FFS Physician Administered Drugs	$18.03	$13.74	$13.97	$13.46	$10.79	$12.59	$13.05	$15.54	$9.49	$13.63	$16.33	$12.46	$13.59
Encounter Physical Health Drugs	$71.94	$67.86	$70.81	$75.24	$77.41	$70.00	$78.25	$76.51	$76.11	$82.19	$74.04	$79.77	$75.01
Encounter Physician Administered Drugs	$23.47	$22.99	$23.23	$24.00	$27.86	$24.98	$25.45	$24.91	$23.64	$27.18	$23.25	$26.21	$24.76

Claim Counts	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
Total Claim Count (FFS & Encounter)	1,280,621	1,228,383	1,279,216	1,317,894	1,332,229	1,218,401	1,284,319	1,255,563	1,242,738	1,344,142	1,237,601	1,322,645	1,278,646
Mental Health Carve-Out Drugs	217,891	202,362	209,977	214,481	215,278	197,586	214,353	208,994	205,829	222,856	205,160	222,061	211,402
FFS Physical Health Drugs	39,560	36,640	37,527	37,416	37,139	32,416	33,070	30,155	29,677	31,901	28,727	31,039	33,772
FFS Physician Administered Drugs	10,113	9,762	9,947	9,210	9,556	8,608	8,692	8,154	7,927	8,229	7,137	7,559	8,741
Encounter Physical Health Drugs	886,919	853,502	889,258	920,152	931,411	851,732	895,095	876,438	872,248	941,259	865,862	926,299	892,515
Encounter Physician Administered Drugs	126,138	126,117	132,507	136,635	138,845	128,059	133,109	131,822	127,057	139,897	130,715	135,687	132,216

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$102.22	$100.08	$99.63	$100.66	$103.98	$102.52	$106.02	$106.78	$106.12	$108.27	$105.41	$108.12	$104.15
Mental Health Carve-Out Drugs	$52.46	$52.53	$52.05	$53.44	$54.20	$55.30	$55.37	$55.49	$55.14	$57.15	$56.29	$60.57	$55.00
FFS Physical Health Drugs	$173.42	$168.32	$162.31	$166.25	$165.53	$169.37	$182.56	$184.55	$184.77	$182.29	$171.97	$176.74	$174.01
FFS Physician Administered Drugs	$210.67	$159.03	$155.66	$153.66	$116.54	$149.87	$148.27	$185.84	$115.97	$164.12	$228.47	$162.98	$162.59
Encounter Physical Health Drugs	$93.93	$91.53	$92.20	$93.56	$94.43	$92.76	$98.61	$99.32	$99.83	$100.30	$98.73	$99.82	$96.25
Encounter Physician Administered Drugs	$215.44	$209.83	$202.97	$201.02	$227.95	$220.17	$215.66	$214.99	$212.90	$223.16	$205.35	$223.88	$214.44

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$24.87	$24.53	$24.86	$25.58	$25.67	$25.18	$26.00	$26.04	$26.01	$25.84	$25.28	$25.44	$25.44
Mental Health Carve-Out Drugs	$17.64	$17.68	$17.48	$17.56	$17.51	$17.36	$17.27	$17.07	$17.10	$17.12	$17.04	$18.62	$17.45
FFS Physical Health Drugs	$118.40	$115.28	$113.36	$116.44	$119.35	$116.94	$120.51	$126.37	$125.98	$126.73	$124.89	$121.00	$120.44
Encounter Physical Health Drugs	$22.82	$22.56	$23.15	$24.04	$24.11	$23.79	$24.93	$25.07	$25.09	$24.80	$24.22	$24.13	$24.06

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$766.66	$761.83	$772.95	$785.06	$793.53	$775.01	$811.95	$800.60	$712.40	$725.78	$751.78	$815.32	$772.74
Mental Health Carve-Out Drugs	$1,390.71	$1,392.53	$1,406.17	$1,434.79	$1,441.60	$1,462.74	$1,437.09	$1,442.57	$1,430.36	$1,469.89	$1,459.15	$1,507.96	$1,439.63
FFS Physical Health Drugs	$506.69	$500.90	$488.12	$505.34	$476.12	$503.63	$564.21	$532.56	$493.85	$515.32	$469.33	$537.22	$507.77
Encounter Physical Health Drugs	$743.90	$738.47	$750.28	$759.90	$769.96	$745.83	$783.76	$772.37	$682.73	$691.90	$721.10	$781.02	$745.10

Generic Drug Use Percentage	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
Generic Drug Use Percentage	91.4%	91.5%	91.7%	91.7%	91.7%	91.6%	91.5%	91.3%	90.1%	90.2%	90.7%	91.3%	91.2%
Mental Health Carve-Out Drugs	97.5%	97.5%	97.5%	97.5%	97.4%	97.4%	97.3%	97.3%	97.3%	97.2%	97.3%	97.2%	97.4%
FFS Physical Health Drugs	85.8%	86.2%	86.9%	87.2%	87.1%	86.4%	86.0%	85.7%	84.0%	85.7%	86.3%	86.6%	86.2%
Encounter Physical Health Drugs	90.1%	90.4%	90.5%	90.6%	90.6%	90.4%	90.3%	90.1%	88.6%	88.7%	89.3%	90.0%	90.0%

Preferred Drug Use Percentage	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Avg Monthly
Preferred Drug Use Percentage	90.01%	89.99%	90.04%	90.00%	89.96%	89.89%	88.93%	88.62%	88.57%	88.52%	88.46%	88.38%	89.3%
Mental Health Carve-Out Drugs	92.70%	92.60%	92.68%	92.54%	92.49%	92.39%	86.72%	86.68%	86.52%	86.50%	86.53%	86.36%	89.6%
FFS Physical Health Drugs	95.29%	95.13%	95.10%	94.99%	95.14%	95.13%	95.10%	95.16%	94.92%	95.05%	95.21%	95.10%	95.1%
Encounter Physical Health Drugs	89.16%	89.19%	89.24%	89.25%	89.21%	89.15%	89.27%	88.90%	88.88%	88.82%	88.73%	88.68%	89.0%

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: July 18, 2025

Drug Use Research & Management Program
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2025

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	VRAYLAR*	Antipsychotics, 2nd Gen	$6,426,968	12.7%	4,702	$1,367	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$5,704,227	11.3%	2,085	$2,736	Y
3	REXULTI*	Antipsychotics, 2nd Gen	$3,277,792	6.5%	2,353	$1,393	V
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,979,345	5.9%	1,205	$2,472	Y
5	CAPLYTA*	Antipsychotics, 2nd Gen	$1,782,510	3.5%	1,216	$1,466	V
6	SPRAVATO*	Antidepressants	$1,663,110	3.3%	1,246	$1,335	V
7	INVEGA TRINZA	Antipsychotics, Parenteral	$1,487,946	2.9%	181	$8,221	Y
8	ARISTADA	Antipsychotics, Parenteral	$1,104,465	2.2%	426	$2,593	Y
9	TRINTELLIX	Antidepressants	$1,068,806	2.1%	2,279	$469	V
10	AUVELITY	Antidepressants	$886,395	1.8%	922	$961	V
11	BUPROPION XL	Antidepressants	$803,499	1.6%	59,200	$14	Y
12	LYBALVI*	Antipsychotics, 2nd Gen	$761,053	1.5%	513	$1,484	V
13	SERTRALINE HCL	Antidepressants	$730,835	1.4%	64,684	$11	Y
14	ABILIFY ASIMTUFII	Antipsychotics, Parenteral	$729,658	1.4%	138	$5,287	Y
15	TRAZODONE HCL	Antidepressants	$668,631	1.3%	54,742	$12	V
16	FLUOXETINE HCL	Antidepressants	$636,716	1.3%	51,033	$12	Y
17	ESCITALOPRAM OXALATE	Antidepressants	$628,755	1.2%	50,092	$13	Y
18	DULOXETINE HCL	Antidepressants	$621,879	1.2%	41,051	$15	Y
19	QELBREE*	ADHD Drugs	$537,675	1.1%	1,158	$464	Y
20	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$429,464	0.8%	32,172	$13	
21	LAMOTRIGINE	Antiepileptics, Outpatient	$400,987	0.8%	32,136	$12	Y
22	INVEGA HAFYERA	Antipsychotics, Parenteral	$371,978	0.7%	21	$17,713	Y
23	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$350,478	0.7%	23,514	$15	Y
24	BIKTARVY	HIV	$343,627	0.7%	113	$3,041	Y
25	Inj Pembrolizumab	Physican Administered Drug	$318,852	0.6%	47	$6,784	
26	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$317,644	0.6%	2	$158,822	
27	BUPROPION XL	Antidepressants	$292,691	0.6%	1,904	$154	V
28	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$287,284	0.6%	22,328	$13	Y
29	ATOMOXETINE HCL*	ADHD Drugs	$273,743	0.5%	10,894	$25	Y
30	VENLAFAXINE HCL ER	Antidepressants	$255,975	0.5%	19,101	$13	Y
31	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$227,943	0.5%	22	$10,361	Y
32	SERTRALINE HCL	Antidepressants	$225,715	0.4%	1,443	$156	V
33	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$220,429	0.4%	114	$1,934	Y
34	COBENFY*	Antipsychotics, 2nd Gen	$218,699	0.4%	139	$1,573	V
35	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$214,054	0.4%	189	$1,133	Y
36	MIRTAZAPINE	Antidepressants	$211,836	0.4%	14,471	$15	Y
37	UZEDY	Antipsychotics, Parenteral	$211,355	0.4%	71	$2,977	Y
38	OLANZAPINE*	Antipsychotics, 2nd Gen	$206,558	0.4%	14,480	$14	Y
39	GUANFACINE HCL ER	ADHD Drugs	$199,435	0.4%	14,128	$14	Y
40	DAYBUE*	STC 99 - Miscellaneous	$191,715	0.4%	9	$21,302	N
		Top 40 Aggregate:	**$38,270,726**		**526,524**	**$6,410**	
		All FFS Drugs Totals:	**$50,592,414**		**786,919**	**$667**	

*** 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

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	BIKTARVY	HIV	$343,627	3.7%	113	$3,041	Y
2	Inj Pembrolizumab	Physican Administered Drug	$318,852	3.4%	47	$6,784	
3	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$317,644	3.4%	2	$158,822	
4	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$227,943	2.4%	22	$10,361	Y
5	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$220,429	2.4%	114	$1,934	Y
6	DAYBUE*	STC 99 - Miscellaneous	$191,715	2.0%	9	$21,302	N
7	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	$190,988	2.0%	351	$544	N
8	HUMIRA(CF) PEN*	Targeted Immune Modulators	$177,021	1.9%	38	$4,658	Y
9	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$160,895	1.7%	7	$22,985	
10	JARDIANCE	Diabetes, SGLT-2 Inhibitors	$148,530	1.6%	388	$383	Y
11	Daratumumab, Hyaluronidase	Physican Administered Drug	$147,466	1.6%	25	$5,899	
12	FINTEPLA*	Antiepileptics, Outpatient	$138,414	1.5%	14	$9,887	N
13	TRIKAFTA*	Cystic Fibrosis	$116,832	1.2%	25	$4,673	N
14	EVEROLIMUS*	Antineoplastics, Newer	$115,949	1.2%	13	$8,919	
15	ELIQUIS	Anticoagulants, Oral and SQ	$112,069	1.2%	292	$384	Y
16	IBRANCE*	Antineoplastics, Newer	$98,855	1.1%	5	$19,771	
17	TRULICITY*	Diabetes, GLP-1 Receptor Agonists and GIP The	$97,513	1.0%	165	$591	Y
18	IMCIVREE*	Weight Management Drugs	$96,401	1.0%	3	$32,134	
19	TALTZ AUTOINJECTOR*	Targeted Immune Modulators	$94,492	1.0%	13	$7,269	Y
20	EPIDIOLEX*	Antiepileptics, Outpatient	$88,707	0.9%	74	$1,199	N
21	KISQALI*	Antineoplastics, Newer	$87,586	0.9%	7	$12,512	
22	ALYFTREK*	Cystic Fibrosis	$85,275	0.9%	5	$17,055	N
23	Canakinumab Injection	Physican Administered Drug	$81,732	0.9%	2	$40,866	
24	MOUNJARO*	Diabetes, GLP-1 Receptor Agonists and GIP The	$76,878	0.8%	132	$582	N
25	Altuviiio Per Factor Viii Iu	Physican Administered Drug	$76,253	0.8%	1	$76,253	
26	COSENTYX SENSOREADY (2 PENS)*	Targeted Immune Modulators	$74,412	0.8%	14	$5,315	N
27	BRIXADI	Substance Use Disorders, Opioid & Alcohol	$71,685	0.8%	42	$1,707	Y
28	LISDEXAMFETAMINE DIMESYLATE*	ADHD Drugs	$66,921	0.7%	830	$81	Y
29	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$66,104	0.7%	1,023	$65	Y
30	SKYRIZI*	Targeted Immune Modulators	$64,990	0.7%	4	$16,248	N
31	Aflibercept Injection	Physican Administered Drug	$64,800	0.7%	163	$398	
32	STELARA*	Targeted Immune Modulators	$59,952	0.6%	18	$3,331	N
33	COSENTYX SYRINGE*	Targeted Immune Modulators	$59,433	0.6%	5	$11,887	N
34	PAXLOVID	Coronavirus Antivirals	$58,960	0.6%	46	$1,282	Y
35	DEXCOM G7 SENSOR*	STC 00 - Medical Supplies	$55,608	0.6%	256	$217	Y
36	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$55,133	0.6%	2,101	$26	Y
37	OFEV*	Interstitial Lung Disease	$54,106	0.6%	4	$13,526	N
38	RINVOQ*	Targeted Immune Modulators	$53,612	0.6%	21	$2,553	N
39	Mifepristone, Oral, 200 Mg	Physican Administered Drug	$52,933	0.6%	672	$79	
40	Etonogestrel Implant System	Physican Administered Drug	$49,380	0.5%	67	$737	
		Top 40 Aggregate:	**$4,720,094**		**7,133**	**$13,156**	
		All FFS Drugs Totals:	**$9,363,323**		**94,300**	**$666**	

*** Drug requires Prior Authorization**

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

Last updated: July 18, 2025

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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
avutometinib and defactinib	AVMAPKI FAKZYNJA CO-PACK
linvoseltamab-gcpt	LYNOZYFIC
penpulimab-kcqx	none
sunvozertinib	ZEGFROVY
taletrectinib	IBTROZI
telisotuzumab vedotin-tllv	EMRELIS
treosulfan	GRAFAPEX

Recommendation:

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

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

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

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

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

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

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

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

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

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

Table 1. Oncology agents which apply to this policy (Updated 7~~3~~/8~~4~~/2025)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

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

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

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

Generic Name	Brand Name
omacetaxine mepesuccinate	SYNRIBO
omidubicel-onlv	OMISIRGE
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
penpulimab-kcqx	none
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
quizartinib	VANFLYTA
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYX
repotrectinib	AUGTYRO
retifanlimab-dlwr	ZYNYZ
revumenib	REVUFORJ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
sunvozertinib	ZEGFROVY

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

Generic Name	Brand Name
ziv-aflibercept	ZALTRAP

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

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. Updated orphan drugs

Generic Name	Brand Name
Nipocalimab-aahu	IMAAVY
Rezafungin	REZZAYO

Recommendation:

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

Orphan Drugs

Goal(s):

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

Length of Authorization:

- Up to 6 months

Requires PA:

- See Table 1 (pharmacy and provider administered claims)

Covered Alternatives:

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

Table 1. Included orphan drugs

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

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

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

Approval Criteria		
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in the FDA label (see links in **Table 1)**? Note: This includes all information required in the FDA-approved indication, including but not limited to, the following as applicable: diagnosis, disease severity, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6

Approval Criteria		
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended baseline and ongoing monitoring parameters described in the FDA label?* *FDA pages for drugs and biologics: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/ approved-cellular-and-gene-therapy-products	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

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

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

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

ProDUR Report for April through June 2025
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	0	0	0	0	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,287	625	0	1,662	1.2%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	10,954	3,747	3	7,183	5.7%	N/A
ER (Early Refill)	**Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)**	**Set alert/Deny claim**	**119,202**	**29,795**	**116**	**89,284**	**62.6%**	**25.0%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	42,938	12,999	2	29,880	22.5%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	973	278	1	693	0.5%	N/A
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	4	2	0	2	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	880	293	0	587	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	386	147	0	239	0.2%	N/A
PA (Drug/Age Precaution)	Products containing Codeine being billed and patient is less than 18 years of age	Set alert/Pay claim	1	1	0	0	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**143**	**73**	**0**	**70**	**0.0%**	**51.0%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	12,657	3,982	0	8,643	6.6%	N/A
		Totals	**190,425**					

ProDUR Report for April through June 2025
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	9,163	2,084	7,079	90,968	10.0%	22.7%
ER	Prozac (Fluoxetine)	7,116	1,662	5,454	72,524	9.8%	23.4%
ER	Lexapro (Escitalopram)	6,592	1,492	5,100	68,676	9.6%	22.6%
ER	Celexa (Citalopram)	1,884	472	1,411	22,765	8.2%	25.1%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	10,089	2,114	7,975	103,015	9.8%	21.0%
ER	Trazodone	8,672	2,120	6,552	74,075	11.7%	24.4%
ER	Cymbalta (Duloxetine)	6,366	1,641	4,725	56,652	11.2%	25.8%
ER	Effexor (Venlafaxine)	3,219	793	2,426	32,307	9.9%	24.6%
ER	Remeron (Mirtazapine)	2,515	623	1,892	20,214	12.4%	24.8%
ER	Elavil (Amitriptyline)	2,015	567	1,448	20,117	10.0%	28.1%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	5,831	1,675	4,155	38,874	15.0%	28.7%
ER	Abilify (Aripiprazole)	4,983	1,103	3,879	36,125	13.7%	22.1%
ER	Zyprexa (Olanzapine)	3,392	922	2,469	23,739	14.2%	27.2%
ER	Risperdal (Risperidone)	2,404	635	1,769	15,447	15.5%	26.4%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	5,002	1,152	3,850	44,030	11.3%	23.0%
ER	Lorazepam	391	148	243	12,938	3.0%	37.9%
ER	Alprazolam	227	74	153	7,521	3.0%	32.6%
ER	Diazepam	103	43	60	4,437	2.3%	41.7%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	8,502	2,137	6,365	58,293	14.5%	25.1%
ER	Intuniv (Guanfacine ER)	2,456	441	2,015	19,464	12.6%	18.0%
ER	Depakote (Divalproex)	2,115	665	1,450	13,869	15.2%	31.4%
ER	Suboxone (Buprenorphine/Naloxone)	64	31	33	1,518	4.1%	48.4%

ProDUR Report for April through June 2025
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC-Other
ER	April	6,227	162	236	687	5	4,899	42	4	192
ER	May	7,359	188	259	762	6	5,868	34	5	237
ER	June	7,469	315	344	814	10	5,708	31	0	247
	Total	**21,055**	**665**	**839**	**2,263**	**21**	**16,475**	**107**	**9**	**676**
	Percentage of Total Overrides		**3.2%**	**4.0%**	**10.7%**	**0.1%**	**78.2%**	**0.5%**	**0.0%**	**3.2%**

ProDUR Report for April through June 2025			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
April	DD	26	$2,522.08
	ER	48	$13,031.42
	ID	11	$995.53
	TD	2	$709.93
	April Total	**87**	**$17,258.96**
May	DC	1	$2.92
	DD	43	$20,931.78
	ER	222	$54,276.56
	HD	3	$58.78
	ID	38	$10,483.64
	LR	2	$360.39
	MC	2	$100.02
	PG	1	$23.69
	TD	15	$6,813.00
	May Total	**327**	**$93,050.78**
June	DC	1	$85.69
	DD	27	$8,131.68
	ER	57	$6,550.45
	ID	13	$2,331.18
	LR	1	$110.40
	June Total	**99**	**$17,209.40**
	Total 2Q2025 Savings		**$127,519.14**

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Billing Correction Review	High Cost OCC 3	Total Patients Identified	56	52	73	4
		Total Claims Identified	59	53	74	4
		Claims reviewed	3	3	4	
		Estimated Savings	$0	$0	$0	
	OCC 4 with OCC 2 for different NDC	Total Patients Identified	16	20	14	4
		Total Claims Identified	17	20	16	4
		Claims reviewed			5	
		Estimated Savings			$8,645	
	OCC 4 with OCC 2 for the same NDC	Total Patients Identified	6	20	4	1
		Total Claims Identified	6	22	5	1
	OCC 4 with Primary Payer Rejection Code	Total Patients Identified	4	5	8	1
		Total Claims Identified	4	5	8	1
		Claims reviewed		2	2	
		Estimated Savings		$0	$0	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	11	11	12	6
		Unique Patients Identified	11	11	12	6
		Total Faxes Successfully Sent	8	8	10	4
		Prescriptions Changed to Recommended Within 6 Months of Intervention	2	4	6	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$565	$1,388	$2,069	
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	96	72	112	49
		Unique Patients Identified	96	72	115	53
		Total Faxes Successfully Sent	79	43	81	42
		Prescriptions Changed to Recommended Within 6 Months of Intervention	43	30	48	11
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$48,409	$23,861	$23,747	$2,666

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	RetroDUR Dose Consolidation	Total Claims Identified	1	1		
		Total Faxes Successfully Sent	1	1		
		Prescriptions Unchanged after 3 Months of Fax Sent	1	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0	$0		

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	876	915	909	304
		High risk patients identified	9	7	15	4
		Prescribers successfully notified	8	7	15	
		Patients with change in antipsychotic drug in following 90 days	1	1		
		Patients with continued antipsychotic therapy in the following 90 days	8	6	12	
		Patients with discontinuation of antipsychotic therapy in the following 90 days			1	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	62	53	44	14
		Total prescribers identified	60	53	44	14
		Prescribers successfully notified	60	53	43	6
		Patients with claims for the same antipsychotic within the next 90 days	33	23	18	2
		Patients with claims for a different antipsychotic within the next 90 days	2	2	2	

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Retro-DUR Intervention History by Quarter FFY 2024 - 2025

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	63	55	65	
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	18	25	26	
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	156	188	155	
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	35	20	37	
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	22	23	29	
		Letters Sent To Providers	15	16	15	
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	28	23	29	
		Letters Sent To Providers	31	25	31	
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	23	24	19	
		Letters Sent To Providers	16	13	9	
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	23	23	19	
		Letters Sent To Providers	5	9	16	
	Lock-In	RetroDUR Profiles Reviewed	8	8	4	
		Locked In	0	0	0	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Antipsychotics for ages <=5 years	Patients identified with an ending PA	15	17	31	8
		Total prescribers identified	14	16	31	7
		Prescribers successfully notified	13	13	25	3
		Patients with paid claims within next 60 days	10	13	23	2
		Patients with denied claim within next 60 days	14	13	16	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	71	47	53	12
		Total prescribers identified	71	47	53	12
		Prescribers successfully notified	67	45	51	5
		Patients with discontinuation of therapy within next 90 days	19	12	24	12
		Patients with new prescription for naloxone within next 90 days		3	1	1
		Average number of sedative drugs dispensed within next 90 days	23	23	16	0
		Average number of sedative prescribers writing prescriptions in next 90 days	23	23	16	0
	Oncology Denials	Total patients identified	3	2	2	
		Total prescribers identified	3	2	2	
		Prescribers successfully notified	2	2	2	
		Patients with claims for the same drug within the next 90 days	2	1	2	
		Patients with claims for any oncology agent within the next 90 days	2	1	2	
	TCAs in Children	TCA Denials in Children	35	36	30	3
		Total patients identified	11	12	11	1
		Total prescribers identified	11	11	10	1
		Prescribers successfully notified	6	5	8	1
		Patients with claims for a TCA within the next 90 days	2	3	2	
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days		1	1	

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Off-label Uses of GLP-1 Receptor Agonists and Dual GLP-1/GIP Receptor Agonists

Kathy Sentena, PharmD, Oregon State University Drug Use Research and Management Group

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) RAs have rapidly gained popularity for glucose lowering in patients with type 2 diabetes (T2D) and as weight management drugs. In addition to Food and Drug Administration (FDA) approved indications (**Table 1**), GLP-1 RAs are being used for additional off-label uses. This newsletter will review the evidence for off-label uses of GLP-1/GIP RAs and discuss important considerations when prescribing these medications.

Table 1. FDA Approved Indications for GLP-1 RAs and Dual GLP-1/ GIP Agonists

Drug*	Indication
Dulaglutide TRULICITY[1]	• Glucose lowering in adults and pediatrics with T2D • Reduce CV events in adults with T2D
Exenatide BYETTA[2]	• Glucose lowering in adults with T2D
Exenatide ER BYDUREON[3]	• Glucose lowering in adults and pediatrics with T2D
Liraglutide[4] SAXENDA[4]1/27/ 2025 12:07:00 PM	• Body weight reduction in the following: Adult patients with an initial body mass index (BMI) of: • 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, T2D, or dyslipidemia) Pediatric patients aged 12 years and older with: • body weight above 60 kg and • an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cut-offs
Liraglutide VICTOZA[5]	• Glucose lowering in adults and pediatrics with T2D • Reduce CV events in adults with T2D
Semaglutide OZEMPIC[6]	• Glucose lowering in adults with T2D • Reduce CV events in adults with T2D
Semaglutide RYBELSUS[7]	• Glucose lowering in adults with T2D
Semaglutide WEGOVY[8]	• Reduce CV events in adults with CV disease and overweight or obesity • Body weight reduction in adults and pediatric patients with obesity and adults with overweight in the presence of at least one weight-related comorbid condition
Tirzepatide+ MOUNJARO[9]	• Glucose lowering in adults with T2D
Tirzepatide+ ZEPBOUND[10]	• Body weight reduction in adults with obesity and overweight in the presence of at least one weight-related comorbid condition • Moderate to severe OSA in adults with obesity

Key: *All drugs are GLP-1 RAs unless indicated; + Dual GLP-1/GIP RA
Abbreviations: CV = cardiovascular; ER = extended release; OSA = obstructive sleep apnea; T2D = type 2 diabetes

Pharmacology of GLP-1 RAs and GLP-1/GIP RAs

GLP-1 RAs bind to the GLP-1 receptor in central (e.g., brain) and peripheral targets (e.g., lungs, pancreas, gastrointestinal tract, kidney, and heart) which triggers the effects of the GLP-1 hormone.[11] The physiological GLP-1 hormone stimulates insulin secretion, lowers glucagon secretion, and delays gastric emptying. Appetite regulation in the brain is also a function of the GLP-1 and GIP receptor.[9,12] Due to the widespread distribution of GLP-1 receptors there are multiple potential therapeutic uses. There is Medicaid compendia support (i.e., Micromedex)/evidence for use in fatty liver disease, polycystic ovary syndrome (PCOS), and heart failure with preserved ejection fraction and obesity. Additional indications where GLP-1/GIP RAs have demonstrated efficacy are: alcohol and substance use disorder (SUD)[11], prediabetes[13], epilepsy[14], Parkinson's disease (PD)[15], Alzheimer's disease (AD)[16], and obstructive sleep apnea (OSA)[17].

GLP-1 RAs use in Heart Failure

A recent trial studying semaglutide in patients with HF with preserved ejection fraction and obesity (STEP-HFpEF) provided evidence for use in this population.[18] Compared to placebo, semaglutide improved symptoms, as measured by the Kansas City Cardiomyopathy Questionnaire, with an estimated difference (ED) of 7.8 points (95% CI, 4.8 to 10.9 points) and reduced body weight (ED -10.7%; 95% confidence interval [CI], -11.9% to -9.4%). This trial provides moderate quality evidence of potential utility in the treatment of heart failure (HF).[19] Outcomes such as hospitalizations for HF, would provide valuable evidence to conclude benefit in this population.

GLP-1 RAs use in Polycystic Ovary Disease

Elevated insulin levels are a known contributor to PCOS. The underlying cause of PCOS is insulin resistance which results in hyperinsulinemia. This leads to exaggerated insulin effects in

the ovary due to the excess insulin levels. The American Society for Reproductive Medicine recommends antidiabetic therapies, such as GLP-1 RAs, as an option for patient with PCOS and obesity.[20] In women with PCOS and overweight or obesity, a meta-analysis of 6 studies (n=327), found liraglutide to be superior to metformin for weight loss.[21] The combination of liraglutide and metformin, compared to placebo, were found to improve body mass index (BMI), fasting blood sugar, and fasting insulin more than metformin alone at 12 weeks.[21] In a second meta-analysis of 176 patients, GLP-1 RAs (i.e., semaglutide and liraglutide) were compared to placebo in women with PCOS and found that GLP-1 RAs statistically significantly reduced BMI (mean difference [MD] -2.42; 95% confidence interval [CI], -3.10 to -1.74); p<0.00001) and serum triglycerides (MD -0.20; 95% CI, -0.30 to -0.11; p<0.00001) and non-significantly total testosterone levels (MD -1.33; 95% CI, -0.10 to 0.01; p=0.15).[20] Results are suggestive of a favorable option for people with PCOS, with additional randomized controlled trials (RCT) studying outcomes such as restoration of ovulatory menstrual cycles and hyperandrogenism, needed to verify benefit.

GLP-1 RAs in Substance Use Disorder

GLP-1 RAs may have utility in the management of alcohol and other substance use disorders (SUD). While most of the evidence is in alcohol use disorder (AUD), research has also been conducted in patients taking psychostimulants, opioids and nicotine.[11] The suggested mechanism of efficacy is related to reward processing, cognitive function, stress adaption and satiety. One prospective, RCT (n=127) found extended-release exenatide had no effect on alcohol consumption in patients with AUD.[22]

Low quality evidence has found no benefit of GLP-1 RAs in those with cocaine use disorder.[11] Preliminary results from one, unpublished trial studying the use of liraglutide in patients with opioid use disorder reported a reduction in cravings in patients receiving liraglutide. GLP-1 RA use for nicotine has been suggested as having potential benefits but additional studies need to be performed.[11]

GLP-1 RAs and GLP-1/GIP RAs and Liver Disease

In 2023, the American Association for the Study of Liver Diseases (AASLD) introduced new nomenclature for fatty liver disease. The terms metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) were introduced in place of nonalcoholic fatty liver disease (NAFLD) and its subcategory nonalcoholic steatohepatitis (NASH). MASLD affects 30% of people worldwide and can progress to more severe forms of liver disease such cirrhosis or MASH and an increased risk of cardiovascular (CV) disease.[23, 24] MASLD has been linked to insulin resistance, and the suggested hepatic benefits of GLP-1 RAs are most likely due to weight loss.

Studies in adults with overweight and MASLD have demonstrated GLP-1 RA and GLP-1/GIP RA benefits in liver inflammation, fibrosis and potential reversal of steatohepatitis with weight loss of 7% or more.[25,26] Results of phase 2 studies of semaglutide and tirzepatide in the treatment of MASH are presented below (**Table 2**). Liraglutide was also studied in a double-blind, phase 2 RCT (n=52) which demonstrated more resolution of definite non-alcoholic steatohepatitis compared to placebo, 39% versus 9% (relative risk [RR] 4.3%; 95% CI, 1.0 to 17.7; p=0.019).[27]

The American Association of Clinical Endocrinology (AACE) recommends semaglutide or liraglutide for people with MASLD and who have a BMI of at least 27 kg/m^2 who are not able to obtain weight management goals with lifestyle modifications.[25]

For a more detailed review on the use of GLP-1/GIP RAs in the treatment of liver disease, visit our newsletter at: https://www.orpdl.org/durm/newsletter/osdr_articles/volume14/osdr_v14_i10.pdf.

Table 2. Selected GLP-1 RAs and GLP-1/GIP RAs phase 2 studies*[28,29]

	MASH Resolution	Fibrosis Improvement
Semaglutide 0.1 mg daily injection	40% OR 3.36 (95% CI 1.29-8.86)	49% OR 1.96 (95% CI 0.86-4.51)
Semaglutide 0.2 mg daily injection	36% OR 2.71 (95% CI 1.06-7.56)	32% OR 1.00 (95% CI 0.43-2.32)
Semaglutide 0.4 mg daily injection	59% OR 6.87 (95% CI 2.60-17.63)	43% OR 1.42 (95% CI 0.62-3.28)
Placebo	17%	33%
Tirzepatide 5 mg injection	44% Difference 34% (95% CI 17-50)	55% Difference 25% (95% CI 5-46)
Tirzepatide 10 mg injection	56% Difference 46% (95% CI 29-62)	51% Difference 22% (95% CI 1-42)
Tirzepatide 15 mg injection	62% Difference 53% (95% CI 36-69)	51% Difference 21% (95% CI 1-42)
Placebo	10%	30%
* Results from unique studies; not for direct comparison. Abbreviations: CI = confidence interval; MASH = metabolic dysfunction-associated steatohepatitis; OR = odds ratio.		

Prediabetes and GLP-1 RAs

Weight loss has demonstrated efficacy in preventing progression to T2D in adults who have prediabetes (hemoglobin A1c [HbA1c) of ≥ 5.7%]).[13] Certain GLP-1 RAs

(i.e., liraglutide, semaglutide and tirzepatide) have been associated with clinically significant weight loss ranging from 5.2 kg to 19 kg in studies lasting around one year.[13] Due to the weight loss benefits demonstrated with the use of GLP-1 RAs and GLP-1/GIP RAs, studies have shown reductions in the development of diabetes. The most evidence is for liraglutide and semaglutide. In a post-hoc analysis of 3 studies (n=3375) evaluating semaglutide for weight loss, the STEP 1-3 trials, glucose level were studied. In patients with prediabetes at baseline, normoglycemia was found to be higher with semaglutide compared to placebo at week 68, (STEP 1, 84.1% vs. 47.8%; STEP 3, 89.5% vs. 55.0%; STEP 4, 89.8% vs. 70.4%; all $P < 0.0001$).[30]

In a double blind, placebo controlled RCT, liraglutide 3.0 mg injected daily in patients with prediabetes and a BMI of 30 kg/m^2, or at least 27 kg/m^2 with comorbidities, was found to decrease the risk of developing diabetes (absolute risk reduction [ARR] 4%; number needed to treat [NNT] 25 over 160 weeks). The study was limited by high dropout rates.[31]

GLP-1 RAs and Epilepsy

There is some preliminary evidence that GLP-1 RAs may decrease neurodegeneration and improve neuroinflammation in people with epilepsy. A recent meta-analysis and systematic review in late-onset epilepsy (those diagnosed after the age of 55 years) compared glucose lowering therapies to placebo.[32] The trials were designed to access long-term CV and renal outcomes. Seizures and epilepsy prevention were analyzed from adverse event outcomes from trial data. In an analysis of 8 RCTs, GLP-1 RAs, compared to placebo, reduced the risk for the composite outcome of epilepsy and seizures with a relative risk of 0.67 (95% CI, 0.46 to 0.98).[32] Results were similar for the newer glucose drugs, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. Additional research is needed to confirm these benefits.

Parkinson's disease and GLP-1 RA

GLP-1 RAs may have efficacy in preventing or treating PD. Neuronal metabolism and repair and synaptic efficacy is influenced by insulin signaling in the brain. The proposed mechanism of the role of GLP-1 RAs is prevention of insulin desensitization in the brain which is often seen in patients with PD. A Cochrane review evaluating exenatide compared to placebo in 2 studies (n=104) found low-quality evidence that motor impairment, accessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, was improved in the off-medication state (12-weeks after exenatide discontinuation) in patients who took exenatide compared to people who took placebo.[15] In one study, the difference compared to placebo and GLP-1 RAs was small and results were not clinically meaningful (i.e., a clinically meaningful change is defined as a change of -3.25 or more) (MD -3.10; 95% CI, -6.11 to -0.09).[15] In the second study (n=44), exenatide was superior to no treatment with results that were considered clinically meaningful (MD -4.5; 95% CI, -8.64 to -0.36).[15] There is a lack of evidence to determine a definitive benefit and additional research is needed.

GLP-1 RAs and Alzheimer's disease

It is known that T2D is a risk factor for developing AD. GLP-1 RAs cross the blood-brain barrier and may improve cognitive function by reducing oxidative stress and neuroinflammation and suppressing neurotoxicity.[16] Modification of the underlying disease process is measured by Aß and tau accumulation.[14] In a systematic review of 3 studies, there was no treatment difference between GLP-1 RAs (i.e., liraglutide and exenatide) and placebo.[16] A second systematic review and meta-analysis found similar results, suggesting that additional research is needed to determine any benefit for the use of GLP-1 RAs in people with AD.[33] There may also be a preventative role of GLP-1 RAs in the development of AD, based on retrospective data in patients with T2D; however, due to the high risk of bias associated with retrospective data, randomized controlled trials need to be done to determine if there is any actual benefit .[25]

Obstructive Sleep Apnea and GLP-1 RAs and GLP-1/GIP RAs

Obstructive sleep apnea is associated with obesity, T2D, and increased risk of CV disease. Intermittent hypoxia associated with OSA can lead to a variety of detrimental physiological changes including weight gain, cognitive impairment and CV events. Weight loss in adults with obesity-associated OSA can decrease or eliminate OSA.[17] The weight loss benefits demonstrated with GLP-1 RAs and GLP-1/GIP RAs, as well as improvement in OSA associated impaired glucose metabolism, suggests a therapeutic use of GLP-1 RAs for the treatment of OSA. A systematic review and meta-analysis of 6 studies demonstrated reductions in the apnea-hypopnea index (AHI) with the use of GLP-1 RAs with an estimated treatment difference of -9.48 events per hour (95% CI, -12.56 to -6.40).[17] In indirect comparisons, tirzepatide was superior to liraglutide with a mean difference in AHI reductions of -21.86 events per hour versus -5.10 events per hour.[17]

Tirzepatide (ZEPBOUND) is FDA-approved for use in OSA associated with obesity based on two RCTs demonstrating reductions in AHI of -20 (95% CI, -25.8 to -14.2) and -23.8

(95% CI, -29.6 to -17.9) in patients with moderate to severe OSA and obesity, based on moderate quality of evidence.[10]

GLP-1 RAs Adverse Reactions

The most common adverse reactions with GLP-1 RAs are gastrointestinal (GI) in nature and include nausea, vomiting, diarrhea, constipation and abdominal pain.[12] Starting at low doses and increasing gradually may help to alleviate GI issues.

Certain patients should may not be candidates for take GLP-1 RAs, including the following[12]:

- Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2
- Gut motility issues or inflammatory bowel disease
- Renal impairment with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2.
- Pregnancy

Additional Considerations

Due to the high demand, high out of pocket costs for some patients, and drug shortages in some cases, patients have sought to obtain GLP-1 RAs by alternative means, such as unapproved, compounded versions.[34] The FDA has advised against the use of these products because they are not regulated for safety and efficacy, and complications and deaths have been reported in users of compounded products. Compounded versions of semaglutide and tirzepatide have been reported to cause hospitalizations related to dosing errors.[34] Dosing errors range from patients administering the wrong dose, being prescribed excessive doses, and miscalculated doses by healthcare professionals.

Counterfeit versions of semaglutide have been marketed in the United States and could potentially contain the incorrect ingredients, or product that is not intended for human use. Illegal online sales of semaglutide and tirzepatide have also been identified and may contain harmful or incorrect ingredients.[34] GLP-1 RAs should only be purchased from state-licensed pharmacies that dispense FDA-regulated products. Adverse events or quality problems should be reported to the FDA at: www.accessdata.fda.gov/scripts/medwatch/index.cfm.

It is also important to note that GLP-1 RAs and GLP-1/GIP RAs used for weight management require lifelong use to maintain weight loss. Studies have demonstrated weight regain when the medication is discontinued.

Conclusion

The existing evidence for GLP-1 RAs and GLP-1/GIP RAs use for off-label indications is limited and mostly low-quality. Most of the current evidence is from small studies that are often not powered to detect differences between groups. Additional studies are needed to verify efficacy and safety for these conditions. GLP-1 RA use for off-label uses is not covered for fee-for-service (FFS) patients, except for MASH patients who meet specifications outlined in the prior authorization criteria available at: https://www.oregon.gov/oha/HSD/OHP/Tools/Oregon%20Medicaid%20PA%20Criteria%20January%201,%202025%20KH.pdf.

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Pharmacologic Management of Vasomotor Menopausal Symptoms

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Most women experience menopause as a natural life-course event due to permanent loss of ovarian follicular activity and related estrogen production.[1] Menopause typically occurs between the age of 45 to 56 years in women with a mean age of onset around 51 years.[1] Perimenopause is characterized by cessation of the menstrual cycle and onset of vasomotor and genitourinary symptoms.[2] This newsletter will review current evidence for medications used to manage vasomotor symptoms associated with menopause and summarize Oregon Health Plan (OHP) fee-for-service (FFS) policies for these medications.

Frequency of Vasomotor Symptoms

During perimenopause, 60% to 80% of women experience vasomotor symptoms.[3] Hot flashes and night sweats are the symptoms associated with sleep and mood disturbances, as well as decreased cognitive function.[4] Hot flashes involve sudden sensations of heat in the upper body that usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety, and occasionally heart palpitations.[5] These symptoms may persist intermittently for an of average of 7 to 10 years and have a substantial negative impact on quality of life, contributing to physical and psychosocial impairment that can affect work performance, social activities, and personal and social relationships.[4]

Prevalence of vasomotor symptoms varies between different ethnic groups.[3] In the United States, the peak incidence of vasomotor symptoms is during late perimenopause with a higher incidence of frequent vasomotor symptoms and a longer duration of symptoms among Black women (median duration,10 years) and non-Hispanic White women (median duration, 9 years) compared with Chinese or Hispanic women (median duration, 5 years).[6] In all racial/ethnic groups, reports of vasomotor symptom increase as women progress from premenopause to early perimenopause and even more dramatically as they make the transition to late perimenopause.[3] Other risk factors related to severity of vasomotor symptoms include older age, body mass index (BMI) greater than 30 kg/m^2, lower education level (college-educated versus less than a college education), smoking history longer than 40 pack-years, and high baseline anxiety or depression scores.[3]

Preferred Management of Vasomotor Symptoms: Hormone Therapy

2022 guidance from North American Menopause Society (NAMS) suggests estrogen products (oral tablets, transdermal patches, topical gel) are the most effective treatment for bothersome vasomotor symptoms. They should be considered in women who need additional treatment for menopausal symptoms who do not have contraindications to estrogen therapy.[7] Estrogen therapy is Food and Drug Administration (FDA)-approved for 4 indications: moderate to severe vasomotor symptoms due to menopause; prevention of osteoporosis in postmenopausal women; treatment of hypoestrogenism caused by hypogonadism; and treatment of moderate to severe vulvovaginal symptoms.[7]

Contraindications to oral and topical estrogen treatment include a history of breast cancer, hepatic disease, cardiovascular disease, stroke, or a venous thromboembolism event (VTE).[7] In women with an intact uterus, estrogen is given in combination with a progestogen to prevent endometrial hyperplasia which increases the risk of developing endometrial cancer associated with unopposed estrogen use.[7] Systemic estrogen alone or combined with a progestogen compared to placebo reduces the frequency of vasomotor symptoms by approximately 75%.[1] A reduction in 50% or more in the severity of vasomotor symptoms is considered a clinically meaningful effect.[8] In clinical trials, a reduction of at least 2 moderate to severe hot flashes per day is considered a clinically significant reduction in frequency of symptoms.[8]

For women who cannot tolerate progestogen therapy due to side effects, bazedoxifene is an alternative treatment.). Bazedoxifene is a selective estrogen-receptor modulator (SERM) and is combined with conjugated estrogen 0.45 mg to form a tissue selective estrogen complex to provide endometrial protection without the need for progestogens.[7] The combination of bazedoxifene/conjugated estrogen (DUAVEE) is FDA-approved for managing vasomotor symptoms associated with menopause and to prevent postmenopausal osteoporosis.[9] Like other SERMs, the risk of VTE is increased with bazedoxifene.[9] The combination of conjugated estrogen 0.45 mg/bazedoxifene 20 mg in women with moderate to severe hot flashes decreases hot flash frequency by approximately 75% (versus 50% for placebo).[10]

Nonhormonal Options for Alleviating Vasomotor Symptoms

The selective serotonin reuptake inhibitor (SSRI) paroxetine at a dose of 7.5 mg, is a non-hormonal product FDA-approved to treat moderate-to-severe vasomotor symptoms associated with menopause.[11] Low-dose paroxetine reduced the frequency and severity of hot flashes by approximately 40% to 65% compared to placebo at 4 weeks, but it can

cause headache, lethargy, nausea, and vomiting.[1,11] There are no comparative trials that have evaluated efficacy of other paroxetine formulations or other antidepressants for treatment of vasomotor symptoms. Paroxetine can interfere with conversion of tamoxifen to its active metabolite, so it should not be used in women who are taking tamoxifen.[11] This SSRI formulation is not indicated for treatment of any psychiatric condition, as the dosing of paroxetine in these conditions ranges from 10 to 60 mg.[11]

In 2023 NAMS issued guidance for nonhormonal therapy for management of vasomotor menopausal symptoms. The publication recommends SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin (strong recommendation for all 3 therapies), and oxybutynin (weak recommendation) to reduce vasomotor symptoms in symptomatic women (see **Table 2**).[12] Typically, the onset of action with these medications is within 2 weeks. There are limited trials comparing nonhormone therapies with hormone therapy to alleviate vasomotor symptoms.[12]

A pooled analysis from 3 randomized controlled trials (RCTs) showed that 10 mg to 20 mg of escitalopram, 0.5 mg of estradiol, or 75 mg of venlafaxine daily resulted in comparable reductions in vasomotor frequency.[13] Hot flash reductions vary from 25% to 69% with these treatments, with improvements in composite hot flash severity and frequency from 27% to 61%.[12] Sertraline and fluoxetine have been studied, but results were not statistically different from placebo; therefore, they are not recommended.[12]

A meta-analysis of 7 RCTs studying gabapentin 900 mg (300 mg three times/day) showed gabapentin improved the frequency and severity of vasomotor symptoms.[14] Possible adverse events with gabapentin include dizziness, unsteadiness, and drowsiness, typically seen during the first week, with improvement during the second week and resolution by week 4.[14] In a placebo-controlled trial, higher doses of gabapentin (titrated to 2,400 mg/day) were as beneficial as conjugated estrogen (0.625 mg/day) in reducing hot flash severity scores.[15] Adverse events of gabapentin at this dose included dizziness, headache, and disorientation, which limit its potential benefits.[12] Because drowsiness is an adverse effect, and the half-life is short, bedtime dosing of gabapentin may be preferable for women with disruptive sleep due to vasomotor symptoms.[12]

One prospective study and 2 double-blind RCTs in postmenopausal women demonstrated that oxybutynin at doses ranging from 2.5 mg or 5 mg twice daily up to 15 mg extended-release daily at bedtime significantly improved moderate to severe vasomotor symptoms compared to placebo.[12] Adverse events of oxybutynin are usually dose-dependent and most commonly include a dry mouth and urinary difficulties. Long-term use of anticholinergics may be associated with cognitive decline, particularly in older people.[12]

Table 2. Alternatives to Hormonal Therapy for Management of Vasomotor Symptoms

Drug	Dose
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Paroxetine mesylate	7.5 mg once a day
Paroxetine HCl	10 mg-20 mg once a day
Citalopram	10 mg-20 mg once a day
Escitalopram	10 mg-20 mg once a day
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	
Venlafaxine	37.5 mg-150 mg once a day
Desvenlafaxine	100mg-150 mg once a day
Gamma-aminobutyric acid (GABA) analog	
Gabapentin	300 mg three times a day
Anticholinergic	
Oxybutynin	5mg-15 mg per day
Neurokinin 3 Receptor Antagonist	
Fezolinetant	45 mg once a day

Fezolinetant (VEOZAH), received FDA-approval in May 2023 for the treatment of moderate-to-severe vasomotor symptoms associated with menopause in people assigned female at birth.[16] Fezolinetant acts as a selective neurokinin 3 receptor antagonist, resulting in reduced episodes of hot flashes.[17] The recommended dose is 45 mg orally once daily with or without food.[16]

Two phase 3 clinical trials, Skylight 1 and Skylight 2, evaluated the efficacy of fezolinetant over 12 weeks. [18,19] The 2 co-primary endpoints were mean change in vasomotor symptom frequency (a reduction of at least 2 events per day was considered clinically significant) and change in severity of moderate-to-severe vasomotor symptoms at Weeks 4 and 12.[18,19] The mean baseline frequency of vasomotor symptoms in Skylight 1 ranged from 10.4 to 10.7 symptoms per day across the 3 treatment groups.[18] In Skylight 2, the mean baseline frequency of vasomotor symptoms ranged from 11.23 to 11.79 vasomotor symptoms per day.[19] Moderate-quality evidence showed a statistically and clinically significant reduction from baseline in vasomotor symptom frequency with fezolinetant 45 mg versus placebo in Skylight 1 and Skylight 2 at week 4 (least squares mean [LSM] difference: −2.07 and −2.55, respectively; $p<0.01$) and week 12 (LSM difference: −2.55 and −2.53, respectively; $p<0.01$).[18,19]

Severity of vasomotor symptoms was defined as mild, moderate, or severe on a 3-point scale and recorded in a daily electronic diary by study participants.[18,19] Mean symptom baseline severity scores in Skylight 1 ranged from 2.39 to 2.43.[18] In Skylight 2, the mean baseline symptom

severity scores ranged from 2.41 to 2.44.[19] Symptom severity was reduced in people taking fezolinetant 45 mg compared to placebo recipients at Week 4 (LSM difference −0.19 and −0.29; p<0.01) and Week 12 (LSM difference: −0.20 and −0.29; p<0.01; moderate-quality evidence for both endpoints).[18,19] Although statistically significant, the clinical impact of a 0.2-to-0.3-point change on a 3-point scale is relatively small.

The most common adverse effects reported with fezolinetant include abdominal pain, diarrhea, insomnia, back pain and hepatic transaminase elevations.[16] The hepatic transaminase elevations were elevated approximately 2-fold greater the upper limit of normal in some of the 45 mg fezolinetant-treated patients compared with placebo-treated patients.[8] These hepatic transaminase elevations were generally transient, and resolved while on fezolinetant 45 mg or shortly after discontinuation.[8]

In these studies, the frequency and severity of vasomotor symptoms were also reduced in the placebo group indicating a placebo effect.[18] A strong placebo effect is widely reported in studies investigating potential treatments for vasomotor symptoms.[18] Trials comparing the efficacy of SSRI's or hormone replacement therapy to neurokinin 3 receptor antagonists have not been conducted. Evidence from comparative trials would provide context for the place in therapy of fezolinetant to manage bothersome vasomotor symptoms associated with menopause.

In September 2024 the FDA issued a drug safety report that fezolinetant can cause rare but serious liver injury based on a post-marketing case in a patient who developed symptomatic acute mixed hepatocellular cholestatic liver injury with elevated liver function tests within 40 days of starting fezolinetant.[20] Liver injury resolved upon drug discontinuation.[20] The FDA added new recommendations for patients and health care professionals to increase the frequency of liver blood testing, adding monthly testing for 3 months after starting fezolinetant, and then at months 6 and 9 of treatment as already recommended.[20] In December 2024 the FDA added a black boxed warning to highlight the known risk of rare but serious liver injury associated with the use of fezolinetant. [5]

Oregon Health Plan Policy

In the Oregon fee-for-service program, claims for preferred estrogen therapies do not require prior authorization due to high-quality evidence of efficacy, safety and cost-effectiveness. Prior authorization (PA) is required before claims can be processed for fezolinetant. The PA requires a diagnosis of moderate-to-severe vasomotor symptoms due to menopause. Inadequate effect, intolerance or contraindication to a 30-day trial of menopausal hormone therapy (e.g., estrogen/progestin) is required. In addition, intolerance or contraindication to a 30-day trial of paroxetine, citalopram, venlafaxine, desvenlafaxine, or gabapentin is also required. The PA criteria require documentation of baseline hepatic function and continued monitoring to ensure safety precautions are in place. **Figure 1** summarizes the preferred and nonpreferred therapies on the Oregon Health Plan Preferred Drug List.

Figure 1. Oregon Health Plan Therapies for Management of Menopausal Vasomotor Symptoms

Preferred Hormonal Therapies: Estradiol (oral, topical, vaginal tablets), Estropipate (oral), Conjugated Estrogens (oral)

Nonpreferred Hormonal Therapies: Estradiol/Norethindrone (oral, topical), Estradiol/Levonorgestrel (topical), Estradiol (vaginal cream and ring), Estrogen/Bazedoxifene (oral)

Preferred Estrogen Alternatives: Citalopram, Desvenlafaxine, Duloxetine, Escitalopram, Gabapentin, Oxybutynin, Paroxetine, Venlafaxine

Nonpreferred Estrogen Alternatives: Fezolinetant, Paroxetine 7.5 mg

Conclusion

Hot flashes and night sweats can disrupt sleep and cause mood disturbance in women experiencing vasomotor symptoms associated with menopause.[4] Estrogen therapies (oral, topical, or vaginal) are the most effective treatment for bothersome vasomotor symptoms and should be considered in women who need treatment for vasomotor symptoms who do not have contraindications to estrogen therapy.[7] In women with an intact uterus, estrogen is given in combination with a progestogen to prevent endometrial hyperplasia or carcinoma associated with unopposed estrogen use. [7] Nonhormonal pharmacologic therapies to alleviate vasomotor symptoms associated with menopause include paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, gabapentin and oxybutynin.[12] Fezolinetant is also included in the NAMS position statement as an alternative to hormonal therapy for management of vasomotor symptoms.[12]

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Prior Authorization Criteria Update: Gene Therapy for Sickle Cell Disease

Plain Language Summary:

- The Centers for Medicare and Medicaid Services is working with two drug companies and state Medicaid agencies to make two gene therapies approved for sickle cell disease more affordable.
- To participate in this program, the current prior authorization criteria must be changed.

Purpose of Update:

The Centers for Medicare & Medicaid Services has developed the Cell and Gene Therapy (CGT) Access Model with the manufacturers of LYFGENIA™ and CASGEVY®. This model allows for outcomes-based supplemental rebate arrangements and includes other features, such as manufacturer coverage of fertility preservation for patients receiving these myeloablative gene therapies. Participation requires modifications to currently approved prior authorization criteria for participation. Both agents will be "carved-out" of the Coordinated Care Organizations to be obtained from Fee-for-Service for the sickle cell disease indications. The carve-out does not extend to other Food and Drug Administration (FDA) approved indications or off-label uses.

Recommendation:

- Modify prior authorization criteria to allow the state to participate in the Cell and Gene Therapy Access Model for sickle cell disease gene therapies.
- Make exagamglogene autotemcel (CASGEVY®) and lovotibeglogene autotemcel (LYFGENIA™) preferred.

~~Exagamglogene Autotemcel~~ Gene Therapies for Sickle Cell Disease

Goal(s):

- Approve Exagamglogene autotemcel (CASGEVY) and Lovotibeglogene autotemcel (LYFGENIA) for conditions supported by evidence of benefit

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Exagamglogene autotemcel (billed as pharmacy or provider administered claim)
- Lovotibeglogene autotemcel (billed as pharmacy or provider administered claim)

Note: Any requests on behalf of a patient enrolled in a coordinated care organization (CCO) for an indication *other than* sickle cell disease should be sent to CCO.

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 for Sickle Cell Disease		
1. What diagnosis is being treated?	Record ICD10 code. • If for sickle cell disease, continue to question #2; • If for beta thalassemia and patient is enrolled in fee-for-service, go to "Approval Criteria for Beta Thalassemia" section below; • If for beta thalassemia and patient is enrolled in a coordinated care organization (CCO), request should be directed to that CCO.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria for Sickle Cell Disease		
3. Is there documentation that the patient has never received another gene therapy or hematopoietic stem cell transplant for any diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the medication being ordered by, or in consultation with, a hematologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
~~Does patient have confirmed beta thalassemia?~~	~~**Yes**: Go to #6~~	~~**No**: Go to #7~~
~~1. Is the patient transfusion dependent, defined as requiring in each of the past 2 years:~~ ~~• 100 mL/kg/year or more of packed red blood cells (any patient age) OR~~ ~~• 8 transfusions or more of packed red blood cells per year~~	~~**Yes**: Go to #8~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
5. Does the patient have Sickle Cell Disease with recurrent vaso-occlusive crisis (VOC)? Note: Recurrent VOC defined as at least 4 or more~~2~~ VOC events~~/~~ in previous 24 months or receiving chronic transfusion therapy for recurrent VOC ~~year for more than one year~~ based on provider attestation. If lacking provider attestation, documentation of VOCs ~~Some E~~examples of VOC ~~s~~ could include, but are not limited to, acute chest syndrome, priapism lasting > 2 hours and requiring visit to medical facility, acute pain event requiring visit to medical facility ~~and~~ (with pain medications ~~[(~~e.g. opioids, injectable non-steroidal anti-inflammatory drugs~~])~~ or red blood transfusion), acute splenic sequestration, or acute hepatic sequestration.	**Yes:** Go to #6~~8~~	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient 12 years old or older?	**Yes**: Go to #7~~9~~	**No:** Pass to RPh. Deny; medical appropriateness
~~Is there documentation that the patient does not have cirrhosis or advanced liver disease?~~	~~**Yes**: Go to #10~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

Approval Criteria for Sickle Cell Disease		
~~Is there documentation that the patient does not have HIV or active infections (acute or chronic) of either hepatitis B or hepatitis C?~~	~~**Yes**: Go to #11~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
7. Does the prescriber attest that the patient's general health and comorbidities have been assessed and that the patient is expected to safely tolerate myeloablation?	**Yes**: ~~Go to #12~~ Approve for one-time infusion treatment for lifetime of the patient. Approval is valid for 12 months and will be extended if needed to cover treatment journey. Notify DMAP of approval.	**No:** Pass to RPh. Deny; medical appropriateness Notify DMAP of denial.
8. ~~Is the patient of childbearing potential OR capable of fathering a child?~~	~~**Yes:** Go to #13~~	~~**No:** Go to #15~~
9. ~~Is the patient pregnant, actively trying to conceive, or trying to father a child?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness.~~	~~**No:** Go to #14~~
10. ~~Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant or father a child during treatment and for at least 6 months after administration of the gene therapy?~~	~~**Yes:** Go to #15~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
11. ~~Is there documentation that the provider and patient have discussed risks of myeloablative treatment on future fertility and options for fertility-preservation?~~	~~**Yes:** Approve for one-time infusion treatment for lifetime of the patient.~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

Approval Criteria for Beta Thalassemia		
1. Is this an FDA approved indication?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is there documentation that the patient has never received another gene therapy or hematopoietic stem cell transplant for any diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being ordered by, or in consultation with, a hematologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does patient have confirmed beta thalassemia?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient transfusion dependent, defined as requiring in each of the past 2 years: • 100 mL/kg/year or more of packed red blood cells (any patient age) OR • 8 transfusions or more of packed red blood cells per year	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient 12 years old or older?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documentation that the patient does not have cirrhosis or advanced liver disease?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there documentation that the patient does not have HIV or active infections (acute or chronic) of either hepatitis B or hepatitis C?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the prescriber attest that the patient's general health and comorbidities have been assessed and that the patient is expected to safely tolerate myeloablation?	**Yes**: Go to #10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria for Beta Thalassemia		
10. Is the patient of childbearing potential OR capable of fathering a child?	**Yes:** Go to #11	**No:** Go to #13
11. Is the patient pregnant, actively trying to conceive, or trying to father a child?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12
12. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant or father a child during treatment and for at least 6 months after administration of the gene therapy?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is there documentation that the provider and patient have discussed risks of myeloablative treatment on future fertility and options for fertility-preservation?	**Yes:** Approve for one-time infusion treatment for lifetime of the patient. Approval is valid for 12 months and will be extended if needed to cover treatment journey.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/25; 6/24 (SF)
Implementation: TBD; 7/1/24

Lovotibeglogene Autotemcel -Retire

Goal(s):

- Approve lovotibeglogene autotemcel (LYFGENIA) for conditions supported by evidence of benefit

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Lovotibeglogene autotemcel (LYFGENIA) (billed as pharmacy or provider administered claim)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documentation that the patient has never received another gene therapy or hematopoietic stem cell transplant for any diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the medication being ordered by, or in consultation with, a hematologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have Sickle Cell Disease with recurrent vaso-occlusive crisis (VOC)? Note: Recurrent VOC defined as at least 2 VOC events/year for more than one year. Examples of VOC include acute chest syndrome, priapism lasting > 2 hours and requiring visit to medical facility, acute pain event requiring visit to medical facility and pain medications (e.g. opioids, injectable non-steroidal anti-inflammatory drugs) or red blood transfusion, acute splenic sequestration, or acute hepatic sequestration.	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient 12 years old or older?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documentation that the patient does not have cirrhosis or advanced liver disease?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is there documentation that the patient does not have α-thalassemia trait (-α3.7/-α3.7) or more than two α-globin gene deletions?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there documentation that the patient does not have HIV or active infections (acute or chronic) of either hepatitis B or hepatitis C?	**Yes**: Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the prescriber attest that the patient's general health and comorbidities have been assessed and that the patient is expected to safely tolerate myeloablation?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the patient (and/or guardian, if applicable) been educated on the risk of insertional oncogenesis and need for lifelong monitoring (bloodwork) at every 6 months?	**Yes**: Go to #12	**No**: Pass to RPh. Deny; medical appropriateness
12. Is the patient of childbearing potential OR capable of fathering a child?	**Yes:** Go to #13	**No:** Go to #15
13. Is the patient pregnant, actively trying to conceive, or trying to father a child?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #14
14. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant or father a child during treatment and for at least 6 months after administration of the gene therapy?	**Yes:** Go to #15	**No**: Pass to RPh. Deny; medical appropriateness
15. Is there documentation that the provider and patient have discussed risks of myeloablative treatment on future fertility and options for fertility-preservation?	**Yes:** Approve for one-time infusion treatment for lifetime of the patient.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/24 (SF)
Implementation: 7/1/24

OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: ~~January~~ August 2025

MISSION:

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

DUTIES:

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

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the OHA for drugs to be included on the preferred drug list (PDL).
    a. The P&T Committee may direct a Subcommittee to prepare these reviews.
2. Advise the OHA on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
3. Advise the OHA on coverage of select non-drug items (e.g., devices, digital health technologies) billed through pharmacy which includes recommending preferred products, utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
4. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs or select non-drug items, as well as the ability of Oregonians to access ~~prescriptions~~ products that are appropriate for their clinical conditions.
~~3.~~5. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs. Meeting materials including written public comments, recordings, documents, and minutes remain publicly available online after the meeting. Comments are subject to Oregon public records law and should not disclose identifiable, personal health information.
~~4.~~6. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.
~~5.~~7. Consider input from Mental Health Clinical Advisory Group (MHCAG) on topics involving mental health. The Mental Health Clinical Advisory Group can make recommendations to both the Oregon Health Authority and the Pharmacy and Therapeutics Committee for:
    a. Implementation of evidence-based algorithms.
    b. Any changes needed to any preferred drug list used by the authority.
    c. Practice guidelines for the treatment of mental health disorders with mental health drugs.

d. Coordinating the work of the group with an entity that offers a psychiatric advice hotline.

~~6.~~8. Guide and approve meeting agendas.

~~7.~~9. Periodically review and update operating procedures and evidence grading methods as needed.

AD HOC SUBJECT MATTER EXPERT INVOLVEMENT:

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

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

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

CONDUCT OF MEETINGS:

1. All meetings and notice of meetings will be held in compliance with the Oregon Public Meetings Law.
2. The P&T Committee will elect a Chairperson and Vice Chairperson to conduct the meetings.~~–~~ Elections shall be held the first meeting of the calendar year.
3. Quorum consists of 6 permanent members of the P&T Committee.~~-~~ Quorum is required for any official vote or action to take place throughout a meeting.
4. All official actions must be taken by a public vote.~~-~~ Any recommendation from the Committee requires an affirmative vote of a majority of the Committee members.
5. The committee shall meet in executive session for purposes of reviewing the prescribing or dispensing practices of individual prescribers or pharmacists; reviewing profiles of individual patients; and reviewing confidential drug or select non-drug items pricing information to inform the recommendations regarding inclusion of drugs on the Practitioner-Managed Prescription Drug Plan (PMPDP) or any preferred drug or select non-drug items lists adopted by the OHA.

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

7. Agenda items for which there are no recommended changes based on the clinical evidence may be included in a consent agenda.

    a. Items listed under the consent agenda will be approved by a single motion without separate discussion. If separate discussion is desired, that item will be removed from the consent agenda and placed on the regular business agenda.
    b. Consent agenda items may include (but are not limited to) meeting minutes, drug class literature scans, and abbreviated drug reviews for unfunded conditions.

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

CONFLICT OF INTEREST POLICY:

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

1. All potential initial committee members, staff members and consultants, future applicants, expert or peer reviewers, and ad-hoc subject matter experts selected for individual P&T Committee meetings are subject to the Conflict of Interest disclosure requirements in ORS Chapter 244 and are required to submit a completed disclosure form as part of the appointment process and annually during their appointment. Any changes in status must be updated promptly.

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

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

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

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

PUBLIC COMMENT:

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

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

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

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

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

    c. Please address written testimony related to final posted documents to the P&T Committee. Interested parties may submit written testimony on agenda items being considered by the P&T committee through the public comment link found on the P&T Committee website: (https://pharmacy.oregonstate.edu/research/drug-use-research-management/oregon-pt-committee/public-comment). Written testimony that includes clinical information should be submitted at least 2 weeks prior to the scheduled meeting to allow staff and Committee members time to review the information.

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

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

3. Written public comment is welcome from all interested parties on draft documents posted prior to the meeting.
    a. Written public comments submitted during the draft comment period are only considered by staff in order to prepare final documents. Only written public comment submitted based on final documents will be submitted to the P&T Committee for consideration.
    b. Interested parties may submit written testimony on posted draft documents through the public comment link found on the P&T Committee website: (https://pharmacy.oregonstate.edu/drug-policy/meetings).

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

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

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

DRUG AND DRUG CLASS REVIEWS:

1. Drug Class Reviews and New Drug Evaluations:

    a. The P&T Committee will review drugs and drug classes that have not been previously reviewed for PDL inclusion or for clinical PA criteria and will be prioritized based on:
        i. Potential benefit or risk
        ii. Use or potential use in covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.

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

    c. Line Extension and Combination Product Policy for existing drugs or active ingredients
        i. Line extensions include new strengths or new formulations of an existing drug.
            1. When a new strength or formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply until the new strength or formulation is presented to the P&T Committee for review.
            2. If a new strength or formulation becomes available for an existing preferred drug and the new product significantly differs from the existing medication in clinical uses or cost, the drug will not be preferred until the drug is reviewed by the P&T Committee.
        ii. When a new combination product becomes available that is a formulation of one or more drugs that have been reviewed for the PDL, the product will be designated a non-preferred drug until the P&T Committee reviews the combination product.
        iii. When a product becomes available that is a biosimilar for one or more drugs that have been reviewed for the PDL, where applicable, the product will be designated a non-preferred drug until the P&T Committee reviews the product. A complete list of biological products and biosimilar products can be accessed at the FDA's Purple Book website.

iv. Over-the-counter (OTC) formulations:
    1. When a product becomes available that is an over-the-counter formulation, the product will be added to the fee-for-service (FFS) benefit if it falls within an existing PDL class previously reviewed by P&T. The policy outlined above for line extensions will apply. Exceptions to the standard rebate process will be determined by the Oregon Health Authority on a case-by-case basis based on access, availability, and affordability.
    2. If OTC formulations that are not in an existing PDL class or are not in a drug category currently on the OTC list, then the product will be designated as not covered until the P&T Committee reviews the product.

2. Drug Class Literature Scans and Abbreviated Drug Reviews:

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

3. Non-drug Items Review:
    a. The P&T Committee will review non-drug items at the request of the OHA.
    b. Coverage decisions including recommendations for coverage, utilization management controls and inclusion of preferred products will be prioritized based on:
        i. Potential benefit or risk to patients and/or health and social care system
        ii. Use or potential use in the covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. Pragmatic usability details (e.g., user experience)
        vi. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.
    c. Evidence evaluation will follow similar methods as medication reviews with a focus on high-quality and comparative evidence that evaluates clinically relevant outcomes.

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

Review Standards and Methods for Quality Assessment of Evidence

Updated: ~~January~~ August 2025

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drugs, ~~and~~ drug classes, and select non-drug item reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the preferred drug list (PDL), preferred non-drug items, and clinical prior authorization (PA) criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices.

2. The types of reviews may include, but are not limited to, the following:

Type of Review	Rationale for Review
Abbreviated Drug Review	New drug with evidence only for non-funded condition(s)
Class Literature Scan	Used when limited literature is found which would affect clinical changes in PDL status or PA criteria based on efficacy or safety data (may include new drug formulations or expanded indications if available literature would not change PDL status or PA criteria). Provides a summary of new or available literature, and outcomes are not evaluated via the GRADE methodology listed in **Appendix D**.
New Drug Evaluation (NDE)	Single new drug identified and the PDL class was recently reviewed, or the drug is not assigned to a PDL drug class
Class Review	New PDL class
Class Update	New systematic review(s) and clinical trials identified that may inform change in PDL status or clinical PA criteria in an established PDL class
Class Update with New Drug Evaluation	New drugs(s) or indication(s) also identified (excludes new formulations, expanded indications, biosimilars, or drugs for unfunded indications)
DERP Summary Report	New DERP report which evaluates comparative evidence
Drug Use Evaluation	Analysis of utilization trends in FFS population in order to identify safety issues or inform future policy decisions
Policy Evaluation	Evaluation safety, efficacy, and utilization trends after implementation of a policy to identify areas for improvement

Prior Authorization Update	To evaluate targeted updates to PA criteria based on current policy guidance from the Health Evidence Review Commission, recommendations from the Mental Health Clinical Advisory Group, or expanded labeling from the FDA
Non-Drug Item Review (Specific non-drug items billed through pharmacy [e.g., non-durable medical equipment] as requested by Oregon Health Authority (OHA)	Assessment of products identified by OHA where pharmacy point-of-sale dispensing is considered necessary.

3. The P&T Committee will rely primarily on high quality systematic reviews and randomized controlled trials in making its evidence summary recommendations. High quality clinical practice guidelines and relevant clinical trials are also used as supplementary evidence.

4. Emphasis will be placed on the highest quality evidence available. Poor quality trials, systematic reviews or guidelines are excluded if higher quality literature is available and results offer no additional value. Unless the trial evaluates an outcome or comparison of high clinical importance, individual RCTs with the following study types will be excluded from class updates, class reviews, and literature scans:
    a. Non-comparative, placebo-controlled trials
    b. Non-inferiority trials
    c. Extension studies
    d. Poor quality studies (as assessed in **Appendix A**)

5. Individual drug evaluations rely primarily on high quality RCTs or clinical trials used for FDA approval. Evidence from poor quality RCTs may be included if there is no higher quality evidence available.

6. Phase 2 trials may be considered if there is a compelling reason to include, such as use for FDA approval. Preference will be given for inclusion of applicable phase 3 and 4 trials over earlier phase studies. If fully published, of adequate duration, and with appropriate clinical outcome measures, authors may include phase 2 studies if phase 3 or 4 trials are inadequate or when direct comparative evidence and/or dose response are reported in a comparable population to available phase 3 or 4 studies.

7. The following are preferred sources that provide high quality evidence at this time:

    a. Drug Effectiveness Review Project at Oregon Health & Science University (OHSU)
    b. U.S. Department of Veterans Affairs/Department of Defense
    c. Agency for Healthcare Research and Quality (AHRQ)
    d. Canadian Agency for Drugs and Technologies in Health (CADTH)
    e. National Institute for Clinical Excellence (NICE)
    f. Scottish Intercollegiate Guidelines Network (SIGN)
    g. Oregon Mental Health Clinical Advisory Group (MHCAG)

8. The following types of evidence are preferred and will be considered only if they are of high methodological quality as evaluated by the quality assessment criteria below:

    a. Systematic reviews of randomized controlled trials
    b. Direct comparative randomized controlled trials (RCTs) evaluating clinically relevant outcomes; placebo-controlled studies not related to initial FDA-drug approval or new indications may be considered if likely to impact current policy
    c. FDA review documents
    d. Clinical Practice Guidelines developed using explicit evidence evaluation processes

9. The following types of literature are considered unreliable sources of evidence and will rarely be reviewed by the P&T Committee:

    a. Observational studies, case reports, case series
        i. However, observational studies and systematic reviews of observational studies will be included to evaluate significant safety data beyond the FDA labeling information. Observational studies will only be included when there is not adequate data from higher quality literature.
    b. Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles) that do not include sufficient methodological details for quality evaluation, with the exception of FDA review documents
    c. Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality compared to other relevant literature, or duplicate information in other materials under review.
    d. Studies not designed to investigate clinically relevant outcomes
    e. Systematic reviews identified with the following characteristics:
        i. Evidence is of poor or very poor quality
        ii. Evidence is of limited applicability to a US population
        iii. Systematic review does not meet defined applicability criteria (PICOTS criteria) for the topic
        iv. Systematic review is of poor methodological quality as evaluated by AMSTAR II criteria (see **Appendix B**)
        v. Evidence is based on indirect comparisons from network meta-analyses
        vi. Conflicts of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)
    f. Guidelines identified with the following characteristics:
        i. There is no systematic guideline development method described
        ii. Strength of evidence for guideline recommendations are not provided
        iii. Recommendations are largely based on expert opinion
        iv. Poor methodological quality as assessed in **Appendix C** (AGREE II score is less than 113 points OR modified AGREE II-GRS score is less than 30 points)
        v. Conflict of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)

10. When assessing efficacy and safety of non-drug items (e.g., devices, digital health technologies), primary emphasis will be on studies that compare the new technology or device to currently available health and social care system technologies or the current standard of care. Included literature for medical technologies and non-drug items will focus on clinical efficacy and safety outcomes measured by relevant outcome indicators. Because the efficacy and safety of medical technologies and non-drug items may be dependent on the training and experience of the user, may be influenced by

organizational factors, and may be influenced by changes in the technology over time, pragmatic usability details (e.g., user experience) will also be included.

QUALITY ASSESSMENT

1. The standard methods used by the DURM faculty to assess quality of evidence incorporated into the evidence summaries for the OHP Pharmacy and Therapeutics Committee are described in detail in **Appendix A-C**.

2. The Cochrane Risk of Bias tool (modified) described in **Appendix A** is used to assess risk of bias (i.e., internal validity) of randomized controlled trials. The quality of non-inferiority trials will be also assessed using the additional criteria for non-inferiority trials in **Appendix A**. Internal validity of clinical trials are graded as poor, fair, or good quality.

3. The AMSTAR II measurement tool is used to assess for methodological quality of systematic reviews and is provided in **Appendix B**. Systematic reviews, meta-analyses or guidance identified from 'best sources' listed in **Appendix B** undergo methodological rigor and are considered to be high quality and are not scored for quality using the AMSTAR II tool.

4. Clinical practice guidelines are considered for inclusion after assessment of methodological quality using the AGREE II global rating scale provided in **Appendix C**. If there are concerns regarding applicability of guidelines to the Medicaid population, the AGREE-REX tool is available for use (https://www.agreetrust.org/resource-centre/agree-rex-recommendation-excellence/).

5. The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability, or directness, of randomized controlled trials to the OHP population. Detailed guidance is provided in **Appendix A**. Only randomized controlled trials with applicability to the OHP population, as assessed by the PICOS framework, are included in evidence summaries.

6. Emphasis of the review will be on clinically relevant outcomes. The following clinically relevant outcomes are graded for quality: mortality, morbidity outcomes, symptom relief, quality of life, functioning (physical, mental, or emotional), early discontinuation due to adverse events, and severe adverse effects. Surrogate outcomes are considered if directly linked to mortality or a morbidity outcome. Clinically meaningful changes in these outcomes are emphasized.

7. The overall quality of evidence is graded for clinically relevant outcomes of efficacy and harm using the GRADE methodology listed in **Appendix D**. Evaluation of evidence for each outcome of interest is graded as **high**, **moderate**, **low**, or **insufficient**. Final evidence summary recommendations account for the availability and quality of evidence for relevant outcomes and perceived clinical impact on the OHP population.

    a. Evidence grades are defined as follows:
        i. High quality evidence: High confidence that the estimated effects produced in the studies reflect the true effect. Further research is very unlikely to change the estimated effect.
        ii. Moderate quality evidence: Moderate confidence that the estimated effects produced in the studies reflect the true effect. Further research may change the estimated effect.
        iii. Low quality evidence: Limited confidence that the estimated effects produced in the studies reflect the true effect. Further research is likely to change the estimated effect.

iv. Insufficient evidence: Evidence is not available or too limited to permit any level of confidence in the estimated effect.

8. Conflict of Interest
    a. Conflict of interest is a critical component of quality assessment. A conflict of interest is "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a second interest." Conflict of interest includes any relationships or activities that could be perceived to have influenced or give the appearance of potentially influencing the literature.
        i. Reference: IOM (Institute of Medicine). 2009. *Conflict of Interest in Medical Research, Education, and Practice*. Washington, DC: The National Academies Press.

    b. Conflict of interest analysis for DURM reviews:
        1. Sources will be excluded due to conflict of interest concerns if they contain one of the "fatal flaws" in **Table 1** below.
        2. If no "fatal flaws" exist, an analysis of the conflicts of interest will be completed and any limitations (examples in **Table 1** below) will be first and foremost discussed in the evidence review.
        3. Conflict of interest is also assessed through the Cochrane risk of bias, AMSTAR II, and AGREE tools (**Appendix A, B, and C**).

Table 1. DURM Conflict of Interest Analysis

Type of literature	"Fatal flaws"	If no "fatal flaws" exist, potential limitations to discuss when including the piece of literature	Other considerations- specific to the type of literature
Randomized controlled trial	• Conflict of interest not documented	• Authors or committee members have significant conflicts of interest • Concerning high dollar amounts of conflicts of interest are documented • Mitigation strategies (described in the article or journal/organization	• Higher risk of bias when the study sponsor is the pharmaceutical manufacturer and is included in data analysis and manuscript writing
Systematic review	• Conflict of interest not documented • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* persons with potential conflicts of interest are excluded from the assessment or review process, independent second review of articles considered for inclusion in SR that are reviewed first by their own author who is on the SR team		• May consider funding sources or conflicts of interest for both the systematic review and the included studies

Guideline	• Conflict of interest not documented • Chair has a conflict of interest • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* excluding persons with significant conflict of interest from the review process, recusing members with significant conflict of interest from voting on recommendations or having them leave the room during the discussion	policies) are documented but could be more robust	• Guidelines with "fatal flaws" which are commonly used in practice may be included for clinical context but will not be considered when creating conclusions or recommendations

APPENDIX A. Methods to Assess Quality of Studies.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	Selection bias refers to **systematic differences** between **baseline characteristics of the groups** that were compared. The unique strength of proper ***randomization*** is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants. Successful randomization depends on fulfilling several interrelated processes. A rule for allocating patients to groups must be specified, based on some chance (random) process. Furthermore, steps must be taken to secure strict implementation of that schedule of random assignments by preventing foreknowledge of the forthcoming allocations. This process if often termed ***allocation concealment***.
Performance Bias	Performance bias refers to **systematic differences** between groups in the **care provided**, or in exposure to factors other than the interventions of interest. After enrolment, ***blinding participants and investigators/care givers*** will reduce the risk that knowledge of which intervention was received affected the outcomes, rather than the intervention itself. Effective blinding ensures that all groups receive a similar amount of attention, ancillary treatment and diagnostic investigations. Therefore, risk of differences in intervention design and execution, care experiences, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations and study duration between study groups are minimized.
Detection Bias	Detection bias refers to **systematic differences** between groups in how **outcomes were assessed**. ***Blinding of outcome assessors*** will reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affected outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes (eg, degree of post-operative pain).
Attrition Bias	Attrition bias refers to **systematic differences** between groups in **withdrawals** (exclusions and attrition) from a study. ***Withdrawals*** from the study lead to incomplete outcome data. There are two reasons for withdrawals or incomplete outcome data in clinical trials. ***Exclusions*** refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to assessors. ***Attrition*** refers to situations in which outcome data are not available.
Reporting Bias	Reporting bias refers to the **selective reporting of pre-specified outcomes**, on the basis of the results. Of particular concern is that statistically non-significant (negative) primary endpoints might be selectively reported while select positive secondary endpoints are over-emphasized. Selective reporting of outcomes may arise in several ways: 1) there can be selective omission of pre-specified outcomes (ie, only some of the pre-specified outcomes are reported); 2) there can also be selection of choice data for an outcome that differs from what was pre-specified (eg, there may be different time points chosen to be reported for an outcome, or different methods used to measure an outcome at the same time point); and 3) there can be selective analyses of the same data that differs from what was pre-specified (eg, use of continuous vs. dichotomous outcomes for A1c lowering, selection from multiple cut-points, or analysis of between endpoint scores vs. change from baseline).
Other Bias	Other sources of bias may be present depending on conflict of interests and funding sources, trial design, or other specific circumstances not covered in the categories above. Of particular concern is how conflicts of interest and funding sources may potentially bias results. Inappropriate influence of funders (or, more generally, of people with a vested interest in the results) is often regarded as an important risk of bias. Information about vested interests should be collected and presented when relevant, with specific regard for methodology that might be been influenced by vested interests and which may lead directly to a risk of bias. Additional sources of bias may result from trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster-randomized trials); some can be found across a broad spectrum of trials, but only for specific circumstances (e.g. contamination, whereby the experimental and control interventions get 'mixed', for example if participants pool their drugs).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials; therefore, it is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Assess each domain separately to determine if risk of each bias is likely **LOW**, **HIGH** or **UNCLEAR** (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix D**).

Conflicts of interest should also be assessed when determining risk of bias. This may be considered part of risk of reporting bias. Funding sources for the trial, conflicts of interest of the authors, and role the study sponsor played in the trial should be considered in this domain.

The quality of each trial will be graded as **good, fair,** or **poor** based on the following thresholds for converting the Cochrane Risk of Bias Tool to AHRQ Standards. A good quality trial will have low risk of bias for all domains. A fair quality trial will have one domain with high risk of bias or 2 domains with unclear bias, with the assessment that the one or more biases are unlikely to influence the outcome, and there are no known limitations which could invalidate results. A poor quality trial will have high risk of bias for one or more domains or have 2 criteria with unknown bias for which there may be important limitations which could invalidate the results or likely bias the outcome. Trials of poor quality will be excluded from review if higher quality sources of evidence are available.

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table • Coin toss	Sequence generated by: • Odd or even date of birth • Rule based on date or admission date • Hospital or clinic number • Alternating numbers	Method of randomization not described or sequence generation process not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Participants or investigators could not foresee assignment because: • Central allocation (telephone, web-based, pharmacy-controlled) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Participants or investigators could possibly foresee assignment because: • Open random allocation • Envelopes without appropriate safeguards (eg, unsealed or not opaque) • Allocation based on date of birth or case record number • Alternating allocation	Method of concealment not described or not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate sequence generation, allocation concealment, or failed randomization. *Statistical tests of baseline imbalance are not helpful for randomized trials.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, other medications, medical/surgical history, etc.)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Systematic differences in how care was provided between groups due to un-blinding of participants or investigators/care providers or because of standard of care was not consistent across all sites.	• Study participants could not identify study assignment because blinding of participants was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • Protocol standardized across all sites and followed consistently	• Study participants could possibly identify study assignment because there was no blinding or incomplete blinding • Blinding potentially broken, which likely influenced effect estimate (eg, differences easily observed in appearance, taste/smell or adverse effects between groups) • Some sites had a different standard of care or varied from protocol which likely influenced effect estimate	Not described or insufficient information to permit definitive judgment

DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Outcome assessors un-blinded	Outcome assessors could not identify study assignment because: • Blinding of assessors was ensured and unlikely broken • No blinding or incomplete blinding, but effect estimate not likely influenced by lack of blinding (ie, objective outcomes)	• Outcome data assessors could possibly identify study assignment because no blinding or incomplete blinding, which likely influenced effect estimate • Blinding potentially broken, which likely influenced effect estimate (eg, large differences in efficacy or safety outcomes between groups)	Not described or insufficient information to permit definitive judgment
ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High Drop-out rate or loss to follow-up (eg, >10% for short-term studies; >20% for longer-term studies) • Differential drop-out or loss to follow-up >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed where appropriate (eg, superiority trials) • Intention-to-treat and per-protocol analyses performed and compared where appropriate (eg, non-inferiority trials) • Reasons for missing outcome data unlikely to influence effect estimates • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.)	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of selective outcome reporting	• Study protocol is available and was followed and all pre-specified primary and secondary outcomes are reported • Study protocol is not available, but it is clear that all expected outcomes are reported	• Not all pre-specified primary and secondary outcomes reported • Primary outcome(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary outcome(s) not pre-specified (unless clear justification provided) • Failure or incomplete reporting of other outcomes of interest • Inappropriate over-emphasis of positive secondary outcomes in study with negative primary outcome	Insufficient information to make determination
OTHER BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**

Evidence of other biases not described in the categories above	• No conflicts of interest present or study sponsor was not involved in trial design, data analysis or publication • No other potential sources of bias identified	• Conflicts of interest are present based on funding source or conflicting interests of authors • Study sponsor is involved in trial design, data analysis, and publication of data • There is a run-in period with pre-randomization administration of an intervention that could enhance or diminish the effect of a subsequent, randomized, intervention • Recruitment bias in cluster-randomized trials with differential participant recruitment in clusters for different interventions • Cross-over trials in which the crossover design is not suitable, there is significant carry-over effects, or incompletely reported data (data reported only for first period) • Conduct of the study is affected by interim results ((e.g. recruiting additional participants from a subgroup showing more benefit) • Deviation from the study protocol in a way that does not reflect clinical practice (e.g. post hoc stepping-up of doses to exaggerated levels).	• Conflicts of interest for authors or funding sources are not reported or not described • Insufficient information regarding other trial methodology and design to make a determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (ie, directness) of the evidence to the OHP population (**Table 3**).

Table 3. PICOS Domains that Affect Applicability.

PICOS Domain	Conditions that Limit Applicability
Patient	• Narrow eligibility criteria and broad exclusion criteria of those with comorbidities • Large differences between the demographic characteristics between the study population and patients in the OHP • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in OHP population
Intervention	• Doses, frequency schedule, formulations or duration of intervention used in study not reflective of clinical practice • Intensity/delivery of behavioral interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparator	• Inadequate dose or frequency schedule of comparator • Use of inferior or substandard comparator relative to alternative comparators that could be used
Outcomes	• Short-term or surrogate outcomes assessed • Composite outcomes used that mix outcomes of different significance
Setting	• Standards of care in study setting differ markedly from clinical practice • Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care from highly trained/proficient practitioners in trial not reflective of typical clinical practice where intervention likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Non-inferiority (NI) trials are designed to prove a new treatment is not worse than the control treatment by a pre-determined difference, with a given degree of confidence. The pre-determined margin of difference in non-inferiority trials is defined as delta. Correctly determining this margin is a challenge in the design and interpretation of NI trials. The greatest challenge in use of NI trials is recognizing inappropriate use.

Non-inferiority trials will only be included in evidence summaries when there is a compelling reason to include them, and higher quality evidence is not available. The compelling reason for inclusion will be clearly stated as an introduction to the reporting of the NI trial.

The following template was developed using CONSORT and FDA guidance[1,2] and will be used as a guideline to evaluate non-inferiority studies included in DURM evidence summaries. Unless the trial evaluates an outcome or comparison of high clinical importance, individual non-inferiority trials will be excluded from class updates, class reviews, and literature scans. Evidence from poor quality RCTs may be included in individual drug evaluations if there is no higher quality evidence available. Items in bold (#1-5) are essential to conducting a non-inferiority trial with good methodological rigor. In general, a non-inferiority trial with high quality methods will score a "yes" on most of the components listed below.

Table 4. Non-inferiority Trial Quality Scoring Template

Developed using CONSORT and FDA guidance[1,2] **Use Template to evaluate trials supporting New Drug Evaluations and Class Update Reports** **A high-quality trial will meet all bolded assessments below**	
1. Rationale for choosing comparator with historical study results confirming efficacy (or safety) of this comparator is provided.	□ **Yes** □ **No** □ **Can't answer**
2. Active control (or comparator) represents current standard of care.	□ **Yes** □ **No** □ **Can't answer**
3. Non-inferiority margin was specified a priori and based on statistical reasoning and clinical considerations regarding benefit, risk, and cost.	□ **Yes** □ **No** □ **Can't answer**
4. Noninferiority margin is not larger than the expected difference between active control (or comparator) and placebo.	□ **Yes** □ **No** □ **Can't answer**
5. If a superiority conclusion is drawn for outcome(s) for which noninferiority was hypothesized, the justification for switching is provided and superiority analysis was defined a priori.	□ **Yes** □ **No** □ **Can't answer**
6. Investigator reported both ITT and per-protocol analysis in detail and the results of both analyses demonstrate noninferiority. (If only one analysis is provided, per protocol is subject to less bias than ITT analysis in noninferiority trials.)	□ **Yes** □ **No** □ **Can't answer**
7. Rationale for using a noninferiority design is included (or why it would likely be unethical to conduct a placebo-controlled superiority trial of the new therapy).	□ Yes □ No □ Can't answer
8. Study hypothesis is stated in terms of noninferiority.	□ Yes □ No □ Can't answer
9.Eligibility criteria for participants and the settings in which the data were collected are similar to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
10. Trial is designed to be consistent with historical placebo-controlled trials.	□ Yes □ No □ Can't answer
11. The reference treatment in the noninferiority trial is identical (or very similar) to that in any trial(s) that established efficacy (or safety).	□ Yes □ No □ Can't answer
12. The outcomes in the noninferiority trial are identical (or very similar) to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
13. The lower bound of that CI is clinically significant.	□ Yes □ No □ Can't answer
14. For the outcome(s) for which noninferiority was hypothesized, a figure showing confidence intervals and the noninferiority margin is included.	□ Yes □ No □ Can't answer
15. Results are interpreted in relation to the noninferiority hypothesis.	□ Yes □ No □ Can't answer

References:
1. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *Jama.* 2012;308(24):2594-2604.
2. FDA Industry Guidance for Noninferiority Trials. November 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.

APPENDIX B. Methods to Assess Methodological Quality of Systematic Reviews.

A measurement tool for the "assessment of multiple systematic reviews" (AMSTAR II) was developed and shown to be a validated and reliable measurement tool to assess the methodological quality of systematic reviews. There are 16 components addressed in the measurement tool below, and questions can be scored in one of four ways: "Yes", "Partial Yes", "No", or "Not Applicable". The AMSTAR II is used as a guideline to identify high quality systematic reviews eligible for inclusion in DURM evidence summaries. High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#4); characteristics of studies not provided (#8); quality of studies were not assessed or considered when conclusions were formulated (#9 and #13)). Other areas identified as important domains in the AMSTAR II criteria include registration of a protocol (#2); justification for excluding individual studies (#7); appropriateness of meta-analysis methods (#11); and assessment of publication bias (#15). In general, a high quality systematic review will score a "yes" on most components presented in the AMSTAR II tool.

Ref. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Systematic reviews or guidance identified from 'best sources' undergo methodological rigor considered to be of high quality and are not scored for quality. 'Best sources' include, but are not limited to: Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center; Agency for Healthcare Research and Quality (AHRQ); National Institute for Health and Care Excellence (NICE); U.S. Department of Veterans Affairs (VA); and Canadian Agency for Drugs and Technologies in Health (CADTH); and BMJ Clinical Evidence.

AMSTAR II Quality Scoring Template

1) Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- □ Population
- □ Intervention
- □ Comparator group
- □ Outcome

Optional (recommended)

- □ Timeframe for follow-up

□ Yes
□ No

2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:

- □ review question(s)
- □ a search strategy
- □ inclusion/exclusion criteria
- □ a risk of bias assessment

For Yes: As for partial yes, plus the protocol should be registered and should also have specified:

- □ a meta-analysis/synthesis plan, if appropriate, and
- □ a plan for investigating causes of heterogeneity
- □ justification for any deviations from the protocol

□ Yes
□ Partial Yes
□ No

3) Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- □ Explanation for including only RCTs
- □ OR Explanation for including only NRSI
- □ OR Explanation for including both RCTs and NRSI

□ Yes
□ No

4) Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes
- Partial Yes
- No

5) Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- No

6) Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- No

7) Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- Justified the exclusion from the review of each potentially relevant study

- Yes
- Partial Yes
- No

8) Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:
- described population in detail
- described intervention in detail (including doses where relevant)
- described comparator in detail (including doses where relevant)
- described study's setting
- timeframe for follow-up

- Yes
- Partial Yes
- No

9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from:
- unconcealed allocation, and
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- allocation sequence that was not truly random, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- from confounding, and
- from selection bias

For Yes, must also have assessed RoB:
- methods used to ascertain exposures and outcomes, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only RCTs

10) Did the review authors report on the sources of funding for the studies included in the review?

For Yes: Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- Yes
- No

11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:
- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- AND investigated the causes of any heterogeneity

- Yes
- No
- No meta-analysis conducted

NRSI	**For Yes:** □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	□ Yes □ No □ No meta-analysis conducted
12)	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** **For Yes:** □ included only low risk of bias RCTs □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	□ Yes □ No □ No meta-analysis conducted
13)	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?** **For Yes:** □ included only low risk of bias RCTs □ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	□ Yes □ No
14)	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** **For Yes:** □ There was no significant heterogeneity in the results □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	□ Yes □ No
15)	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** **For Yes:** □ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	□ Yes □ No □ No meta-analysis conducted
16)	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** **For Yes:** □ The authors reported no competing interests OR □ The authors described their funding sources and how they managed potential conflicts of interest	□ Yes □ No

APPENDIX C. Methods to Assess Methodological Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument (www.agreetrust.org) assesses the methodologic rigor in which a guideline is developed and used. The AGREE II is an updated instrument that has been validated. It consists of 23 items in 6 domains (scope, stakeholder involvement, rigor of development, clarity, applicability, and editorial independence) to rate (**Table 1**). Because it is time-consuming to administer, a consolidated global rating scale (GRS) was developed, and is generally a reasonable alternative to AGREE II if resources are limited. The AGREE II-GRS instrument consists of only 4 items (**Table 2**). As the AGREE II-GRS does not take into account conflicts of interest, questions 22 and 23 regarding "Editorial Independence" will also be evaluated in conjunction with the AGREE II-GRS. With both instruments, each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. High quality clinical practice guidelines are eligible for inclusion in DURM evidence summaries. These guidelines will score 6-7 points for each component on rigor of development. In general, a high quality clinical practice guideline will score 5-7 points on most components presented in the AGREE II and each component of the AGREE II-GRS.

Table 1. AGREE II Instrument.

	ITEM	DESCRIPTION
SCOPE AND PURPOSE		
1	The overall objective(s) of the guideline is (are) specifically described.	The overall objective(s) of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem or health topic. **[SCORE:]**
2	The health question(s) covered by the guideline is (are) specifically described.	A detailed description of the health questions covered by the guideline should be provided, particularly for key recommendations, although they need not be phrased as questions. **[SCORE:]**
3	The population to whom the guideline is meant to apply is specifically described.	A clear description of the population (ie, patients, public, etc.) covered by a guideline should be provided. The age range, sex, clinical description, and comorbidities may be provided. **[SCORE:]**
STAKEHOLDER INVOLVEMENT		
4	The guideline development group includes individuals from all relevant professional groups.	This may include members of the steering group, the research team involved in selection and review of the evidence and individuals involved in formulation of the final recommendations. **[SCORE:]**
5	The views and preferences of the target population have been sought.	Information about target population experiences and expectations of health care should inform the development of guidelines. There should be evidence that some process has taken place and that stakeholders' views have been considered. For example, the public was formally consulted to determine priority topics, participation of these stakeholders on the guideline development group, or external review by these stakeholders on draft documents. Alternatively, information could be obtained from interviews of these stakeholders or from literature reviews of patient/public values, preferences or experiences. **[SCORE:]**
6	The target users of the guideline are clearly defined.	The target users should be clearly defined in the guideline so the reader can immediately determine if the guideline is relevant to them. For example, the target users for a guideline on low back pain may include general practitioners, neurologists, orthopedic surgeons, rheumatologists, and physiotherapists. **[SCORE:]**
RIGOR OF DEVELOPMENT		
7	Systematic methods were used to search for evidence.	Details of the strategy used to search for evidence should be provided, which include search terms used, sources consulted, and dates of the literature covered. The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated. **[SCORE:]**
8	The criteria for selecting the evidence are clearly described.	Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. **[SCORE:]**

9	The strengths and limitations of the body of evidence are clearly described.	Statements that highlight the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions, using informal or formal tools/methods, to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. **[SCORE:]**
10	The methods for formulating the recommendations are clearly described.	A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, or formal consensus techniques (eg, Delphi, Glaser techniques). **[SCORE:]**
11	The health benefits, adverse effects, and risks have been considered in formulating the recommendations.	The guideline should consider both effectiveness/efficacy and safety when recommendations are formulated. **[SCORE:]**
12	There is an explicit link between the recommendations and the supporting evidence.	An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. **[SCORE:]**
13	The guideline has been externally reviewed by experts prior to its publication.	A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include both clinical and methodological experts. **[SCORE:]**
14	A procedure for updating the guideline is provided.	A clear statement about the procedure for updating the guideline should be provided. **[SCORE:]**
CLARITY OF PRESENTATION		
15	The recommendations are specific and unambiguous.	A recommendation should provide a precise description of which option is appropriate in which situation and in what population. It is important to note that in some instances, evidence is not always clear and there may be uncertainty about the best practice. In this case, the uncertainty should be stated in the guideline. **[SCORE:]**
16	The different options for management of the condition or health issue are clearly presented.	A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. **[SCORE:]**
17	Key recommendations are easily identifiable	Users should be able to find the most relevant recommendations easily. **[SCORE:]**
APPLICABILITY		
18	The guideline describes facilitators and barriers to its application.	There may be existing facilitators and barriers that will impact the application of guideline recommendations. **[SCORE:]**
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	For a guideline to be effective, it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer/online support. **[SCORE:]**
20	The potential resource implications of applying the recommendations have been considered.	The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff or expensive drug treatment. These may have cost implications on health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources. **[SCORE:]**
21	The guideline presents monitoring and/or auditing criteria	Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline (eg, HbA1c <7%, DBP <95 mm Hg). **[SCORE:]**
EDITORIAL INDEPENDENCE		
22	The views of the funding body have not influenced the content of the guideline.	Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations. **[SCORE:]**
23	Competing interests of guideline development group members have been recorded and addressed	There should be an explicit statement that all group members have declared whether they have any competing interests. **[SCORE:]**

Table 2. AGREE II Global Rating Scale (modified).

	ITEM	DESCRIPTION
1	Rate the guideline development methods. **[SCORE:]**	• Appropriate stakeholders were involved in the development of the guideline. • The evidentiary base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs was made.
2	Rate the guideline presentation. **[SCORE:]**	• The guideline was well organized. • The recommendations were easy to find.
3	Rate the guideline recommendations. **[SCORE:]**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
4	Rate the completeness of reporting, editorial independence. **[SCORE:]**	• The information is complete to inform decision making. • The guideline development process is transparent and reproducible.
5	The views of the funding body have not influenced the content of the guideline. **[SCORE:]**	• Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.
6	Competing interests of guideline development group members have been recorded and addressed. **[SCORE:]**	• There should be an explicit statement that all group members have declared whether they have any competing interests. • All competing interests should be listed • There should be no significant competing interests

APPENDIX D. GRADE Quality of Evidence.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) provides a framework to assess quality of evidence for an *outcome* that emphasizes transparency of how evidence judgments are made, though it does not necessarily guarantee consistency in assessment. Quality assessment in GRADE is 'outcome-centric' and distinct from quality assessment of an individual study. Information on risk of bias (internal validity), indirectness (applicability), imprecision, inconsistency, and publication bias is necessary to assess quality of evidence and overall confidence in the estimated effect size. The GRADE framework provides an assessment for each outcome.

DURM evidence summaries, unless a single drug is evaluated, depend on the whole body of available evidence. Evidence from high quality systematic reviews is the primary basis for recommendations in the evidence summaries. High quality evidence-based clinical practice guidelines and relevant randomized controlled trials are used to supplement the whole body of evidence.

High quality systematic reviews and clinical practice guidelines often use the GRADE framework to assess overall quality of evidence for a given outcome. In such cases, the grade of evidence provided in the respective report can be directly transferred to the DURM evidence summary. When an evidence summary includes relevant clinical trials, or when high quality systematic reviews or clinical practice guidelines that did not use the GRADE framework were identified, quality of evidence will be graded based on hierarchy of available evidence, homogeneity of results for a given outcome, and methodological flaws identified in the available evidence (**Table 1**).

Table 1. Evidence Grades for Benefit and Harm Outcomes When a Body of Evidence is Evaluated.

GRADE	TYPE OF EVIDENCE
High	• Evidence is based on data derived from multiple randomized controlled trials with homogeneity with regard to the direction of effect between studies AND • Evidence is based on multiple, well-done randomized controlled trials that involved large numbers of patients.
Moderate	• Evidence is based on data derived from randomized controlled trials with some conflicting conclusions with regard to the direction of effect between studies OR • Evidence is based on data derived from randomized controlled trials that involved small numbers of patients but showed homogeneity with regard to the direction of effect between studies OR • Some evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.)
Low	• Most evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.) OR • Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with homogeneity with regard to the direction of effect between studies
Insufficient	• Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with some conflicting conclusions with regard to direction of effect between studies OR • Evidence is based on data derived from expert opinion/panel consensus, case reports or case series OR • Evidence is not available

New Drug Evaluations cannot depend on evidence from systematic reviews and clinical practice guidelines. A body of evidence that solely consists of one or more clinical trials is initially assigned 4 points. For every relevant limitation, points are deducted; but points are added for consistently large effect sizes between studies or for a consistent dose-response observed in the studies (**Table 2**). The quality of evidence is subsequently graded as shown:

QUALITY OF EVIDENCE GRADES:

- ≥4 points = **HIGH**
- 3 points = **MODERATE**
- 2 points = **LOW**
- ≤1 point = **INSUFFICIENT**

Table 2. Domains to Grade Evidence for Benefit and Harm Outcomes from Clinical Trials: Cochrane Evidence Grades (modified).

DOMAIN	DESCRIPTION	SCORE DEMOTION/PROMOTION (start with 4 points)
Risk of Bias (internal validity)	Risk of bias is the likelihood to which the included studies for a given comparison and outcome has an inadequate protection against bias that affects the internal validity of the study. • *Did any studies have important limitations that degrade your confidence in estimates of effectiveness or safety?*	• No serious limitation: all studies have low risk of bias: **(0)** • Serious limitations: ≥1 trial has high or unclear risk of bias: **(-1)** • Very serious limitations: most studies have high risk of bias: **(-2)**
Indirectness (applicability)	Directness (applicability) relates to evidence that adequately compares 2 or more reasonable interventions that can be directly linked to a clinically relevant outcome in a population of interest. • *Do studies directly compare interventions of interest in populations of interest using outcomes of interest (use of clinically relevant outcomes)?*	• Direct: clinically relevant outcomes of important comparisons in relevant populations studied: **(0)** • Indirect: important comparisons missing; surrogate outcome(s) used; or population not relevant: **(-1)**
Inconsistency	Inconsistency (heterogeneity) is the degree to which reported effect sizes from included studies appear to differ in direction of effect. Effect sizes have the same sign (ie, are on the same side of ''no effect'') and the range of effect sizes is narrow. • *Did trials have similar or widely varying results? Can heterogeneity be explained by differences in trial design and execution?*	• Large magnitude of effect consistent between studies: **(+1)** • Dose-response observed: **(+1)** • Small magnitude of effect consistent between studies: **(0)** • 1 study with large magnitude of effect: **(0)** • 1 study with small magnitude of effect: **(-1)** • Inconsistent direction of effect across studies that cannot be explained: **(-1)**
Imprecision	Imprecision is the degree of uncertainty surrounding an effect estimate with respect to a given outcome (ie, the confidence interval for each outcome is too wide to rule out no effect). • *Are confidence intervals for treatment effect sufficiently narrow to rule out no effect?*	• Precise: all studies have 95% confidence intervals that rule out no effect: **(0)** • Imprecise: ≥1 study demonstrated 95% confidence interval fails to rule out no effect: **(-1)**
Publication Bias	Publication bias is the degree in which completed trials are not published or represented. Unpublished studies may have negative outcomes that would otherwise change our confidence in the body of evidence for a particular comparison and outcome. • *Is there evidence that important trials are not represented?*	• No publication bias: all important trials published or represented: **(0)** • Serious publication bias: ≥1 important trial(s) completed but not published: **(-1)**

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

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Prior Authorization Review: New Drug Policy

Purpose for the Review:
In January 2018, the following prior authorization (PA) criteria for new drugs was implemented. At this time, the policy was modified to include evaluation of new drugs costing more than $5000 per claim or per month. The goal of this policy was to evaluate use of high cost agents and prevent inappropriate off-label use until reviewed by the Oregon Pharmacy & Therapeutics Committee. Due to system limitations and because new physician administered drugs often do not have specific billing codes, this PA was only implemented for point-of-sale pharmacy claims.

Since implementation of the new drug policy, other criteria for orphan drugs and newer oncology agents have been implemented. The purpose of this review is to assess the ongoing utility of the new drug policy.

Since the 1/1/2022, there have been 64 new molecular entities that have been included in this policy upon approval by the Food and Drug Administration (FDA). Of these, 31 (48%) have been subsequently included in the orphan drug policy, and specific prior authorization criteria has been developed or implemented for 25 (39%) drugs. The remaining 8 agents (13%) to which this policy currently applies are listed in **Table 1**. The majority of agents which meet criteria for this policy have an orphan drug designation from the Food and Drug Administration (FDA), and claims for these agents are generally infrequent. No new safety concerns were identified.

Table 1. New high cost drugs

Generic	Brand	Orphan Drug Status	Indication
Atrasentan	VANRAFIA	N	Primary immunoglobulin A nephropathy
Concizumab-mtci	ALHEMO	Y	Hemophilia
Fidanacogene elaparvovec-dzkt	BEQVEZ	Y	Hemophilia
Fitusiran sodium	QFITLIA	Y	Hemophilia
Marstacimab-hncq	HYMPAVZI	Y	Hemophilia
Nipocalimab-aahu	IMAAVY	Y	Myasthenia gravis
Olezarsen	TRYNGOLZA	Y	Familial chylomicronemia syndrome
Resafungin acetate	REZZAYO	Y	Invasive candidiasis

Conclusion and Recommendation:

- The majority of drugs which qualify for this criteria are orphan drugs or are eventually reviewed by P&T Committee.
- No policy changes are recommended.

New Drug Policy

Goal:

- Restrict coverage of selected new drugs until the Oregon Pharmacy & Therapeutics Committee can review the drug for appropriate coverage. New drug criteria will apply until drug specific criteria are developed or for a maximum of 1 year (whichever is less). This policy does not apply to new oncology drugs.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 6 months

Requires PA:

A new drug, identified by the reviewing pharmacist during the weekly claim processing drug file load, which is not subject to existing prior authorization criteria, costing more than $5,000 per claim or $5,000 per month based on wholesale acquisition cost.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the medication FDA-approved for the requested indication and does the requested dosing align with the FDA-approved dosing?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
5. Is baseline monitoring recommended for efficacy or safety and has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the requested therapy have an orphan drug designation and is this the only FDA-approved therapy for the funded condition?	**Yes:** Approve for up to 6 months or length of treatment (whichever is less).	**No:** Go to #7

7. Pass to RPh.
   If funded: The prescriber must provide documentation that alternative drugs approved by the FDA for the funded condition are not appropriate due to history of therapeutic failure, an adverse event, or a contraindication. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.

   If not funded:
   a. If member is eligible for EPSDT review; Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?
      i. Is yes, The prescriber must provide documentation that alternative drugs approved by the FDA for the funded condition are not appropriate due to history of therapeutic failure, an adverse event, or a contraindication. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.
      ii. If No, Deny (medical appropriateness)
   b. If member is not eligible for EPSDT review: Deny; not funded by the OHP.

P&T / DUR Review: *7/18 (SS); 11/17; 11/15; 12/09*
Implementation: *8/15/18; 1/1/18; 1/1/16; 1/1/10*

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Drug Class Update: Antipsychotics
New Drug Evaluation: LYBALVI (olanzapine/samidorphan) oral tablets

Date of Review: August 2025

Date of Last Review: August 2020
April 2021 (pediatrics)

Dates of Literature Search: 1/1/2020-4/22/2025

Generic Name: olanzapine/samidorphan

Brand Name (Manufacturer): LYBALVI (Alkermes, Inc).

Dossier Received: no

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

Purpose for Class Update:
Evidence for antipsychotics was last reviewed by the Oregon Pharmacy & Therapeutic (P&T) Committee in August 2020. This review examines recently published comparative evidence of antipsychotics for major depressive disorder (MDD), schizophrenia, and bipolar disorder. In addition, evidence for the safety and efficacy of LYBALVI (olanzapine/samidorphan) oral tablets for treatment of schizophrenia and bipolar I disorder in adults will be evaluated.

Plain Language Summary:
- Antipsychotics are used to relieve symptoms such as delusions (false beliefs) or hallucinations (seeing or hearing something that is not there) that can occur in people with schizophrenia. In people with bipolar disorder, antipsychotics can help manage mania or depression. When people with major depressive disorder do not respond to antidepressant medicines, certain antipsychotics can be added to help manage the symptoms of depression.
- Most studies of antipsychotic medicines compare their effects to placebo (a sugar pill). No studies have shown that one antipsychotic is better than another in treating mental health symptoms.
- Side effects reported with antipsychotics include tremors, restlessness, muscle stiffness, dizziness, weight gain, diabetes, or sleepiness. Providers will often prescribe the lowest dose that helps with symptoms to reduce risk of these side effects.
- The Food and Drug Administration approved a combination medicine, LYBALVI (olanzapine/samidorphan) for adults with schizophrenia or bipolar I disorder. The antipsychotic in this medication, olanzapine, is effective for symptoms of schizophrenia and bipolar disorder, but it can cause weight gain. Samidorphan is combined with olanzapine to reduce the amount of weight people gain from taking olanzapine. In a 24-week study, people taking samidorphan/olanzapine gained an average of 7 pounds, compared with people taking only olanzapine, who gained 11 pounds.
- The Oregon Health Plan will pay for most antipsychotic medicines for members with a valid prescription. The Oregon Health Authority requires providers to submit documentation before they will pay for an antipsychotic when there are specific safety concerns for the medicine or the member (such as people less than 6 years old).

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Research Questions:

Antipsychotic Class Update

- What is the comparative effectiveness of antipsychotic drugs for people with MDD, schizophrenia, or bipolar disorder?
- What are the harms of antipsychotic drugs for people with MDD, schizophrenia, or bipolar disorder?
- Does effectiveness or safety of antipsychotics vary by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing)?

New Drug Evaluation: Olanzapine/Samidorphan

- What is the effectiveness of olanzapine/samidorphan in treating adults with schizophrenia or bipolar I disorder?
- What are the harms of olanzapine/samidorphan in treating adults with schizophrenia or bipolar I disorder?
- Does the effectiveness or safety of olanzapine/samidorphan vary by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing)?

Conclusions:

- Since the last P & T Committee review, 7 high-quality systematic reviews[1-7] have been published and 6 high-quality guidelines[8-14] have been updated.

<u>Major Depressive Disorder</u>

- A 2024 DERP systematic review identified that adjuvant use of the following second-generation antipsychotics (SGAs) improved symptoms of MDD compared to placebo: aripiprazole (12 RCTs), brexpiprazole (5 RCTs), cariprazine (5 RCTs), olanzapine (1 RCT), olanzapine/fluoxetine (5 RCTs), pimavanserin (2 RCTs), quetiapine (10 RCTs), risperidone (5 RCTs), and ziprasidone (2 RCTs).[2] Moderate-quality evidence showed aripiprazole, brexpiprazole, cariprazine and quetiapine improved results in assessments of depression when compared to placebo.[2]
- Pimavanserin and ziprasidone, which are not approved by the FDA for MDD, have insufficient evidence or appear to be ineffective for use as adjunctive treatments for depression.[2]
- The most common adverse events with adjunct use of SGAs in MDD included akathisia and weight gain.[2] Rates of akathisia were highest with aripiprazole and were slightly lower in patients taking brexpiprazole and cariprazine.[2] Patients taking the olanzapine/fluoxetine combination, quetiapine, ziprasidone, risperidone, and pimavanserin did not experience any significant movement AEs, including akathisia over the 6 to 12 week study periods.[2] When using aripiprazole, there is a moderate risk of akathisia, and patients prescribed olanzapine/fluoxetine should be monitored for weight gain.[2]

<u>Schizophrenia</u>

- A 2025 Drug Effectiveness Review Project (DERP) systemic review evaluating COBENFY (xanomeline/trospium) for schizophrenia found low-quality evidence that xanomeline/trospium is effective in alleviating symptoms of schizophrenia when compared to placebo.[1] Primary adverse effects observed with xanomeline/trospium include gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal pain and constipation.[1]
- There is insufficient evidence to determine the comparative efficacy of lurasidone versus haloperidol in adults with schizophrenia based on results from 2 RCTs (n=308) that were conducted over 4 to 6 weeks.[3] The evidence is very uncertain about the effects of lurasidone compared with haloperidol on change in mental state as measured by the Brief Psychiatric Rating Scale (BPRS) (mean difference [MD] 3.74, 95% confidence interval [CI] 0.57 to 6.90; 1 RCT, 281 participants; very low-certainty evidence); and the Positive and Negative Syndrome Scale PANSS (MD 6.68, 95% CI 2.45 to 10.91; 1 RCT, 281 participants; very low-certainty evidence). The evidence is also very uncertain about the effects of lurasidone compared to haloperidol on total serious adverse events (RR 0.98, 95% CI 0.37 to 2.60; 2 RCTs, 303 participants; very low certainty of evidence) and on severe adverse events (RR 1.70, 95% CI 0.46 to 6.32; 1 RCT, 281 participants; very low certainty of evidence).[3]

- A 2025 Cochrane review concluded that there was insufficient evidence to examine the effects of switching antipsychotic drugs in adults with schizophrenia who had not responded to initial antipsychotic treatment compared to continuing the same therapy.[4] The evidence is very uncertain regarding the effect of switching antipsychotics on clinically relevant response, quality of life, PANSS score change, duration of hospitalization, and the number of people experiencing at least one adverse effect.[4] Most of the studies were small; only 3 studies had more than 100 patients.[4]
- Compared to oral olanzapine in people with schizophrenia, oral haloperidol may have similar effects on clinically important change in global state using the Clinical Global Impression Scale (CGI) scale (RR 0.84, 95% CI 0.69 to 1.02; I^2 =73%; 6 studies, 3078 participants; very low-certainty evidence) and similar incidence of relapse (RR 1.42, 95% CI 1.00 to 2.02; I^2 =75%; 7 studies, 1499 participants; very low-certainty evidence).[5] Haloperidol may result in more extrapyramidal side effects compared to olanzapine (RR 3.38, 95% CI 2.28 to 5.02; 14 studies, I^2 =72%; 3290 participants; low-certainty evidence), but less weight gain (RR 0.47, 95% CI 0.35 to 0.61; I^2 = 57%; 18 studies, 4302 participants; low-certainty evidence).[5]
- In people with agitation and psychosis related to Alzheimer's disease and vascular dementia, it is uncertain if first-generation antipsychotics (FGAs) improve agitation compared to placebo (standardized mean difference (SMD) -0.36, 95% CI -0.57 to -0.15, 4 studies, n = 361; very low-certainty evidence), but they may have a small improvement for psychosis (SMD -0.29, 95% CI -0.55 to -0.03, 2 studies, n= 240; low-certainty evidence).[6] SGAs probably reduce agitation by a small amount (SMD -0.21, 95% CI -0.30 to -0.12, 7 studies, n = 1971; moderate-certainty evidence), but probably have very little effect on psychosis (SMD -0.11, 95% CI -0.18 to -0.03, 12 studies, n = 3364; moderate-certainty evidence) compared with placebo.[6] Both FGAs and SGAs probably increase the risk of somnolence and extrapyramidal symptoms.[6]
- In people with schizophrenia spectrum disorders and antipsychotic-induced weight gain, off-label use of metformin, topiramate, and aripiprazole improved metabolic symptoms, such as weight loss and reduction in waist circumference.[7] Aripiprazole augmentation (SMD = –0.73, 95% CI –0.97 to –0.48, p<0.001; 9 trials, N=813, I^2=68%), topiramate (SMD = –0.72, 95% CI –1.56 to –0.33, p<0.001; 15 trials, N=783, I^2=92.7%), and metformin (SMD = –0.53, 95% CI –0.69 to –0.38, p<0.001; 29 trials, N=1,279, I^2=39.4%) had a medium effect size on the combined outcomes of weight loss and reduction in weight circumference.[7]
- In 2023, the Veterans Affairs (VA)/Department of Defense (DoD) updated guidance for schizophrenia.[8] Because antipsychotics (with the exception of clozapine) have similar efficacy, recommendations were issued for antipsychotics as a class, rather than each medication individually.[8]
    - The VA/DoD recommends antipsychotics other than clozapine for an acute schizophrenia episode, for first-episode psychosis, and for maintenance treatment of schizophrenia to prevent relapses and hospitalization in people who have previously responded to an antipsychotic (Strong Recommendation; Moderate-Quality Evidence).[8]
    - The VA/DoD suggests a trial of another antipsychotic for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic medication (Weak Recommendation; Very Low-Quality Evidence).[8]
    - The VA/DoD suggests offering long-acting injectable (LAI) antipsychotics to improve medication adherence in individuals with schizophrenia (Weak Recommendation; Very Low-Quality Evidence).
    - The VA/DoD recommends clozapine for people with treatment-resistant schizophrenia (Strong Recommendation; Moderate-Quality Evidence).[8]
    - The VA/DoD suggests augmenting clozapine with another second-generation antipsychotic medication for individuals with treatment-resistant schizophrenia who have not experienced an adequate response to clozapine (Weak Recommendation; Very Low-Quality Evidence).[8]
    - The VA/DoD suggests using metformin, topiramate, or aripiprazole augmentation for treatment of metabolic side effects of antipsychotic medication and weight loss for individuals with schizophrenia (Weak Recommendation; Moderate-Quality Evidence).[8]

<u>Bipolar Disorder</u>

- The VA/DoD updated guidance in 2023 for management of bipolar disorder including treatment for: (1) acute mania, (2) acute depression, and (3) maintenance to prevent recurrences of both mania or depression.[9]
  For Treatment of Acute Bipolar Mania, the VA/DoD:
    - suggests lithium or quetiapine as monotherapy (Weak Recommendation; Low-Quality Evidence).[9]

- suggests olanzapine, paliperidone, or risperidone as monotherapy if lithium or quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Very Low-Quality Evidence).[9]
- suggests aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy if the options above are not selected based on patient preference and characteristics (Weak Recommendation; Low-Quality Evidence).[9]
- suggests lithium or valproate in combination with haloperidol, asenapine, quetiapine, olanzapine, or risperidone in individuals who had an unsatisfactory response or a breakthrough episode on monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
- suggests against the addition of aripiprazole, paliperidone, or ziprasidone after unsatisfactory response to lithium or valproate monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
- suggests against brexpiprazole, topiramate, or lamotrigine as a monotherapy (Weak Recommendation; Very Low-Quality Evidence).[9]

For Treatment of Acute Bipolar Depression, the VA/DoD:

- recommends quetiapine as monotherapy (Strong Recommendation; Moderate-Quality Evidence).[9]
- suggests cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy if quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Low-Quality Evidence).[9]
- suggests lamotrigine in combination with lithium or quetiapine (Weak Recommendation; Very-Low Quality Evidence).[9]

Maintenance Treatment to Prevent Relapse:

- To prevent recurrence of mania, the VA/DoD:
  - recommends lithium or quetiapine (Strong Recommendation; Moderate-Quality Evidence).[9]
  - suggests oral olanzapine, oral paliperidone, or LAI risperidone If lithium or quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Low-Quality Evidence).[9]
  - suggests against lamotrigine as monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
  - suggests aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate (Weak Recommendation; Very Low-Quality Evidence).[9]
- To prevent recurrence of bipolar depressive episodes, the VA/DoD:
  - recommends lamotrigine (Strong Recommendation; Moderate-Quality Evidence).[9]
  - suggests lithium or quetiapine as monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
  - suggests olanzapine as monotherapy if lithium or quetiapine is not selected based on patient preference and characteristics (Weak Recommendation; Moderate-Quality Evidence).[9]
  - suggests olanzapine, lurasidone, or quetiapine in combination with lithium or valproate (Weak Recommendation; Low-Quality Evidence).[9]

- Guidance updated from the VA/DoD in 2022 suggests adding an SGA for people with MDD who have not responded (< 50% improvement in symptoms) to adequate antidepressant treatment trials (i.e., bupropion, mirtazapine, trazodone, vilazodone, vortioxetine, selective serotonin reuptake inhibitors [SSRIs], or serotonin norepinephrine reuptake inhibitors [SNRIs]) for 6 to 12 weeks (Weak Recommendation; Low-Quality Evidence).[10]
- The Oregon Mental Health Clinical Advisory Group (MHCAG) has developed treatment algorithms for management of schizophrenia,[11] MDD,[14] and bipolar disorder.[12,13] The MHCAG recommendations are similar to the guidance developed by the VA/DoD.

<u>New Indications and Formulations</u>

- December 2021: CAPLYTA (lumateperone) oral capsules received an expanded FDA-approved indication for treatment of depressive episodes associated with bipolar I or II disorder in adults, as monotherapy or as adjunctive therapy with lithium or valproate.[15] Prior to this approval, lumateperone was FDA-approved for the treatment of adults with schizophrenia.[15]
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- December 2021: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for management of schizophrenia in pediatric patents aged 13 to 17 years.[17] Prior to this approval, brexpiprazole was approved for use as adjunctive therapy for treatment of MDD in adults and treatment of schizophrenia in adults.[17]
- December 2022: VRAYLAR (cariprazine) oral capsules were approved as adjunctive therapy to antidepressants for the treatment of MDD in adults.[16] Prior to this approval, cariprazine was FDA-approved for treatment of schizophrenia and bipolar disorder in adults.[16]
- May 2023: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for treatment of agitation associated with dementia due to Alzheimer's disease (AAD).[17] Although the current standard of care for AAD consists of non-pharmacological and off-label pharmacological treatments (e.g., antipsychotics, benzodiazepines, antidepressants, antiepileptics), prior to this approval there were no FDA-approved treatment options for AAD.[18] Brexpiprazole has a boxed warning for increased risk of mortality in elderly patients with dementia-related psychosis, based on a meta-analysis the FDA conducted in 2005.[18]
- April 2024: FANAPT (iloperidone) received an expanded indication for acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.[19] Prior to this approval, iloperidone was FDA-approved to treat schizophrenia in adults.[19]
- March 2024: A new extended-release injectable formulation of risperidone, RISVAN, received FDA-approval for treatment of schizophrenia in adults.[20]
- July 2024: OPIPZA, a new oral film formulation of aripiprazole, received FDA approval for: treatment of schizophrenia in patients ages 13 years and older, adjunctive treatment of MDD in adults, irritability associated with autistic disorder in pediatric patients aged 6 years and older, and treatment of Tourette's disorder in pediatric patients aged 6 years and older.[21]
- July 2024: ERZOFRI, a new formulation of extended-release injectable paliperidone received FDA-approval for treatment of schizophrenia in adults and treatment of schizoaffective disorder in adults as monotherapy or as an adjunct to mood stabilizers or antidepressants.[22]
- There is insufficient evidence to determine if antipsychotic effectiveness or safety varies by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing).

<u>New Drug Evaluation: Olanzapine/Samidorphan</u>

- LYBALVI, a combination of olanzapine and samidorphan, is FDA-approved for adults with schizophrenia or bipolar I disorder as maintenance monotherapy or adjunct to lithium or valproate for acute manic or mixed episodes.[23]
- There is insufficient evidence to compare olanzapine/samidorphan to other therapies for patients with bipolar I disorder. FDA-approval was based upon studies of oral olanzapine.[23]
- In adult patients (n=403) hospitalized with an acute exacerbation of schizophrenia, olanzapine/samidorphan improved symptoms compared with placebo at Week 4 (least square mean [LSM] change in PANSS from baseline, -17.5 vs. -23.9; difference, -6.4; 95% CI -10.0 to -2.8; moderate-quality evidence).[24] There is no MICD for changes in PANSS total score, although response to treatment is typically defined in most clinical trials as greater than 20% improvement in the PANSS score.[25]
- In clinically stable outpatients (n=561) with schizophrenia, olanzapine/samidorphan had a smaller percent change in body weight over 24 weeks (4.21%) compared to 6.59% with olanzapine (difference, -2.38%; 95% CI, -3.88% to -0.88%; p=0.002; low-quality evidence).[26] The proportions of people with weight gain of 10% or more from baseline was 17.8% in the olanzapine/samidorphan group and 29.8% in the olanzapine group (difference, 12%; 95% CI, -22.8 to -4.6; p=0.003; number needed to treat (NNT) = 8; low-quality evidence).[26]
- The most common adverse effects reported with olanzapine/samidorphan were increased weight, somnolence, dry mouth, and headache.[23] The adverse effects reported in the 4-week ENLIGHTEN-1 trial are presented in **Table 13**. Adverse reactions that led to study discontinuation in ENLIGHTEN-1 included abnormal liver function tests and worsening schizophrenia in 1% of participants.[23] Adverse effects reported in the 24-week ENLIGHTEN-2 trial are summarized in **Table 14**.

- There is insufficient evidence to show that the effectiveness or safety of olanzapine/samidorphan varies by patient characteristics (e.g. diagnosis, age, duration of disease) or social determinant of health status (e.g. lack of stable housing).

Recommendations:

- Based on review of recent clinical evidence, no changes to the Preferred Drug List (PDL) are recommended for FGA, SGA, or parenteral antipsychotics.
- Evaluate medication costs in executive session.

Summary of Prior Reviews and Current Policy:

- The last P &T Committee review of antipsychotics drugs was at the August 2020 meeting. No changes to the preferred drug list (PDL) were recommended for oral or parenteral antipsychotics based on efficacy or safety data. After evaluating costs in the executive session, aripiprazole tablets and ziprasidone capsules were designated as preferred on the PDL.
- In the Oregon Health Plan, antipsychotic medications are exempt from traditional PDL requirements. However, clinical PA criteria, which address safety concerns or medically inappropriate use, may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use, for pimavanserin to promote safe use in patients with Parkinson's disease psychosis, for antipsychotics in children to discourage off-label use not supported by compendia, and to ensure safety of xanomeline/trospium in combination with other mental health drugs. The PA criteria for these safety edits are outlined in **Appendix 6**.
- The FGA, SGA, and parenteral antipsychotics included on the Oregon PDL are presented in **Appendix 2.** The preferred FGAs include oral chlorpromazine, fluphenazine, haloperidol, thioridazine, thiothixene, and trifluoperazine. Oral aripiprazole, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone are preferred SGAs on the PDL. Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, paliperidone, risperidone, and trifluoperazine are preferred on the PDL.
- Each quarter, approximately 33,000 patients receive a prescription for an SGA and 1,200 patients have claims for an FGA. Most of the antipsychotic drug use in the Oregon Medicaid population is for preferred oral SGAs, including aripiprazole, quetiapine, and olanzapine. Approximately 5% of antipsychotic drug claims are for parenteral formulations. Paliperidone and aripiprazole are the most frequently prescribed injectable agents in this class.
- Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms for schizophrenia, bipolar mania or MDD. There is insufficient evidence to determine if new formulations of long acting injectable (LAI) aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents.

Background:

Antipsychotic medications are typically categorized as first-generation and second-generation. First generation antipsychotics (FGAs) such as haloperidol and chlorpromazine are dopamine receptor antagonists and block histamine, muscarinic and alpha-1 receptors.[27] Second generation antipsychotics (SGAs) are serotonin-dopamine antagonists, and carry less risk of extrapyramidal symptoms, such as dystonic reactions, akathisia and tardive dyskinesia, that are associated with FGAs.[27] The main adverse effects of SGAs include weight gain, glucose intolerance and hyperprolactinemia.[27] Antipsychotic medications are indicated for a variety of conditions including schizophrenia and schizoaffective disorder, bipolar disorder (acute and maintenance treatment), adjunct treatment for depression, autism, and Tourette's syndrome.[27] They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression and nausea or vomiting.[27]

Major Depressive Disorder

Major depressive disorder is defined as the presence of a depressed mood or a loss of interest or pleasure in normally enjoyable activities that occurs along with at least 4 additional diagnostic criteria or symptoms for at least 2 weeks (see **Appendix 3, Table 17** for specific diagnostic criteria).[28] Based upon functional impairment, severity of symptoms, and level of patient distress, MDD can be assessed as mild, moderate or severe (see **Appendix 3, Table 18** for severity assessments). One-third of patients with MDD have severe MDD, which is more difficult to treat and achieve remission than other forms of MDD.[29]

Major depressive disorder is a common cause of disability, leading to substantial costs to individuals and society.[30,31] Costs to an individual may include emotional suffering, reduced quality of personal relationships, possible adverse effects from treatment, cost of mental health and medical visits and medications, time away from work and lost wages, and cost of transportation.[31] Costs to society may include loss of life, reduced productivity (because of both diminished capacity while at work and absenteeism from work), and increased costs of mental health and medical care.[31] In the United States (U.S.), more than 20% of adults experience MDD in their lifetime, with around 10% experiencing MDD in a given year.[32]

Over 60% of patients with MDD have no response or achieve only a partial response to an antidepressant.[2] Guideline directed therapies to achieve remission in treatment-resistant depression include addition of lithium or a SGA to antidepressant therapy.[33] Antipsychotics are effective adjunctive treatments for patients who have not responded to multiple antidepressant trials.[34] The FDA-approved SGAs for adjunctive treatment of MDD include aripiprazole, brexpiprazole, cariprazine, lurasidone, quetiapine, and the combination of olanzapine with fluoxetine.[27]

Goals of treatment for depression include symptom and function improvement, remission, and relapse prevention.[33] Rating scales used to assess symptom improvement include the MADRS and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[35] The HAM-D is a clinician-rated, 17- item scale with a range of 0 to 52 points, with higher scores indicating more severe depression.[35] Remission is defined being free from depressive symptoms for several months after two or more depressive episodes.[35] Response to therapy is typically defined as a 50% improvement in symptom score from baseline.[35] A 2-point improvement on the MADRS may be associated with a minimum clinically important improvement and decreases in HAM-D scores of 3 to 7 points may be clinically significant.[35] Additional outcome assessments for MDD are presented in **Appendix 3, Table 19**.

Schizophrenia

Schizophrenia is a mental health disorder characterized by presence of positive symptoms (delusions, hallucinations, disorganized speech, thought and behavior), negative symptoms (blunted affect, lack of speech or social interactions, anhedonia, and decreased motivation), and cognitive symptoms (impaired executive function, attention, and memory).[36] Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of: 1) at least one positive symptom with 2 or more total symptoms characteristic of schizophrenia and 2) social or occupational disruption in work, relationships, or self-care.[37] Symptoms and social dysfunction generally persist for at least 6 months in the absence of alternative medical causes.[37] Schizophrenia has a lifetime prevalence of about 1%.[38] The prevalence of schizophrenia based on gender, race and ethnicity may vary.[36] Diagnosis of schizophrenia may be 3-5-times more common in Black and Hispanic populations compared to white populations and more common in males than females.[36,39] However, data also shows there may be an increased risk for misdiagnoses of psychiatric conditions in non-white populations.[39]

Onset of schizophrenia symptoms occurs most commonly in early adulthood and can have a significant impact on quality of life, social relationships, and occupational status.[39] Less than 20% of patients who experience first-episode psychosis will remain relapse-free over their lifetime, and at least one-third of patients continue to have symptoms despite treatment.[39] Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, slow symptom onset, and symptom presentation at an earlier age.[39] Schizophrenia has been associated with increased

risk of overall mortality, mortality due to suicide, substance use disorders, cognitive impairment, and chronic medical conditions (e.g., diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease).[39] Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within 1 year after their last episode; most relapses occur when patients stop taking their medication.[26]

Antipsychotic medications are the primary treatment recommended for schizophrenia. Medication selection is dependent on risks for adverse effects, patient preferences, prior treatment response, and availability of a long-acting formulation.[40] All antipsychotic medications are associated with adverse effects that limit medication tolerability and contribute to treatment discontinuation. Adverse effects related to antipsychotic use include sedation, metabolic (e.g., weight gain, diabetes, hypertension, dyslipidemia), cardiovascular (e.g., QT prolongation), hormonal (e.g., elevated prolactin levels, sexual dysfunction), and movement disorders (e.g., akathisia, dyskinesias, dystonia, parkinsonism).[36,39] Antipsychotics with LAI formulations include aripiprazole, risperidone, paliperidone, fluphenazine, and haloperidol. The Oregon Mental Health Clinical Advisory Group recommends that providers consider use of these specific medications because LAI antipsychotics have shown lower risk of hospitalization and relapse when compared to oral antipsychotics.[40] Clozapine is usually recommended for people who have had inadequate response to more than 2 antipsychotics.[40] Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also recommended in conjunction with pharmacological therapy.[40]

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The CGI evaluates disease severity and improvement using a 7-point analog scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimal clinically important difference (MCID).[41] The PANSS evaluates 30 items in patients with schizophrenia. Each item is scored on a 7-point scale, with lower scores indicating less severe symptoms (range 30-210).[41] This scale can also be subdivided to assess general psychopathology (16 items), positive symptoms (7 items), or negative symptoms (7 items). The 7 negative symptom questions are also commonly referred to as the Marder negative factor score.[42] There is no established MCID for the PANSS, though improvements of 16-34% have been correlated to 1 point improvements in CGI-S,[43,44] 4-8 points have been correlated to increases in employment[45] and improvements of 10 points have been correlated with reduced hospitalization.[25] Response to treatment is typically defined in most clinical trials as greater than 20% improvement in the PANSS score.[25] Additional details about outcomes assessment in schizophrenia are presented in **Appendix 3, Table 20.**

Bipolar Disorder

Bipolar disorder is characterized by episodes of mania and in the majority of cases, episodes of major depression.[46] It is classified as bipolar I disorder (characterized by at least one manic episode) or bipolar II disorder (primarily characterized by history of depressive and hypomanic episodes).[46] The World Mental Health Survey Initiative reported lifetime and 12-month prevalence estimates for bipolar disorders of 2.4% and 1.5%, respectively.[47] The prevalence of bipolar I disorder is similar for males and females, while bipolar II disorder occurs more frequently among females.[46] The onset of bipolar disorder typically occurs around 20 years of age.[46] Bipolar disorder is frequently associated with other mental health conditions including anxiety disorder, attention-deficit/hyperactivity disorder (ADHD) and substance use disorders.[46] After one manic episode, greater than 90% of individuals have recurrent mood episodes, and suicide risk is estimated to be at least 15 times higher than the general population risk.[26] Functional impairment is significant. One study found that individuals with bipolar I disorder had severe impairment in occupational functioning about 30% of the time, and individuals with bipolar I disorder attain lower levels of socioeconomic status than members of the general population with equivalent educational levels.[26]

Goals of treatment include resolution of acute symptoms and long-term prevention of recurrent mania or depressive episodes.[48] Typically, if acute symptoms do not resolve with treatment, the patient is switched to an alternative medication or an additional medication is added.[46] Other treatments include electroconvulsive therapy (ECT), psychoeducational therapy, cognitive behavioral therapy and social therapy.[46] The recommended pharmacological treatments

for bipolar disorder vary depending on the phase of the disorder (acute mania, acute depression, or maintenance). The mainstay of treatment for acute mania and hypomania is pharmacologic treatment with antipsychotic agents (e.g., aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, ziprasidone) or mood stabilizers (e.g., lithium, divalproex, carbamazepine, lamotrigine).[46] The FDA has approved 4 atypical antipsychotics for the treatment of bipolar depression: quetiapine, lurasidone, cariprazine, and the combination of olanzapine with fluoxetine.[46] Lithium remains one of the most effective drugs for the prevention of both depressive and manic recurrences in bipolar disorder.[46] Quetiapine alone and the combination of quetiapine–lithium or quetiapine–divalproex have also been shown to be effective maintenance treatments for bipolar disorder.[46] Meaningful differences in efficacy among these treatments have not been observed in head-to-head trials.[46]

For patients with bipolar I disorder, symptom improvement is commonly evaluated using the 11-item Young Mania Rating Scale (YMRS). Using this scale, changes of at least 6 points have been correlated with clinically significant improvements.[48,49] Symptom improvement and severity for patients with bipolar disorder may also be evaluated using the CGI scale (range 1-7 with a minimum clinically important difference of 1 point).[48,50] Additional details about outcome assessments in bipolar disorder are presented in **Appendix 3, Table 20**.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 5**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:
Drug Effectiveness Review: Newer Pharmacologic Agents for Treatment of Schizophrenia, Psychosis and Bipolar Disorder
In 2025, DERP published a systemic review of newer pharmacologic agents for treatment of schizophrenia and bipolar disorder.[1] The literature search for this report was completed on November 12, 2024.[1] Nine placebo-controlled RCTs inpatients with schizophrenia met inclusion criteria.[1] Three RCTs evaluated xanomeline/trospium and 6 RCTs evaluated 3 investigational agents: roluperidone, ulotaront, and valbenazine.[1] This evidence summary will focus on the data for the FDA-approved product, xanomeline/trospium, which is a new treatment for psychosis with a different mechanism of action than FGAs and SGAs. Unlike other antipsychotic agents, which antagonize one or more dopamine receptors, this agent is not expected to cause extrapyramidal effects, as it is not known to exhibit antagonist activity on dopamine in the nigrostriatal tracts.[1]

The 3 placebo-controlled RCTs (n=690) that studied xanomeline/trospium had a moderate risk of bias (RoB).[1] DERP assessments of results and certainty of evidence (CoE) include:

- Xanomeline 125 mg/trospium 30 mg reduced the PANSS total score from baseline to week 5 by 8.4% to 10% (3 RCTs, low CoE).[1]
- Xanomeline 125 mg/trospium 30 mg reduced the PANSS positive symptom score from baseline to week 5 by 8% to 12% (3 RCTs, low CoE).[1]

- Xanomeline 125 mg/trospium 30 mg reduced the PANSS negative symptom score from baseline to week 5 by 1.8% to 2.3% (3 RCTs, low CoE).[1]
- Response, measured by a Clinical Global Impression–Improvement (CGI-I) score of 1 or 2, was not significantly different between xanomeline 125 mg/trospium 30 mg and placebo (6% vs. 1%, MD, 4%; 955 CI -3 to 12; 1 RCT; n=182; very low CoE).[1]
- Response, measured by at least a 30% improvement in PANSS scores at endpoint, was greater for xanomeline 125 mg/trospium 30 mg (51% to 55%) compared with placebo (25% to 28%) (2 RCTs, n=508; low CoE).[1]
- The primary AEs with xanomeline/trospium are associated with the muscarinic receptors, leading primarily to gastrointestinal effects such as nausea, vomiting, constipation, and hypersalivation (3 RCTs; moderate CoE).[1]

Drug Effectiveness Review: Second Generation Antipsychotics as Adjuvant Therapy in Treatment of Major Depressive Disorder

In 2024, DERP issued a systematic review that evaluated adjuvant SGAs for treatment of MDD.[2] Literature was searched through October 20, 2023 and 47 RCTs met inclusion criteria.[2] Antipsychotics of interest included aripiprazole (12 RCTs), brexpiprazole (5 RCTs), cariprazine (5 RCTs), olanzapine (1 RCT), olanzapine/fluoxetine (5 RCTs), pimavanserin (2 RCTs), quetiapine (10 RCTs), risperidone (5 RCTs), and ziprasidone (2 RCTs).[2] Pimavanserin, risperidone, and ziprasidone are not FDA-approved as adjunctive therapy for MDD and do not have compendial indications for off-label use in MDD.[27] Limitations to the overall body of evidence included short study durations (most studies were conducted over 6 to 12 weeks) and lack of comparative studies, as most of the RCTs were placebo-controlled in combination with an antidepressant.[2]

Evidence from the 2024 DERP report is summarized below for each of the FDA-approved SGAs. Adjunctive antipsychotic efficacy was evaluated using the MADRS, CGI-I scoring, and treatment response (≥ 50% improvement from baseline on applicable depression scale). Most agents showed a 2 to 3–point improvement in MADRS scores during the first 5 to 8 weeks of treatment.[2] In a clinical setting many practitioners prefer for a patient to experience a 50% or greater reduction in their depression assessments to determine efficacy.[2] Adverse effects were assessed using the Barnes Akathisia Rating Scale (BARS) and change in body weight from baseline.

Adjunctive Aripiprazole vs. Placebo/Monotherapy

Findings for aripiprazole as adjunctive treatment to ADT versus placebo in MDD were included in 12 RCTs (see **Table 1**).[2] Two of the RCTs were conducted in older adults (aged ≥ 60 years) with treatment-resistant depression.[2] Four of the studies were rated as high risk of bias (RoB), 7 studies were rated as moderate RoB, and 1 study was rated as low RoB.[2] Studies ranged from 6 to 12 weeks in duration.[2] Efficacy outcomes were rated as high CoE due to the large number of studies that showed consistent improvement in assessment scales and treatment response.[2]

Table 1. Adjunctive Aripiprazole Versus Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in Body Weight
Number of RCTs, Total Population	9 RCTs, N = 2,795	8 RCTs, N = 3,874	9 RCTs, N = 3,975	7 RCTs, N = 2,372	11 RCTs, N = 4,208
DERP Certainty of Evidence Assessment	High	High	High	High	High
Notes	MADRS scores typically improved 2 to 3 points during treatment compared	Modest improvement in CGI-I scores compared with placebo.	Aripiprazole showed higher response rates	Aripiprazole showed modestly higher scores in akathisia in short-	Aripiprazole typically showed 1 to 1.5 kg increase in body

	with placebo. (MCID = 2-point increase). DERP meta-analysis from 3 RCTs (n=882) showed more improvement in MADRS scores with aripiprazole vs. placebo (MD, 2.74; 95% CI 0.87 to 4.60; I^2 = 79%).	DERP meta-analysis from 6 RCTs (n=1,856) showed more improvement in the CGI-I score with aripiprazole vs. placebo (MD, 0.30; 95% CI 0.28 to 0.32; I^2 = 20%).	compared to placebo (10% to 28% absolute change). DERP meta-analysis from 8 RCTs (n=2,359) showed higher rates of response with aripiprazole vs. placebo (RR, 1.51; 95% CI 1.33 to 1.71; I^2 = 0%)	term studies. Unknown if this AE resolves with extended therapy.	weight in the first 6 weeks of therapy.
Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio					

Adjunctive Brexpiprazole vs. Placebo/Monotherapy

Five RCTs evaluated brexpiprazole as adjunctive treatment with ADT versus placebo for MDD (see **Table 2**).[2] Two of the studies were rated as high RoB and 3 studies were rated as having a moderate RoB.[2] Most of the RCTs were conducted over 6 to 8 weeks, with one study lasting 24 weeks.[2] Efficacy outcomes were rated as moderate to high CoE due to consistent improvement in MADRS scores, with greater inconsistency for CGI-I assessments.[2]

Table 2. Adjunctive Brexpiprazole Versus Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	5 RCTs, N = 2,829	4 RCTs, N = 2,326	5 RCTs, N = 2,829	3 RCTs, N = 1,932	5 RCTs, N = 2,829
DERP Certainty of Evidence Assessment	High	Moderate	High	Low	High
Notes	MADRS scores typically improved 1.5 to 3 points during treatment compared with placebo. Improvements may not be clinically important for all patients. (MCID = 2-point increase). DERP meta-analysis from 2 RCTs (n=789) showed more improvement in MADRS scores with brexpiprazole vs. placebo (MD, 1.68; 95% CI 0.75 to 2.60; I^2 = 0%).	Modest improvement in CGI-I scores compared with placebo, inconsistent results. DERP meta-analysis from 4 RCTs (n=1,558) showed more improvement in the CGI-I score with brexpiprazole vs. placebo (MD, 1.36; 95% CI 1.12 to 1.65; I^2 = 0%).	Brexpiprazole showed variable response rates compared to placebo (3% to 5% absolute difference).	Brexpiprazole showed modestly higher scores in akathisia in short term studies. Unknown if this AE resolves with extended therapy.	Brexpiprazole typically showed up to 1.6 kg increase in body weight in first 6 weeks of therapy.

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

Adjunctive Cariprazine vs. Placebo/Monotherapy

Five RCTs evaluated adjunctive cariprazine with ADT versus placebo in people with MDD (see **Table 3**).[2] Four studies were rated as high RoB due to numerous conflicts of interest by the authors and significant manufacturer involvement in study design, data collection, and assessment.[2] One study was rated as moderate RoB.[2] Three of the studies were Phase 3 trials and 2 of the studies were Phase 2 RCTs.[2] Studies were conducted over 6 to 8 weeks.[2]

Table 3. Adjunctive Cariprazine Versus Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	5 RCTs, N = 3,068	5 RCTs, N = 3,068	5 RCTs, N = 3,068	5 RCTs, N = 3,068	5 RCTs, N = 3,068
DERP Certainty of Evidence Assessment	High	Moderate	High	High	High
Notes	MADRS scores typically improved 1 to 3 points during treatment compared with placebo. Improvements may not be clinically important for all patients. (MCID = 2-point increase). DERP meta-analysis from 4 RCTs (n=1,680) showed more improvement in MADRS scores with cariprazine vs. placebo (MD, 1.26; 95% CI 0.34 to 2.19; I^2 = 0%).	Modest improvement in CGI-I scores compared with placebo, with inconsistent results. DERP meta-analysis from 4 RCTs (n=1,620) showed more improvement in the CGI-I score with cariprazine vs. placebo (MD, 0.2; 95% CI 0.06 to 0.34; I^2 = 0%).	Cariprazine showed higher response rates compared to placebo, but they were not significant (1% to 10% absolute change). DERP meta-analysis from 5 RCTs (n=2,214) showed higher rates of response with cariprazine vs. placebo (RR, 1.18; 95% CI 1.06 to 1.31; I^2 = 0%).	Cariprazine showed modestly higher scores in akathisia severity.	Cariprazine typically showed a 0.4 to 0.9 kg increase in body weight in first 6 weeks of therapy.

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

Adjunctive Olanzapine/Fluoxetine vs. Placebo/Monotherapy

Five RCTs evaluated adjunctive olanzapine/fluoxetine versus placebo or fluoxetine monotherapy in people with treatment-resistant depression (see **Table 4**).[2] Four studies were rated as high RoB due to most authors being employees of the manufacturer of olanzapine/fluoxetine and extensive manufacturer involvement in study design and data collection.[2] One small study was rated as moderate RoB.[2] Most studies were conducted over 8 to 12 weeks, and one study was conducted over 27 weeks.[2] There were consistent improvements in MADRS scores (high CoE), but inconsistent adverse event outcome results (low CoE).[2]

Table 4. Adjunctive Olanzapine/Fluoxetine Versus ADT Monotherapy or Fluoxetine Alone[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	5 RCTs, N = 2,077	NR	4 RCTs, N = 1,633	4 RCTs, N = 2,049	5 RCTs, N = 3,068
DERP Certainty of Evidence Assessment	High	NR	High	Low	High
Notes	MADRS scores typically improved 3 to 5 points during treatment compared with placebo. (MCID = 2-point increase). DERP meta-analysis from 2 RCTs (n=709) showed more improvement in MADRS scores with olanzapine/fluoxetine vs. placebo (MD, 3.01; 95% CI 1.47 to 4.55; I^2 = 0%).	NR	Olanzapine/Fluoxetine showed inconsistent results (1% to 18% absolute change). DERP meta-analysis from 4 RCTs (n=1,012) showed higher rates of response with olanzapine/fluoxetine vs. placebo (RR, 1.26; 95% CI 1.04 to 1.52; I^2 = 42%).	Olanzapine/fluoxetine did not increase scores significantly during treatment compared with placebo.	Olanzapine/fluoxetine typically showed up to 6 kg increase in body weight in the first 8 weeks of therapy.

Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

An additional, small (n=30) RCT compared olanzapine head-to-head with aripiprazole or lithium as augmentation therapy in combination with paroxetine.[2] At 4 weeks, no significant differences in the 17-item Hamilton Depression Rating Scale (HAM-D17) were found between therapies (very low CoE).[2] No harm outcomes were reported in this study.[2]

Adjunctive Quetiapine vs. Placebo/Monotherapy

Eight RCTs evaluated adjunctive quetiapine versus placebo in MDD treatment (see **Table 5**). Two studies were rated as having a high RoB while 6 RCTs were at moderate RoB.[2] Studies were conducted over 6 to 12 weeks.

Table 5. Adjunctive Quetiapine vs. Placebo[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight

Number of RCTs, Total Population	5 RCTs, N = 1,159	5 RCTs, N = 1,253	4 RCTs, N = 1,083	2 RCTs, N = 560	7 RCTs, N = 1,329
DERP Certainty of Evidence Assessment	Moderate	Moderate	High	Low	Moderate
Notes	MADRS scores typically improved 3 points during treatment compared with placebo. (MCID = 2-point increase). DERP meta-analysis from 2 RCTs (n=112) showed no differences in MADRS scores between quetiapine and placebo (MD, 1.92; 95% CI -5.57 to 1.74; I^2 = 0%).	Modest 1 point improvement in CGI-I scores compared with placebo. DERP meta-analysis was not conducted for this outcome.	Quetiapine showed higher response rates compared to placebo (10% to 13% absolute change). DERP meta-analysis from 2 RCTs (n=619) showed quetiapine had higher rates of response compared with placebo (RR, 1.26 95% CI 1.08 to 1.47; I^2 = 0%).	No significant differences in akathisia assessments were reported.	Quetiapine typically showed 1 kg increase in body weight in first 6 weeks of therapy
Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; CI = confidence interval; DERP = Drug Effectiveness Project; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio					

Quetiapine vs. Lithium Monotherapy

Two RCTs evaluated adjunctive quetiapine versus lithium in MDD treatment (see **Table 6**). Both studies were rated as having a moderate RoB.[2] These studies were conducted over 6 to 8 weeks.

Table 6. Quetiapine vs Lithium Monotherapy[2]

	Montgomery-Åsberg Depression Rating Scale	Clinical Global Impressions-Improvement	Treatment Response	Barnes Akathisia Rating Scale (BARS)	Change in body weight
Number of RCTs, Total Population	2 RCTs, N = 708	2 RCTs, N = 708	1 RCT, N = 688	NR	1 RCT, N = 688
DERP Certainty of Evidence Assessment	Low	Low	Very Low	NR	Low
Notes	Quetiapine showed a significant improvement in MADRS in 1 study and no difference in 1 study.	Quetiapine showed a significant improvement in CGI-I in 1 study and no difference in 1 study.	There was no difference between groups, with both reporting high response rates.	NR	More participants reported weight gain as an AE in the quetiapine group.
Abbreviations: AE = adverse effect; CGI-I = Clinical Global Impressions-Improvement; kg = kilograms; MADRS = Montgomery=Åsberg Depression Rating Scale; MD = mean difference; RCT = randomized controlled trial					

In summary, moderate-quality evidence showed that aripiprazole improved depression outcomes compared with placebo.[2] Brexpiprazole and cariprazine also appear to be efficacious compared with placebo in MDD, based upon the DERP meta-analyses of available moderate-quality evidence.[2] Quetiapine seemed to

show improvement at around 3 points on the MADRS assessment compared with placebo (moderate-quality evidence).[2] Pimavanserin and ziprasidone have insufficient evidence or appear to be ineffective for use as adjunctive treatments for depression.[2]

The most common adverse events seen with SGAs used adjunctively with ADTs included akathisia and weight gain.[2] Rates of akathisia were highest in those on aripiprazole and were slightly lower in patients taking brexpiprazole and cariprazine.[2] Patients taking the olanzapine/fluoxetine combination, quetiapine, ziprasidone, risperidone, and pimavanserin did not experience any significant movement AEs, including akathisia.[2] When using aripiprazole, there is a moderate risk of akathisia, and if using the olanzapine/fluoxetine combination therapy, patients should be monitored for weight gain.[2]

Cochrane: Lurasidone Versus Typical Antipsychotics for Schizophrenia

The purpose of a 2025 Cochrane review was to review the comparative efficacy and safety of lurasidone versus typical antipsychotics in adults with schizophrenia.[3] Literature was searched through April 2024 and 2 RCTs (n=308) met inclusion criteria.[3] A total of 223 participants received lurasidone (20, 40, or 80 mg/day), and 82 participants received haloperidol (up to 10 mg/day).[3] The duration of the follow-up was 4 to 6 weeks.[3] The evidence is very uncertain about the effects of lurasidone compared with haloperidol on change in mental state as measured by the BPRS (MD 3.74, 95% CI 0.57 to 6.90; 1 RCT, 281 participants; very low-certainty evidence); and the PANSS (MD 6.68, 95% CI 2.45 to 10.91; 1 RCT, 281 participants; very low-certainty evidence).[3] The evidence is also very uncertain about the comparative effects of lurasidone and haloperidol on total serious adverse events (RR 0.98, 95% CI 0.37 to 2.60; 2 RCTs, 303 participants; very low certainty of evidence) and on severe adverse events (RR 1.70, 95% CI 0.46 to 6.32; 1 RCT, 281 participants; very low certainty of evidence).[3] The authors concluded there is insufficient evidence to evaluate the comparative efficacy of lurasidone and other antipsychotics in people with schizophrenia.[3]

Cochrane: Switching Antipsychotics Versus Continued Current Treatment in People with Non-Responsive Schizophrenia

A 2025 Cochrane review examined the effects of switching antipsychotic drugs adults with schizophrenia who had not responded to initial antipsychotic treatment.[4] Literature was searched through December 2022.[4] Ten RCTs (n=997) met inclusion criteria.[4] Seven studies were double-blind, 2 were single-blind and one study did not provide any detail regarding blinding.[4] The minimum duration of the ongoing antipsychotic treatment ranged from 3 days to 2 years.[4] The length of the comparison phase varied from 2 weeks to 6 months.[4] In about half of the studies, the methods of randomization, allocation and blinding were poorly reported.[4]

All studies compared switching antipsychotics versus continuation of the same (ongoing) antipsychotic drug. Some studies switched antipsychotics with similar receptor-binding profiles (e.g. from risperidone to paliperidone), while others switched between relatively different drugs (e.g. amisulpride and olanzapine).[4] Few studies clearly described how the antipsychotic drug was switched (e.g. abrupt discontinuation, cross-tapering, or double prescription until efficacy was achieved).[4] All in all, the heterogeneity of the included studies was high, which made pooling data difficult.[4] Trials evaluated a variety of drug switches including changing to clozapine, switching from risperidone to paliperidone, switching between risperidone and olanzapine (or vice versa), switching from fluphenazine to haloperidol, switching from haloperidol to perphenazine, from a FGA to clozapine or to a typical antipsychotic, and switching between olanzapine and amisulpride.[4]

The evidence is very uncertain regarding the effect of switching antipsychotics on clinically relevant response (RR 1.25, 95% CI 0.77 to 2.03; I^2 = 43%; 7 studies, 693 participants), quality of life (MD -1.30, 95% CI -3.44 to 0.84; 1 study, 188 participants), PANSS score change (MD -0.92, 95% CI -4.69 to 2.86; I^2 = 47%; 6 studies, 777 participants), duration of hospitalization (in days) (MD 9.19, 95% CI -8.93 to 27.31; I^2 = 0%; 2 studies, 34 participants) and the number of people experiencing at least one adverse effect (RR 1.29, 95% CI 0.81 to 2.05; I^2 = 36%; 3 studies, 412 participants).[4] Compared to continuing current treatment, switching antipsychotics may result in little to no difference in tolerability, defined as the number of participants leaving the study early due to adverse effects

(RR 0.73, 95% CI 0.24 to 2.26; I^2 = 31%; 6 studies, 672 participants; low-certainty evidence) and leaving the study early for any reason (RR 0.91, 95% CI 0.71 to 1.17; I^2 = 0%; 6 studies, 672 participants; low-certainty evidence).[4]

Overall, the evidence remains highly uncertain regarding the effects of continuing the same therapy or switching to another agent on efficacy and safety outcomes, and no definitive recommendations can currently be made.[4] Most of the studies were small; only 3 studies had more than 100 patients.[4] Although no differences were observed between the 2 strategies (switching medication versus continuation of the same drug) in the key outcomes, including response to the medicines, tolerability (measured as the number of people who left the studies early due to adverse effects), and quality of life, the evidence was very uncertain for most of these outcomes.[4]

Cochrane: Haloperidol Versus Olanzapine for People with Schizophrenia and Schizophrenia-Spectrum Disorders

A 2024 Cochrane review assessed the benefits and harms of oral haloperidol compared to oral olanzapine for people with schizophrenia.[5] Literature was searched through January 2023.[5] Sixty-eight (n=9,132) RCTs comparing haloperidol with olanzapine for adults with schizophrenia and schizophrenia-spectrum disorders met inclusion criteria.[5] Overall, the quality of the included studies was very low to moderate.[5] The most common risks of bias were blinding (performance bias) and selective reporting (reporting bias).[5] Most of the trials (57/68) were short-term RCTs, lasting less than 7 months.[5] The studies were carried out in various settings (e.g., inpatient and outpatient) and used different study populations (e.g., acute episodes of schizophrenia, first-episode schizophrenia, drug-naïve, stable schizophrenia).[5] The doses of haloperidol studied in the included trials was higher than current international best practice guidelines, while the mean doses of olanzapine were in line with guideline recommendations.[5] Most studies were carried out in stable, higher-income settings under controlled conditions and may be less applicable to crisis-affected and low-income settings, where access to specialized clinical mental health care and stable supplies is very often less available.[5]

The main outcomes of interest were clinically important change in global state, relapse, clinically important change in mental state, extrapyramidal side effects, weight increase, clinically important change in quality of life and leaving the study early due to adverse effects.[5] There is only low-certainty comparative evidence which shows no difference between haloperidol and olanzapine in terms of clinically important change in global state using the CGI scale (RR 0.84, 95% CI 0.69 to 1.02; I^2 =73%; 6 studies, 3078 participants; very low-certainty evidence) or incidence of relapse (RR 1.42, 95% CI 1.00 to 2.02; I^2 =75%; 7 studies, 1499 participants; very low-certainty evidence).[5] Haloperidol may reduce the incidence of clinically important change in overall mental state compared to olanzapine (RR 0.70, 95% CI 0.60 to 0.81; I^2 = 0%; 13 studies, 1210 participants; low-certainty evidence).[5] A single study suggests that haloperidol may reduce the incidence of clinically important change in quality of life compared to olanzapine (RR 0.72, 95% CI 0.57 to 0.91; 828 participants; low-certainty evidence).

Haloperidol may result in a large increase in extrapyramidal side effects compared to olanzapine (RR 3.38, 95% CI 2.28 to 5.02; 14 studies, I^2 =72%; 3290 participants; low-certainty evidence) and reduced risk of weight gain with haloperidol compared to olanzapine (RR 0.47, 95% CI 0.35 to 0.61; I^2 = 57%; 18 studies, 4302 participants; low-certainty evidence).[5] More people receiving haloperidol left the study early due to adverse effects compared to olanzapine (RR 1.99, 95% CI 1.60 to 2.47; I^2 = 0%; 21 studies, 5047 participants; low-certainty evidence).[5]

In summary, the certainty of the evidence was low to very low for the main outcomes in this review, making it difficult to draw reliable conclusions.[5] It is uncertain if there is a difference between haloperidol and olanzapine in terms of clinically important change in global state and incidence of relapse.[5] While there was a trend towards an increased risk of relapse with haloperidol, evidence was very uncertain and there is considerable discrepancy between some of the studies.[5] Olanzapine may result in a slightly greater overall clinically important change in mental state and in a clinically important change in quality of life.[5] Weight gain was more common with olanzapine (1 in 5 with olanzapine versus 1 in 11 with haloperidol), whereas extrapyramidal side effects were more

common with haloperidol (1 in 3 with haloperidol versus 1 in 6 with olanzapine).[5] Haloperidol likely increases the rate of people leaving the study early due to adverse effects compared with olanzapine (1 in 10 versus 1 in 20).[5] While there is insufficient information to understand the reason for this outcome, it is possible this may be linked to using higher equivalent doses of haloperidol compared to olanzapine in some trials.[5]

Cochrane: Antipsychotics For Agitation and Psychosis in People with Alzheimer's Disease and Vascular Dementia

A 2021 Cochrane review assessed the efficacy and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.[6] Literature was searched through January 2021.[6] Twenty-four RCTs (n=6,090) met inclusion criteria.[6] Six trials tested an FGA, 4 for agitation and 2 for psychosis.[6] Twenty trials tested an SGA, 8 for agitation and 12 for psychosis.[6] Two trials tested both drug types. Seventeen of 26 comparisons were performed in patients with Alzheimer's disease.[6] The other 9 comparisons also included patients with vascular dementia or mixed dementia.[6] The trials were performed in institutionalized, hospitalized and community-dwelling patients, or a combination of those.[6] Most studies were at high risk of bias in at least one domain.[6]

Overall, 6 trials tested FGA: 4 trials tested haloperidol and 2 trials tested thiothixene.[6] It is uncertain whether FGAs improve agitation compared with placebo (SMD -0.36, 95% CI -0.57 to -0.15, 4 studies, n=361; very low-certainty evidence), but FGAs may improve psychosis slightly (SMD -0.29, 95% CI -0.55 to -0.03, 2 studies, n=240; low-certainty evidence) compared with placebo.[6] These drugs probably increase the risk of somnolence (RR 2.62, 95% CI 1.51 to 4.56, 3 studies, n=466; moderate-certainty evidence) and increase extrapyramidal symptoms (RR 2.26, 95% CI 1.58 to 3.23, 3 studies, n=467; high-certainty evidence).[6] There was no evidence regarding the risk of any adverse event.[6] The risks of serious adverse events (RR 1.32, 95% CI 0.65 to 2.66, 1 study, n=193) and death (RR 1.46, 95% CI 0.54 to 4.00, 6 studies, n=578) may be increased slightly, but these estimates were very imprecise, and the certainty was low.[6]

Twenty RCTs evaluated SGAs including risperidone, olanzapine, aripiprazole, brexpiprazole, and quetiapine.[6] The SGAs probably reduce agitation slightly (SMD -0.21, 95% CI -0.30 to -0.12, 7 studies, n=1971; moderate-certainty evidence) and probably have a very small effect on psychosis (SMD -0.11, 95% CI -0.18 to -0.03, 12 studies, n=3364; moderate-certainty evidence) compared with placebo.[6] The SGAs increase the risk of somnolence (RR 1.93, 95% CI 1.57 to 2.39, 13 studies, n=3878; high-certainty evidence) and are probably also associated with slightly increased risk of extrapyramidal symptoms (RR 1.39, 95% CI 1.14 to 1.68, 15 studies, n=4180; moderate-certainty evidence), serious adverse events (RR 1.32, 95% CI 1.09 to 1.61, 15 studies, n= 4316; moderate-certainty evidence) and death (RR 1.36, 95% CI 0.90 to 2.05, 17 studies, n= 5032; moderate-certainty evidence), although the latter estimate was imprecise.[6] The SGAs probably increase risk of any adverse event by a very small amount (RR 1.05, 95% CI 1.02 to 1.09, 11 studies, n=2785; moderate-certainty evidence).[6]

In summary, there is low certainty about the effect of FGAs on psychosis in dementia, due to a small number of studies (only 2 studies), and studies evaluating the effect of FGAs on agitation were too small to provide a precise estimate (4 studies).[6] FGAs might improve psychosis slightly compared with placebo, while the effect on agitation is uncertain.[6] The FGAs probably increase the risk of somnolence and extrapyramidal symptoms.[6] There was no evidence regarding the risk of at least one adverse event, and a slight increase in the risk of a serious adverse event or death.[6]

In contrast, there was a large number of studies that tested the effect of SGAs on psychosis and agitation in dementia (12 and eight studies, respectively), and most studies were relatively large.[6] As a result, the effect estimates are very precise and give certainty that these drugs only have a small effect on agitation and little or no effect on psychosis.[6] The SGAs probably increase the risk of somnolence and extrapyramidal symptoms.[6] The risk of a serious adverse event and the risk of death are slightly increased with SGAs.[6]

The Impact of Pharmacological and Non-Pharmacological Interventions to Improve Physical Health Outcomes in People with Schizophrenia

People with schizophrenia have substantially poorer physical health than the general population, which is often attributed to an interaction between social circumstances, lifestyle factors and treatment effects.[7] Behavioral research has demonstrated that people with schizophrenia are less physically active and exhibit more sedentary behavior than the general population, have a higher quantity but lower quality of dietary food intake, and increased adverse health behaviors, such as smoking.[7] In addition, psychiatric treatment with antipsychotics, mood stabilizers and antidepressants, further increases the risk of physical health conditions.[7] Consequently, people with schizophrenia more frequently have cardio-metabolic diseases, respiratory diseases, chronic pain, fractures, and lower physical fitness than the general population.[7]

A 2019 systematic review evaluated the efficacy for pharmacological and non-pharmacological interventions targeting physical health outcomes among people with schizophrenia spectrum disorders.[7] Literature was searched through June 1, 2018 and 27 meta-analyses (128 RCTs, n=47,231) met inclusion criteria.[7] Only eleven meta-analyses (41%) were rated as high-quality.[7] Seven of the 27 meta-analyses included only double-blind trials (26%).[7] In 16 meta-analyses (59%), the total pooled sample was less than 500 cases, while only five meta-analyses (18%) had a total sample of more than 1,000 participants.[7] Only two meta-analyses (7%) had one included trial with at least 200 participants.[7]

There were meta-analytic data for 17 different pharmacological interventions: aripiprazole augmentation, fluoxetine, metformin, nizatidine, amantadine and memantine, ranitidine, topiramate, dextroamphetamine, famotidine, metformin in combination with sibutramine, orlistat, rosiglitazone, fluvoxamine, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and switching from olanzapine to quetiapine or aripiprazole.[7] Meta-analytic data were available for six different non-pharmacological interventions: individual lifestyle counseling, group lifestyle counseling, cognitive behavioral therapy, psychoeducation, exercise, and dietary interventions.[7]

Individual lifestyle counseling was the most effective intervention for weight reduction (SMD = –0.98, 95% CI –1.15 to –0.81, p<0.001; 14 trials, N=411, I^2=0%), followed by exercise interventions alone (SMD = –0.96, 95% CI –1.27 to –0.66, p<0.001; 4 trials, N=183, I^2=0).[7] Generally, an SMD less than 0.2 is considered negligible, an SMD between 0.2 and less than 0.5 is small, an SMD between 0.5 and less than 0.8 is medium, and an SMD of at least 0.8 is large effect size.[7] Changes in metabolic symptoms, such as weight loss and reduction in waist circumference, were observed with the use of metformin, topiramate, and aripiprazole.[7] A medium effect size was observed for aripiprazole augmentation (SMD = –0.73, 95% CI –0.97 to –0.48, p<0.001; 9 trials, N=813, I^2=68%), topiramate (SMD = –0.72, 95% CI –1.56 to –0.33, p<0.001; 15 trials, N=783, I^2=92.7%), and metformin (SMD = –0.53, 95% CI –0.69 to –0.38, p<0.001; 29 trials, N=1,279, I^2=39.4%).[7] The use of topiramate for antipsychotic-induced weight gain is off-label, and not recommended by guidelines due to its side effect profile.[51] The use of metformin for antipsychotic weight gain is off-label, but listed as a compendial indication in Micromedex.[27] No beneficial effects were found for fluoxetine, ranitidine, orlistat, dextroamphetamine and famotidine for any physical health outcome.[7]

In summary, based on the SMDs and the overall high methodological quality of the original meta-analyses (but with lower quality of the studies included in the meta-analysis), individual lifestyle counseling and exercise interventions showed the largest weight reducing effect, followed by aripiprazole augmentation, topiramate, and metformin.[7]

After review, 69 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).

New Guidelines:

High Quality Guidelines:

Veterans Administration/Department of Defense: Management of First-Episode Psychosis and Schizophrenia

In 2023, the VA/DoD issued updated guidance for the management of patients with schizophrenia.[8] Pharmacotherapy typically begins with a low dose of a single antipsychotic medication and involves monitoring for symptom response, side effects, and attitudes toward medication at every visit.[8] Consideration of use of a LAI formulation as part of a holistic approach is common practice.[8] Special emphasis on monitoring and managing cardiometabolic risk factors, such as smoking, weight gain, hypertension, dyslipidemia, and pre-diabetes should be part of the treatment plan.[8] There is insufficient evidence to recommend for or against a specific duration for treatment with antipsychotic medication after response or remission for individuals with first-episode psychosis.[8]

Antipsychotic medications share similar efficacy (with the exception of clozapine, which is reserved primarily for the treatment of people who either failed to adequately respond to other antipsychotic medications or for the treatment of suicidality).[8] Therefore, the VA/DoD Work Group considered antipsychotic medications as a class, rather than considering each medication individually.[8] The benefits of antipsychotic medications for the treatment of an acute episode of schizophrenia (e.g., symptom reduction, which is associated with reduced patient distress and increased availability for complementary nonpharmacologic treatments, such as supported employment) and the potential harms of not providing these medications (e.g., increased risk of self-harm or harm to others; impaired work or social functioning or both; decreased quality of life; distress from untreated symptoms; and family burden) outweighed the potential harm of adverse events (e.g., cardiovascular, metabolic, and motor side effects; sedation; and others).[8]

The use of augmenting agents should be considered in addition to lifestyle modifications, including exercise and counseling about lifestyle modifications.[8] Another strategy is to change to an antipsychotic medication that is less likely to cause weight gain and other metabolic side effects.[8] The benefits of using metformin, topiramate, or aripiprazole as an augmenting agent for weight loss slightly outweighed the harms or burdens of use or both.[8] There was concern regarding the adverse cognitive effects of using topiramate including increased risk of congenital anomalies, low birth weight, and low vitamin K with resultant bleeding risk in pregnant women.[8] Metformin was the agent used most frequently in clinical practice.[8]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- The choice of antipsychotic medication should be based on an individualized evaluation that considers patient characteristics and side effect profiles of the different antipsychotic medications.
- We recommend the use of an antipsychotic medication other than clozapine for the treatment of an acute episode in individuals with schizophrenia or first-episode psychosis who have previously responded to antipsychotic medications (Strong Recommendation; Moderate-Quality Evidence).[8]
- We recommend the use of an antipsychotic medication for the maintenance treatment of schizophrenia to prevent relapse and hospitalization in individuals with schizophrenia who have responded to treatment (Strong Recommendation; Moderate-Quality Evidence).[8]
- We suggest a trial of another antipsychotic medication for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic medication (Weak Recommendation; Very Low-Quality Evidence).[8]
- We suggest offering LAI antipsychotics to improve medication adherence in individuals with schizophrenia (Weak Recommendation; Very Low-Quality Evidence).
- We recommend the use of clozapine for individuals with treatment-resistant schizophrenia (Strong Recommendation; Moderate-Quality Evidence).[8]
- We suggest augmenting clozapine with another second-generation antipsychotic medication for individuals with treatment-resistant schizophrenia who have not experienced an adequate response to clozapine (Weak Recommendation; Very Low-Quality Evidence).[8]
- We suggest using metformin, topiramate, or aripiprazole augmentation for treatment of metabolic side effects of antipsychotic medication and weight loss for individuals with schizophrenia (Weak Recommendation; Moderate-Quality Evidence).[8]

Veterans Administration/Department of Defense: Management of Bipolar Disorder

The VA/DoD updated guidance for managing patients with bipolar disorder in 2023.[9] There are three distinct phases of the pharmacological management for bipolar disorder, including: (1) treatment for acute mania, (2) treatment for acute depression, and (3) maintenance treatment to prevent recurrences of both mania or depression.[9] It has been common practice to treat individuals experiencing mania or bipolar depression with medications that have evidence of effectiveness for their current episodes and to continue them on agents to which they have responded without considering the impact on long-term outcomes.[9] This approach is often taken even though most individuals with bipolar disorder spend more time in the maintenance and prevention phases than in periods of acute illness.[9] This practice could lead to greater risks for relapses if the medications used to treat acute episodes are not optimal for maintenance.[9] Moreover, if additional medications are added when there are recurrences, it can lead to unnecessary polypharmacy and an increase in the burden of side effects.[9]

As summarized in **Table 7**, there is evidence that some agents (quetiapine, lithium, and olanzapine) are effective for preventing both manic and depressive episodes, others (risperidone and paliperidone) are effective for preventing mania but not depression, and another (lamotrigine) is effective for preventing depression but not mania.[9] Based on these findings, when providers choose monotherapies to treat acute episodes of mania or depression, medications with evidence of effectiveness for the acute episode, a breadth of effectiveness that includes prevention of both mania and depression, and a low side effect burden should be viewed as preferred or first-line treatments.[9]

Table 7. Monotherapies for Bipolar Disorder Management[9]

Medication	Acute Treatment of Mania	Prevention of Mania	Acute Treatment of Bipolar Depression	Prevention of Bipolar Depression
Quetiapine	X	X	X	X
Olanzapine	X	X	X	X
Lithium	X	X		X
Cariprazine	X		X	
Paliperidone	X	X		
Risperidone	X	X		
Aripiprazole	X			
Asenapine	X			
Carbamazepine	X			
Haloperidol	X			
Valproate	X			
Ziprasidone	X			
Lumateperone			X	
Lurasidone			X	
Lamotrigine				X

Management of Acute Bipolar Mania

Planning for the pharmacologic treatment of acute mania should always consider that the treatments effective for acute episodes will most often be continued after the resolution of mania and will form the basis of maintenance treatment to prevent the recurrence of mania.[9] For most individuals receiving treatment for bipolar disorder, prevention of depressive episodes should be considered when formulating any treatment plan.[9] Because lithium and quetiapine have demonstrated efficacy for acute mania, prevention of recurrence of episodes of mania, and prevention of recurrence of depression (with quetiapine additionally having efficacy for acute depression), the VA/DoD Work Group suggested their use as preferred or first-line monotherapies for the treatment of acute mania.[9] The Work Group acknowledged that lithium is approved by the FDA as maintenance monotherapy for bipolar disorder; however, quetiapine is FDA-approved for maintenance treatment only as an adjunct to lithium or valproate.[9] The benefits of lithium and quetiapine as treatments for acute mania and maintenance treatments to prevent both manic and depressive episodes outweighed the potential harms, including the risk of QT corrected for heart rate (QTc) interval prolongation, sedation, and metabolic effects as well as (in the case of lithium) tremor, renal effects, hypothyroidism, and the need for close monitoring.[9]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- We suggest lithium or quetiapine as monotherapy for acute mania (Weak Recommendation; Low-Quality Evidence).[9]
- If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest olanzapine, paliperidone, or risperidone as monotherapy for acute mania (Weak Recommendation; Very Low-Quality Evidence).[9]
- If lithium, quetiapine, olanzapine, paliperidone, or risperidone is not selected based on patient preference and characteristics, we suggest aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone as monotherapy for acute mania (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest lithium or valproate in combination with haloperidol, asenapine, quetiapine, olanzapine, or risperidone for acute mania symptoms in individuals who had an unsatisfactory response or a breakthrough episode on monotherapy (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania (Weak Recommendation; Very Low-Quality Evidence).[9]
- We suggest against the addition of aripiprazole, paliperidone, or ziprasidone after unsatisfactory response to lithium or valproate monotherapy for acute mania (Weak Recommendation; Low-Quality Evidence).[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics or second-generation antipsychotics, gabapentin, oxcarbazepine, or benzodiazepines as monotherapy or in combination for acute mania.[9]

Management of Bipolar Depression

Evidence from randomized, placebo-controlled clinical trials demonstrates that quetiapine is effective for the acute treatment of bipolar depression.[9] The effectiveness of quetiapine for acute episodes of bipolar depression must be interpreted in the context of its evidence for the prevention of mania and prevention of bipolar depression.[9] When considered together, the breadth of effectiveness is high indicating treatment of bipolar depression with quetiapine can reduce current symptoms, and when continued, can prevent recurrences of depression as well as the onset of mania.[9] The effectiveness for cariprazine, lurasidone, and lumateperone for the treatment of acute episodes of bipolar depression must be interpreted in the context of the current lack of evidence for their effectiveness as monotherapies for maintenance treatment for the prevention of mania or bipolar depression.[9] In this regard, the breadth of effectiveness is lower, and the established benefits for these agents are less comprehensive than those for quetiapine.[9]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- We recommend quetiapine as monotherapy for acute bipolar depression (Strong Recommendation; Moderate-Quality Evidence).[9]

- If quetiapine is not selected based on patient preference and characteristics, we suggest cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy for acute bipolar depression (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest lamotrigine in combination with lithium or quetiapine for acute bipolar depression (Weak Recommendation; Very-Low Quality Evidence).[9]
- There is insufficient evidence to recommend for or against antidepressants or lamotrigine as monotherapy for acute bipolar depression.[9]
- There is insufficient evidence to recommend for or against ketamine or esketamine as either a monotherapy or an adjunctive therapy for acute bipolar depression.[9]
- There is insufficient evidence to recommend for or against antidepressants to augment treatment with second-generation antipsychotics or mood stabilizers for acute bipolar depression.[9]

Preventing Symptom Recurrence

Evidence from recent systematic reviews suggests that lithium and quetiapine are the most effective maintenance medications to prevent recurrence of mania.[9] The efficacy of both medications appears to be similar, but each has unique advantages and disadvantages that would be relevant individual patients.[9] The systematic evidence review conducted to inform this guideline provides some support for LAI olanzapine, paliperidone, and risperidone as maintenance medications for the prevention of recurrence of mania, but this support is weaker than that for lithium and quetiapine.[9] Evidence does not support the use of lamotrigine to prevent recurrence of mania.[9] However, the evidence does support the use of lamotrigine to prevent bipolar depressive episodes.[9] Evidence suggests using the following antipsychotics in combination with lithium or valproate as maintenance medication for the prevention of recurrence of mania: aripiprazole, olanzapine, quetiapine, and ziprasidone.[9]

Evidence suggests that treatment with lithium, quetiapine, or olanzapine can help prevent the recurrence of depressive episodes in individuals with bipolar disorder.[9] Evidence regarding which of the 3 medications is the most efficacious is mixed, though there is some evidence that quetiapine and olanzapine performed better than other SGAs in the prevention of depression.[9] The body of evidence had some limitations because no studies directly compared the effectiveness of these medications against each other, so ascertaining whether one of these medications is more effective than the other is difficult.[9] The benefits of using lithium or quetiapine to prevent depressive episodes and for their effects on other outcomes (e.g., to decrease the risk of suicide, hospitalization) outweighed the potential harm of medication side effects.[9] The benefits of using olanzapine to prevent depressive episodes and other outcomes slightly outweighed the potential harm of medication side effects.[9]

VA/DoD pharmacologic recommendations and strength of evidence are as follows:

- We recommend lithium or quetiapine for the prevention of recurrence of mania (Strong Recommendation; Moderate-Quality Evidence).[9]
- If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest oral olanzapine, oral paliperidone, or risperidone long-acting injectable for the prevention of recurrence of mania (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania (Weak Recommendation; Low-Quality Evidence).[9]
- We suggest aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate for the prevention of recurrence of mania (Weak Recommendation; Very Low-Quality Evidence).[9]
- We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes (Strong Recommendation; Moderate-Quality Evidence).[9]
- We suggest lithium or quetiapine as monotherapy for the prevention of recurrence of bipolar depressive episodes (Weak Recommendation; Low-Quality Evidence).[9]

- If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest olanzapine as monotherapy for the prevention of recurrence of bipolar depressive episodes (Weak Recommendation; Moderate-Quality Evidence).[9]
- We suggest olanzapine, lurasidone, or quetiapine in combination with lithium or valproate for the prevention of recurrence of bipolar depressive episodes (Weak Recommendation; Low-Quality Evidence).[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics, second-generation antipsychotics, and anticonvulsants (including valproate) for the prevention of recurrence of mania.[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants (including valproate) as monotherapies for the prevention of recurrence of bipolar depressive episodes.[9]
- There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants in combination with a mood stabilizer for the prevention of recurrence of bipolar depressive episodes.[9]

Safety Concerns

- For individuals with bipolar disorder who are or might become pregnant and are stabilized on lithium, we suggest continued treatment with lithium at the lowest effective dose in a framework that includes psychoeducation and shared decision making (Weak Recommendation; Very Low-Quality Evidence).[9]
- We recommend against valproate, carbamazepine, or topiramate in the treatment of bipolar disorder in individuals of child-bearing potential (Strong Recommendation; Very-Low Quality Evidence).[9]

Veterans Administration/Department of Defense: Management of Major Depressive Disorder

The VA/DoD updated guidance for managing patients with MDD in 2022.[10] Treatment options include adding an SGA for patients who have not responded (<50% improvement in symptoms) to adequate antidepressant treatment trials (i.e. bupropion, mirtazapine, trazodone, vilazodone, vortioxetine, SSRIs, SNRIs) for 6 to 12 weeks.[10] Five atypical antipsychotics are FDA-approved for MDD as adjunctive treatment: aripiprazole, brexpiprazole, cariprazine, lurasidone, and quetiapine.[27] Olanzapine is approved for the treatment of acute treatment-resistant MDD when used in combination with fluoxetine, but olanzapine by itself is not indicated for treatment-resistant depression.[10] Other SGAs such as cariprazine and risperidone, while not indicated, are used off-label for augmentation.[10]

While there is a significant benefit with augmentation using SGAs, there is also the potential for significant side effects.[10] Fair-quality evidence found that compared to placebo, aripiprazole had an increased incidence of akathisia and weight gain; olanzapine had an increased incidence of weight gain and sedation; quetiapine had more weight gain and sedation; and risperidone had greater, but not statistically significant, weight gain when compared to antidepressants plus placebo.[10] While the risk is generally lower than FGAs, another significant adverse effect associated with SGAs is tardive dyskinesia.[10] Due to the possibility of additional side effects and the potential for drug-drug interactions with augmentation, SGAs require appropriate monitoring (e.g., glucose, complete blood count, hepatic panel, lipid panel, body mass index, waist circumference, blood pressure, involuntary movements/tardive dyskinesia, slit lamp exam [quetiapine-only]).[10]

VA/DoD pharmacologic recommendation and strength of evidence:

- For patients with MDD who have demonstrated partial or no response to an adequate trial of initial pharmacotherapy, we suggest (not rank ordered):
  - Switching to another antidepressant (including tricyclic antidepressants, monoamine oxidase inhibitors, esketamine, ketamine, or nefazodone)
  - Switching to psychotherapy
  - Augmenting with psychotherapy

- Augmenting with an SGA (Weak Recommendation; Low-Quality Evidence).[10]

Oregon Health Authority: Mental Health Clinical Advisory Group

The MHCAG has developed treatment algorithms and clinical practice recommendations to guide clinicians, patients, and caregivers in several mental health disorders. Specific algorithms were developed for schizophrenia, MDD, and bipolar disorder and are summarized below.

- In 2023, updated recommendations for management of schizophrenia were reviewed by the MHCAG.[11] Two algorithms were developed to guide treatment with either FGA or SGA medications. They can be accessed here: MHCAG Treatment of Schizophrenia with Antipsychotic Medications
  - Choice of treatment should be based on the side effect profiles of medications, the individual's treatment-related preferences, and prior treatment response.[11]
  - When initially choosing an oral antipsychotic medication for maintenance treatment, discuss the feasibility of using a LAI formulation long-term with the patient.[11] The oral and LAI formulations of a specific medication are comparable, so trial the oral formulation first to assure efficacy and tolerability.[11]
  - People who do not respond to two trials of antipsychotic medication with adequate dosage, duration, and adherence should be offered clozapine. Clozapine is associated with better outcomes in people whose condition has not sufficiently responded to other antipsychotic medications.[11]

- In 2023, the MHCAG updated recommendations for the treatment of MDD.[14] The algorithm can be accessed here: MHCAG Medication Algorithm for the Treatment of Major Depressive Disorder
  - Recommended first-line agents include SSRIs, SNRIs, bupropion, and mirtazapine.[14]
  - Second-generation antipsychotics include those with FDA approval as adjunct treatment (aripiprazole, brexpiprazole, quetiapine, and olanzapine in combination with fluoxetine) and risperidone (with evidence to support off-label use).[14]

- In 2019, MHCAG evaluated bipolar disorder and developed an algorithm for managing acute bipolar depression[13] and another algorithm for managing acute bipolar mania.[12] They can be accessed here: MHCAG Acute Bipolar Depression Algorithm and MHCAG Acute Bipolar Mania Algorithm.
  - Bipolar depression management recommendations:
    - First-line monotherapy medication options for treatment of bipolar depression include lamotrigine, lithium, or quetiapine.[13]
    - Second-line monotherapy medications include cariprazine, divalproex, and lurasidone.[13]
    - Combination therapy with lamotrigine and another treatment medication is recommended as a second-line alternative option.[13] Other options include:
      - Combination of lurasidone and lithium OR divalproex
      - Combination of olanzapine and fluoxetine
      - Bupropion OR a combination of SSRI and another bipolar medication treatment.[13]
    - Aripiprazole should be avoided in treatment of acute bipolar depression due to evidence of ineffectiveness.[13]
    - Antidepressant monotherapy should also be avoided due to ineffectiveness and the risk of triggering a manic or mixed episode.[13]
  - Acute bipolar mania management recommendations:
    - First-line combination therapy recommendations are quetiapine combined with lithium OR quetiapine combined with divalproex.[12]
    - Second-line monotherapy options include: aripiprazole, asenapine, cariprazine, risperidone, and ziprasidone.[12]
    - Lamotrigine should be avoided for treatment of acute mania only.[12]

New Formulations and Indications:

New Formulations

- March 2024: A new extended-release injectable formulation of risperidone, RISVAN, received FDA-approval for treatment of schizophrenia in adults.[20] The manufacturer recommends that tolerability to this medication should be established with oral risperidone prior to initiating treatment with the extended-release risperidone intramuscular injection.[20] The recommended dose is 75 mg (for maintenance of 3 mg orally once daily) to 100 mg (for maintenance of 4 mg orally once daily) injected once monthly.[20] Patients who are stable on oral risperidone less than 3 mg per day or higher than 4 mg per day may not be candidates for this formulation.[20] Neither a loading dose or supplemental oral risperidone is recommended.[20] Other risperidone LAI injections include RISPERIDAL CONSTA, which is administered every 2 weeks; PERSERIS, which is administered once a month; and UZEDY, which can be administered at 1- and 2-month dosing intervals.

  One 12-week placebo-controlled trial evaluated the safety and efficacy of RISVAN in adults with schizophrenia (Study 1; NCT03160521).[20] This study compared extended-release risperidone injection (75 mg and 100 mg intramuscular every 4 weeks) with placebo in adults (aged 18 to 65 years) experiencing acute exacerbations of schizophrenia.[20] Patients were required to have a PANSS total score of 80 to 120 (moderate to severely ill) for study inclusion.[20] The primary endpoint was the change in PANSS total score from baseline to end of study at Day 85. Both risperidone 75- and 100-mg doses demonstrated a statistically and clinically significant improvement in PANSS total score compared with placebo (see **Table 8**).[20]

  Table 8. Mean Change from Baseline in PANSS Total Score at day 85 with ER Risperidone in Adults with Schizophrenia[20]

Treatment Group (n = number of patients)	Mean Baseline PANSS Score	LSM Change from Baseline	Placebo-Subtracted Difference (95% CI)
Extended-release risperidone 75 mg injection (n=129)	96.3	-24.6	-13.0 (-17.3 to -8.8)
Extended-release risperidone 100 mg injection (n=129)	96.1	-24.7	-13.3 (-17.6 to -8.9)
Placebo (n=132)	96.4	-11.0	-
Abbreviations: CI = confidence interval; ER = extended release; LSM = least squares mean; mg = milligrams; PANSS = Positive and Negative Syndrome Scale			

  Adverse reactions that led to discontinuation in risperidone-treated patients in this trial included: abscess limb (0.3%), skin infection (0.3%), fall (0.3%), humerus fracture (0.3%), liver function test increased (0.3%), neutrophil count decreased (0.3%), mental impairment (0.3%), erectile dysfunction (0.3%), galactorrhea (0.3%), lactation disorder (0.3%), and pruritus (0.3%).[20] The most frequently reported adverse reactions (≥5% and twice placebo) were blood prolactin increase, hyperprolactinemia, akathisia, headache, sedation (including somnolence), weight increased, injection site pain, and increased alanine aminotransferase.[20]

- July 2024: OPIPZA, a new oral film formulation of aripiprazole, received FDA approval for treatment of schizophrenia in patients ages 13 years and older, adjunctive treatment of MDD in adults, irritability associated with autistic disorder in pediatric patients aged 6 years and older, and treatment of Tourette's disorder in pediatric patients aged 6 years and older.[21] Daily dosing depends upon the indication, age, and weight (for pediatric patients). The safety and efficacy of aripiprazole oral film in the FDA-approved indications is based on studies of another oral aripiprazole product.[21]

- July 2024: ERZOFRI, a new formulation of extended-release injectable paliperidone received FDA-approval for treatment of schizophrenia in adults and treatment of schizoaffective disorder in adults as monotherapy or as an adjunct to mood stabilizers or antidepressants.[22] The recommended dose is 351 mg

as an initial dose followed by 39 mg to 234 mg once a month via provider-administered intramuscular injection.[22] The safety and efficacy of this new extended-release paliperidone product is based upon studies of a different once-a-month paliperidone extended-release injectable suspension.[22]

New Indications

- December 2021: CAPLYTA (lumateperone) oral capsules received an expanded FDA-approved indication for treatment of depressive episodes associated with bipolar I or II disorder in adults, as monotherapy or as adjunctive therapy with lithium or valproate.[15] Prior to this approval, lumateperone was FDA-approved for the treatment of adults with schizophrenia.[15]

  The efficacy of lumateperone monotherapy was evaluated in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adults who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 3; NCT03249376).[15] The primary efficacy measure was the change from baseline in MADRS total score at Week 6.[15] A total of 381 patients were randomized to receive lumateperone 42 mg or placebo.[15] Demographic and baseline characteristics were similar for both groups.[15] The median age was 45 years, 58% were female, 91% were White, and 8% were Black.[15] Compared to the placebo group, patients randomized to lumateperone showed a statistically significant improvement from baseline to Day 43 in the MADRS total score (least squares mean [LSM] change, -12.1 vs. -16.7; difference; -4.6; 95% CI -6.3 to -2.8).[15]

  The efficacy of lumateperone, as adjunctive therapy with lithium or valproate, was assessed in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 4; NCT02600507). The primary efficacy measure was the change from baseline in MADRS total score at Week 6. A total of 529 patients were randomized to receive lumateperone 28 mg (two-thirds the recommended daily dose), lumateperone 42 mg, or placebo.[15] Demographic and baseline characteristics were similar for the lumateperone and placebo groups.[15] The median age was 46 years, 58% were female, 88% were White, and 11% were Black.[15] Compared to the placebo group, patients randomized to adjunctive lumateperone 42 mg showed a statistically significant improvement from baseline to Day 43 in the MADRS total score (LSM change -14.5 vs. -16.9; difference -2.4; 95% CI -4.4 to -0.4).[15] The treatment effect in the lumateperone 28 mg group vs. placebo was not statistically significant.[15]

- December 2022: VRAYLAR (cariprazine) oral capsules were approved as adjunctive therapy to antidepressants for the treatment of MDD in adults.[16] Prior to this approval, cariprazine was FDA-approved for treatment of schizophrenia and bipolar disorder in adults.[16] The safety and efficacy of cariprazine as adjunctive therapy in MDD was evaluated in 2 RCTs conducted in adults. The mean age of enrolled patients was 45 years, 72% were female and 85% were White.[16] The primary endpoint was change from baseline in MADRS total score to Week 6 compared with placebo.[16] In study 1, the treatment effect on MADRS improvement was statistically significant with cariprazine 1.5 mg per day, but not for 3 mg per day (see **Table 9**). In study 2, the MADRS improvement with cariprazine 2 to 4.5 mg per day (mean dose = 2.6 mg) was statistically significant compared to placebo, but not for doses of cariprazine 1 to 2 mg per day (see **Table 9**).

  The FDA recommended dosing for cariprazine as adjunctive therapy to antidepressants for MDD is a starting dose of 1.5 mg once daily with a recommended maintenance dose of 3 mg once daily.[16] In people with schizophrenia, the recommended maintenance dose of cariprazine is 1.5 to 6 mg once daily.[16] For bipolar mania, the recommended cariprazine maintenance dose is 3 mg to 6 mg once daily. [16]

Table 9. Change in MADRS with Adjunctive Cariprazine in Adults with MDD over 6 Weeks[16]

Treatment Group (n = number of patients)	Mean Baseline MADRS Score	LSM Change from Baseline	Placebo-Subtracted Difference (95% CI)

Study 1			
Cariprazine 1.5 mg/day + ADT (n=250)	32.8	-14.1	-2.5 (-4.2 to -0.9)
Cariprazine 3 mg/day + ADT (n=252)	32.7	-13.1	-1.5 (-3.2 to 0.1)
Placebo + ADT (n=249)	31.9	-11.5	-
Study 2			
Cariprazine 1 to 2 mg/day + ADT (n=273)	29.0	-13.4	-0.9 (-2.4 to 0.6)
Cariprazine 2 to 4.5 mg/day + ADT	29.3	-14.6	-2.2 (-3.7 to -0.6)
Placebo	28.9	-12.5	-
Abbreviations: ADT = antidepressant therapy; CI = confidence interval; LSM = least squares mean; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; mg = milligrams			

The adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in cariprazine-treated patients and at least twice the rate of placebo was akathisia (2%).[16] Overall, 6% of the patients who received cariprazine discontinued treatment due to an adverse reaction, compared with 3% of placebo-treated patients in these trials.[16] The most common adverse effects observed in the two 6-week trials included akathisia, extrapyramidal symptoms, nausea, and insomnia.[16]

- December 2021: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for management of schizophrenia in pediatric patents aged 13 to 17 years.[17] Prior to this approval, brexpiprazole was approved for use as adjunctive therapy for treatment of MDD in adults and treatment of schizophrenia in adults.[17] Safety and effectiveness of brexpiprazole for treatment of schizophrenia in pediatric patients 13 years of age and older is supported by evidence from studies in adults with schizophrenia, pharmacokinetic data from adults and pediatric patients, and safety data in pediatric patients 13 to 17 years of age.[17] Adverse reactions reported in clinical studies for this age group were generally similar to those observed in adult patients.[17]

- May 2023: REXULTI (brexpiprazole) oral tablets received an expanded FDA-approved indication for treatment of agitation associated with dementia due to Alzheimer's disease (AAD).[17] Prior to this approval there were no FDA-approved treatment options for AAD.[18] Like all antipsychotics, brexpiprazole has a boxed warning for increased risk of mortality in elderly patients with dementia-related psychosis, based on a meta-analysis the FDA conducted in 2005.[18]

  Two multi-center, double-blind, placebo-controlled, phase 3 RCTs evaluated brexpiprazole over a 12-week treatment period in patients with AAD.[18,52] Study 1 (n=433) used fixed brexpiprazole 1 mg and 2 mg once daily dosing, while Study 2 (n=270) employed flexible brexpiprazole dosing (0.5 mg to 2 mg once daily).[52] Eligible patients were 55 to 90 years of age, with a diagnosis of AAD and a Mini-Mental State Examination (MMSE) score of 5 to 22.[52] The mean age of enrolled patients was 74 years, 58% were female, and 95% were White.[52] Two-thirds (67%) of enrolled patients were institutionalized, with moderate cognitive impairment (mean MMSE score = 62).[18] In general, demographic characteristics were similar between males and females, age groups, and race groups across treatment arms.[18]

  The primary endpoint for both studies was the mean change from baseline in the Cohen Mansfield Agitation Inventory (CMAI) at Week 12.[18,52] The purpose of the CMAI is to assess the frequency of agitated behaviors in elderly patients and was originally developed for use in the nursing home, but has since been expanded for use in community dwelling patients with AAD.[52] The CMAI-Long Form is a caregivers' rating instrument consisting of 29 items all rated on a 1 to 7 scale with 1 being the "best" rating (no occurrence) and 7 being the "worst" rating (frequency of several times an hour).[18] The CMAI Total Score is the sum of ratings for all 29 items and ranges from 29 to 203.[52] Higher scores indicate more frequent agitated behaviors.[52] The key secondary efficacy measure was the Clinical Global Impression – Severity of illness (CGI-S) score as related to agitation.[52] MCIDs were not established for either outcome measurement.

In Study 1, brexpiprazole 2 mg had a small improvement in CMAI total score from baseline to Week 12 compared with placebo (see **Table 10**).[52] The brexpiprazole 1 mg group did not show meaningful difference from placebo on the primary efficacy endpoint (see **Table 10**).[52] In Study 2, there was no difference between brexpiprazole and placebo in the CMAI change from baseline at Week 12.[52] Changes from baseline in the CGI-S score at Week 12 were not statistically significant between brexpiprazole and placebo in either study.[52]

Table 10. Effects Of Brexpiprazole On Symptoms Of Agitation (CMAI Change From Baseline at Week 12)[52]

Dose (number of patients)	Baseline Mean CMAI score	Change from baseline at Week 12	Adjusted Mean Difference
Study 1			
Brexpiprazole 2 mg (n=138)	71.0	-21.6	-3.77 (95% CI, -7.38 to -0.17) p = 0.04
Brexpiprazole 1 mg (n=134)	70.5	-17.6	0.23 (95% CI, -3.40 to 3.86) p = 0.90
Placebo (n=131)	72.2	-17.8	-
Study 2			
Brexpiprazole 0.5 to 2 mg (n=131)	71.5	-18.9	-2.34 (95% CI, -5.49 to 0.82) p = 0.15
Placebo (n=135)	68.6	-16.5	-
Abbreviations: CI = confidence interval; CMAI = Cohen-Mansfield Agitation Inventory; mg = milligram			

In study 1, treatment-emergent adverse events (TEAEs) with incidence of 5% or more among patients receiving brexpiprazole 2 mg/day were headache (9.3% versus 8.1% with placebo), insomnia (5.7% versus 4.4%), dizziness (5.7% versus 3.0%), and urinary tract infection (5.0% versus 1.5%).[52] In Study 2, TEAEs with incidence of 5% among patients receiving brexpiprazole 0.5–2 mg/day were headache (7.6% versus 12.4% with placebo) and somnolence (6.1% versus 3.6%).[52] In both studies, the majority of TEAEs were mild or moderate in severity.[52]

- April 2024: FANAPT (iloperidone) received an expanded indication for acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.[19] Prior to this approval, iloperidone was FDA-approved to treat schizophrenia in adults.[19] The efficacy of iloperidone in the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults was evaluated in one multicenter, randomized, double-blind, placebo-controlled, 4-week study that enrolled patients who met the DSM-5 criteria for bipolar I disorder, manic or mixed type (Study 1; NCT04819776).[19] The median age was 46 years, 45% were female, 64% were White, and 28% were Black.[19] The primary endpoint was change in manic symptoms assessed with the Young Mania Rating Scale (YMRS) total score from baseline to Day 28 (n=392). Iloperidone 24 mg/day was superior to placebo with a LSM change in YMRS score of -10.0 versus -14.0 (difference -4.0 (95% CI -5.70 to -2.25)).[19] In this trial, the following adverse reactions occurred in 5% or more incidence in the patients treated with iloperidone and at least twice the placebo rate: tachycardia, dizziness, dry mouth, hepatic enzymes increased, nasal congestion, weight increased, hypotension, and somnolence.[19]

New FDA Safety Alerts:

Table 11. Description of new FDA Safety Alerts[53]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Brexpiprazole	REXULTI	5/10/23	Warnings and Precautions	Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis *without* agitation associated with Alzheimer's disease.
Brexpiprazole	REXULTI	5/7/24	Pediatric Use	**Schizophrenia** The safety and effectiveness of REXULTI for the treatment of schizophrenia has not been established in pediatric patients less than 13 years of age. **Irritability Associated with Autism Spectrum Disorder** The safety and effectiveness of REXULTI for the treatment of irritability associated with autism spectrum disorder have not been established in pediatric patients. Effectiveness was not demonstrated, in an 8-week, double-blind, placebo-controlled, flexible-dose clinical study conducted in 119 REXULTI-treated pediatric patients 5 to 17 years of age with irritability associated with autism spectrum disorder diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] criteria. In this study, somnolence (including sedation) occurred at a higher rate than reported in other REXULTI studies evaluating adults and elderly patients (16% in REXULTI-treated pediatric patients versus 5% for placebo). The mean increase in age-and-gender adjusted body weight z-score from baseline to last visit was 0.3 for REXULTI-treated patients versus 0.1 for placebo-treated patients. Increases in age-and-gender adjusted body weight z-score of at least 0.5 SD from baseline was higher in REXULTI-treated patients versus placebo (19% versus 5%).
Clozapine	CLOZARIL	1/22/25	Boxed Warning	Pericarditis added to the boxed warning statement about the risk of myocarditis, pericarditis, cardiomyopathy and mitral valve incompetence: Fatal myocarditis and cardiomyopathy have occurred with CLOZARIL treatment. Discontinue CLOZARIL and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with CLOZARIL-related myocarditis or cardiomyopathy should not be rechallenged with CLOZARIL. Consider the possibility of myocarditis, pericarditis, or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur.

Olanzapine Olanzapine/Fluoxetine Olanzapine/Samidorphan Quetiapine Ziprasidone	ZYPREXA SYMBYAX LYBALVI SEROQUEL GEODON	1/22/25	Warnings and Precautions	**Hyperprolactinemia** Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.
Ziprasidone	GEODON	1/22/25	Contraindications Warnings and Precautions	Ziprasidone is contraindicated in patients taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome. **Serotonin Syndrome** Ziprasidone can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, tramadol, meperidine, methadone, lithium, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., monoamine oxidase inhibitors (MAOIs).
Aripiprazole	ABILIFY	1/22/25	Use in Specific Populations	**Lactation** Aripiprazole is present in human breast milk. Based on published case reports and pharmacovigilance reports, aripiprazole exposure during pregnancy and/or the postpartum period can lead to variable effects on milk supply in the post-partum period, including clinically relevant decreases in milk supply which may be reversible with discontinuation of the drug. There are also reports of aripiprazole exposure during pregnancy and no maternal milk supply in the post-partum period. Effects on milk supply are likely mediated through decreases in prolactin levels, which have been observed. Monitor the breastfed infant for dehydration and lack of appropriate weight gain.
Olanzapine/Samidorphan	LYBALVI	1/22/25	Use in Specific Populations	**Lactation** Clinical Considerations: Infants exposed to LYBALVI should be monitored for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements). Data: A single dose milk-only lactation study was conducted in 12 healthy adult lactating women. Following a 5 mg/10 mg oral dose of olanzapine and samidorphan, the mean quantities in human milk were detected to be 0.002 mg

				and 0.006 mg, respectively. The calculated weight-adjusted infant daily oral dose for olanzapine (~ 0.0005 mg/kg) and samidorphan (0.001 mg/kg) was less than 1% of the weight-adjusted maternal dose for olanzapine (0.07 mg/kg) and samidorphan (0.15 mg/kg), respectively.

Randomized Controlled Trials:

A total of 571 citations were manually reviewed from the initial literature search. After further review, 570 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. The full abstract is included in **Appendix 4**.

Table 12. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Reif, et al.[54] ESCAPE-TRD OL, single-blind, MC Phase 3 RCT	1.Esketamine nasal spray flexibly dosed: 18-64 yrs: 56 or 84 mg 65-74 yrs: 28 mg Administered twice weekly during Weeks 1-4, then weekly during Weeks 5-8, and weekly or every 2 weeks during Weeks 9 to 32 + ADT Vs. 2. Quetiapine extended-release oral 150-300 mg/day + ADT	1. n=336 2. n=340 Adults aged 18 to 74 yrs with MDD with no response to ADT	Remission: MADRS score $\leq$ 10 at Week 8	1. n=91; 27.1% 2. n=60; 17.6% Difference: 9.5%; p=0.003 OR 1.74; 95% CI 1.20 to 2.52 Esketamine was superior to quetiapine in achieving remission at Week 8	-Open label, single bind (raters unaware of patient assignments) -Trial designed and coordinated by the manufacturer of esketamine -Each medication had a distinct adverse effect profile, which could have led to unblinding by the raters
Abbreviations: ADT = antidepressant therapy; CI = confidence interval; MADRS = Montgomery-Åsberg Depression Scale; MC = multi-center; MDD = major depressive disorder; mg = milligrams; OL = open label; OR = odds ratio; RCT = randomized controlled trial; yrs = years					

New Drug Evaluation: LYBALVI (olanzapine/samidorphan)
LYBALVI, a combination of olanzapine and samidorphan (an opioid receptor antagonist), is indicated for treatment of schizophrenia in adults, and maintenance monotherapy for bipolar I disorder in adults, and acute treatment of manic or mixed episodes of bipolar I disorder as monotherapy or adjunct to lithium or valproate.[23] A fixed dose of samidorphan 10 mg is combined with olanzapine 5, 10, 15 or 20 mg to mitigate olanzapine-associated weight gain.[26] The risk of weight gain with olanzapine is generally dose dependent, with higher doses often associated with a greater likelihood of weight gain.[26] The exact mechanism by which samidorphan mitigates olanzapine-associated weight gain is not known.[23] As with other oral antipsychotics, olanzapine/samidorphan carries a black box warning of increased mortality in elderly patients with dementia-related psychosis.[23] It is contraindicated in patients using opioids or undergoing acute opioid withdrawal.[23]

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

Clinical Efficacy:
The efficacy of olanzapine/samidorphan in the treatment of adult patients with bipolar I disorder is based upon studies of orally administered olanzapine as monotherapy and adjunctive therapy to lithium or valproate.[23] One clinical trial evaluated the safety and efficacy of olanzapine/samidorphan in schizophrenia (ENLIGHTEN-1)[24] and another clinical trial (ENLIGHTEN-2)[26] evaluated the weight-mitigation effect of samidorphan on olanzapine in patients with schizophrenia. Both studies are described and evaluated below in **Table 16**.

The efficacy of olanzapine/samidorphan for schizophrenia in adults was assessed in a 4-week, double-blind, placebo-controlled, phase 3 RCT (ENLIGHTEN-1).[24] Adult patients (n=403) with an acute exacerbation of schizophrenia were randomized in a 1:1:1 ratio to olanzapine/samidorphan, olanzapine monotherapy, or placebo.[24] Patients assigned to olanzapine/samidorphan could receive either 10 mg/10 mg or 20 mg/10 mg once a day, and patients assigned to olanzapine could receive either 10 mg or 20 mg a day.[24] The study was designed to compare olanzapine/samidorphan with placebo, not with olanzapine.[24]
Eligible patients were 18 to 70 years of age, with a body mass index (BMI) of 18.0–40.0 kg/m^2, PANSS total score of 80 or more, and a score of 4 or more on at least 3 of the selected Positive Scale items (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution).[24] Patients were also required to have a Clinical Global Impression-Severity (CGI-S) score of 4 or more.[24] For the first 2 weeks of the study, patients were hospitalized and dose titration was permitted. In the last 2 weeks of the RCT, patients could be treated as inpatients or outpatients with a fixed dose of study medication. Approximately 89% of enrolled subjects were hospitalized for the entire study.[24] Sixty-one percent of enrolled patients were male and 69% were White, with an average age of 41 years and mean baseline BMI of 26.6 kg/m^2.[24]

The primary efficacy endpoint was change from baseline in PANSS total score at Week 4.[24] Compared with patients on placebo, a statistically significant improvement in the change from baseline in PANSS total score at Week 4 was observed in patients treated with olanzapine/samidorphan (LSM change, -17.5 vs. -23.9; difference, -6.4; 95% CI -10.0 to -2.8).[24] There is no MICD for changes in PANSS total score, although response to treatment is typically defined in most clinical trials as greater than 20% improvement in the PANSS score.[25] The inclusion of samidorphan did not negatively impact the antipsychotic efficacy of olanzapine, and PANSS scores were similar in people randomized to olanzapine and olanzapine/samidorphan.

A second study (ENLIGHTEN-2) evaluated the weight-mitigation effect of samidorphan. In this 24-week, double-blind, phase 3 RCT, once daily olanzapine/samidorphan (10 mg/10 mg) or (20 mg/10 mg) was compared to once daily olanzapine 10 mg or 20 mg in clinically stable outpatients (n=561) with

schizophrenia.[26] The efficacy of olanzapine/samidorphan on psychotic symptoms was not evaluated in this study.[26] Most of the patients were African American males with average age of 40 years old and a mean baseline BMI 25.45 kg/m^2.[26] Co-primary endpoints were the percent change from baseline in body weight and the proportion of subjects with 10% or more weight gain from baseline at Week 24. The percent change in body weight from baseline to week 24 was 4.21% with olanzapine/samidorphan and 6.59% with olanzapine (difference, -2.38%; 95% CI -3.88% to -0.88%; p=0.002).[26] The proportions of subjects with weight gain of 10% or more from baseline was 17.8% in the olanzapine/samidorphan group and 29.8% in the olanzapine group (difference 12%; 95% CI -22.8 to -4.6; p=0.003; NNT = 8).[26]

Study Limitations:
ENLIGHTEN-1 was a short-term, 4-week study. High placebo response was observed in PANSS improvement (LSM improvement =-17.5), which is consistent with reported trends in placebo-controlled schizophrenia trials.[24] ENLIGHTEN-2 restricted BMI to 18-30 kg/m^2 in patients with long history of illness and may have inadvertently included patients relatively resistant to antipsychotic associated weight gain. In addition, almost 40% of patients discontinued the study early and no adherence measures were performed.

Clinical Safety:
The safety of olanzapine/samidorphan was evaluated in 1262 patients (18 to 67 years of age) diagnosed with schizophrenia in 4 double-blind, controlled studies and 3 long-term safety extension studies of up to 3 years of duration.[23] The most common adverse effects reported with olanzapine/samidorphan were increased weight, somnolence, dry mouth, and headache.[23] The adverse effects reported in the 4-week ENLIGHTEN-1 trial are presented in **Table 13**. Adverse reactions that led to study discontinuation in ENLIGHTEN-1 included abnormal liver function tests and worsening schizophrenia in 1% of participants.[23] Adverse effects reported in the 24-week ENLIGHTEN-2 trial are summarized in **Table 14**. Adverse reactions that led to discontinuation of olanzapine/samidorphan in more than one patient in the ENLIGHTEN-2 RCT included somnolence (2%), increased weight(2%), neutropenia (2%), increased glycosylated hemoglobin (1%), worsening schizophrenia (1%), and abnormal liver function test abnormal (1%).[23]

Table 13. Adverse Reactions Reported in ≥ 2% of Olanzapine/Samidorphan-Treated Patients and Greater than Placebo Over 4 Weeks[23]

Adverse Reaction	Placebo (n=134)	Olanzapine/Samidorphan (n=134)
Increased Weight	3%	19%
Somnolence	2%	9%
Dry Mouth	1%	7%
Headache	3%	6%
Increased Blood Insulin	1%	3%
Sedation	0%	2%
Dizziness	1%	2%
Decreased Neutrophil Count	0%	2%

Table 14. Adverse Reactions Reported in ≥ 5% of Olanzapine/Samidorphan-Treated and Olanzapine-Treated Patients Over 24 Weeks[23,26]

Adverse Reaction	Olanzapine (n=276)	Olanzapine/Samidorphan (n=274)
Increased Weight	36%	25%
Somnolence	18%	21%

Dry Mouth	8%	13%
Increased Appetite	12%	11%
Increased Waist Circumference	8%	6%
Increased Blood Creatinine Phosphokinase	4%	5%

Other safety considerations:
Olanzapine/samidorphan may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.[23] This medication is not recommended for use in patients with end-stage renal disease (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m^2).[23] Use with strong CYP3A4 inducers should be avoided due to potential drug interactions.[23]

Look-alike / Sound-alike Error Risk Potential: No results available

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduction of psychosis symptoms
2) Improved quality of life or function
3) No significant weight gain
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint(s):
1) LSM improvement in PANSS score from baseline to week 4
2) Change in body weight
3) Proportion of people with ≥ 10% change in body weight

Table 15. Pharmacology and Pharmacokinetic Properties.[23]

Parameter	
Mechanism of Action	Olanzapine: second generation antipsychotic -dopamine and serotonin antagonist Samidorphan: opioid receptor antagonist
Absolute Oral Bioavailability	Olanzapine: NA Samidorphan: 69%
Protein Binding	Olanzapine: 93% Samidorphan: 23%-33%
Elimination	Olanzapine: Hepatic Samidorphan: Hepatic
Half-Life	Olanzapine: 35-52 hours Samidorphan: 7-11 hours
Metabolism	Olanzapine: CYP1A2, UGT1A4, CYP2D6 Samidorphan: CY3A4, CYP3A5, CYP2C19, CYP2C8
Abbreviations: CYP=cytochrome P450; NA = Not Applicable; UGT=Uridine 5'-diphospho-glucuronosyltransferase	

Table 16. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Potkin, et al.[24] ENLIGHTEN-1 Phase 3, DB, MC RCT	1. Olanzapine/ Samidorphan: 10 mg/10mg or 20mg/10mg orally once a day 2. Olanzapine 10 or 20mg orally once a day 3. Placebo orally once a day	Demographics: -Mean age: 41 yrs -Male: 61% -Race White: 69% Black: 28% Asian: 1% Other: 1.7% -Mean BMI: 26.6 kg/m^2 Key Inclusion Criteria: -Adults aged 18-70 yrs with diagnosis of acute schizophrenia or relapse of schizophrenia symptoms -BMI 18-40 kg/m^2 -PANSS score > 80 -CGI-S score ≥ 4 Key Exclusion Criteria: -History of treatment-resistant schizophrenia - Less than 1 yr since onset of symptoms -History of diabetes - Opioid agonist use with 14 days of screening -Use of olanzapine, chlorpromazine, thioridazine, or long-acting injectable antipsychotic within 12 months of screening -Use of clozapine within 6 months of screening	ITT: 1. 132 2. 132 3. 133 PP: 1. 122 2. 119 3. 111 Attrition: 1. 12 (9%) 2. 14 (10.5%) 3. 23 (17.2%)	Primary Endpoint: LSM improvement in PANSS score from baseline to Week 4 in ITT population 1.-23.9 2.-22.8 3.-17.5 Difference 1 vs 3 = -6.4 95% CI -10.0 to -2.8 P<0.001 Difference 2 vs. 3 = -5.3 95% CI -8.9 to -1.7 P=0.004 Secondary Endpoint: LSM change in CGI-S from baseline to Week 4 1. -1.21 2. -1.27 3. -0.84 Difference 1 vs 3 = -0.38 95% CI -0.61 to -0.14 P=0.002 Difference 2 vs 3 = -0.44 95% CI -0.67 to -0.20 P<0.001	NA NA NA NA	Any Adverse Effect 1. 73 (54.5%) 2. 73 (54.9%) 3. 60 (44.8%) Serious Adverse Effects 1. 1 (0.7%) 2. 1 (0.8%) 3. 0 Weight Gain 1. 25 (18.7%) 2. 19 (14.3%) 3. 4 (3.0%) p-values and 95% CI NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IWRS. Baseline characteristics were balanced between groups. Performance Bias: Low. All study medications were single, coated, bi-layer tablets. Patients and investigators blinded to treatment assignments. Detection Bias: Unclear. Method of blinding of outcome assessors not described. Attrition Bias: High. More placebo-treated patients withdrew compared to active treatment arms due to lack of efficacy, withdrawal by patients, or adverse effects. Missing data was imputed using the last observation carried forward. Reporting Bias: Low. Protocol available on-line. All outcomes reported as planned. Other Bias: Unclear. Trial funded by manufacturer. The manufacturer was also involved in design, data collection and analysis. The primary author has received research support from manufacturer. **Applicability**: Patient: Patients who were experiencing acute schizophrenia episode or relapse were included in this trial. Patients with bipolar disorder were not included in this trial. Intervention: Samidorphan dosing determined in Phase 2 trials. Olanzapine dosing is within FDA-approved therapeutic ranges. Comparator: Placebo is an appropriate comparator for efficacy. Outcomes: PANSS and CGI scores are validated outcomes used in other schizophrenia trials. Setting: A total of 38.4% of the patients were from the United States. All other patients were from Bulgaria, Ukraine, or Serbia.
2. Correll, et al[55] ENLIGHTEN-2	1. Olanzapine/ Samidorphan: 10 mg/10 mg and 20 mg/10 mg orally once a day	Demographics: -Mean age: 40.2 yrs -Male: 72.7% -Race White: 23.3% Black: 71.3%	ITT: 1. 276 2. 274 PP:	Co-Primary Endpoints: LSM percent change from baseline in body weight at Week 24 1. 4.21% 2. 6.59%	NA	Any Adverse Effect 1. 203 (74.1%) 2. 227 (82.2%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Randomized 1:1. Method of randomization not described. Baseline characteristics were balanced between groups. Performance Bias: Low. Patients, investigators, and outcomes assessors blinded to treatment assignment.

Phase 3 MC, DB, RCT	2. Olanzapine 10 mg and 20 mg orally once a day	Asian: 1.5% Key Inclusion Criteria: -Adults aged 18-55 yrs with diagnosis of schizophrenia -BMI 18-30 kg/m^2 -Stable body weight (≤ 5% self-reported change for ≥ 3 mos prior to study entry) Key Exclusion Criteria: -History of treatment-resistant schizophrenia - Less than 1 yr since onset of symptoms - Naïve to antipsychotic medications - Opioid agonist use with 14 days of screening	1. 176 2. 176 Attrition: 1. 98 (36%) 2. 100 (36%)	Difference: -2.38 95% CI -3.88 to -0.88 P=0.003 Co-Primary Endpoints: Proportion of patients with ≥ 10% weight gain at Week 24 1. 47 (17.8%) 2. 81 (29.8%) Difference: -12% 95% CI -22.8 to -4.6 P=0.003 Secondary Endpoints: Proportion of patients with ≥ 7% weight gain at Week 24 1. 73 (27.5%) 2. 116 (42.7%) Difference: -15.9% 95% CI -25.3 to -6.5 P=0.001	12%/8 15.9%/7	Serious Adverse Events: 1. 10 (3.6%) 2. 7 (2.5%) Adverse Events Leading to Treatment Discontinuation 1. 33 (12%) 2. 27 (9.8%) 95% CI and p value NR	NA	Medication supplied in identical formulations for both study arms. Detection Bias: Low. Assessors were blinded to treatment assignment. Attrition Bias: High. Only 64% of enrolled patients completed the 24-week trial. Attrition rates were due to AEs, withdrawal, loss to follow-up. Missing data were imputed using a multiple imputation regression method. Reporting Bias: Low. Protocol available online at clinical trials.gov website. All outcomes reported as planned. Other Bias: Unclear. Funded by manufacturer. **Applicability**: Patient: BMI restricted to a range of 18-30 kg/m^2 may have selected patients resistant to antipsychotic weight gain. Patients older than 55 years excluded from study, limiting applicability to older patients. Intervention: Dosing determined in Phase 2 and Phase 3 RCTs. Comparator: Active comparator of olanzapine is appropriate to determine impact on weight gain. Outcomes: RCT primarily evaluated the proportion of patients with weight gain in the 2 different treatment arms. Setting: 54 sites in the United States

Abbreviations: AE = adverse events; ARR = absolute risk reduction; BMI = body mass index; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; DB = double blind; ITT = intention to treat; IWRS = interactive web response system; LSM = least squares mean; MC = multi-center; mg = milligram; mITT = modified intention to treat; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PANSS = Positive and Negative Syndrome Scale ; PP = per protocol; RCT = randomized controlled trial; yrs = years

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LYBALVI® (olanzapine and samidorphan) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis. (5.1)

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

Warnings and Precautions (5.17) 1/2025

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

LYBALVI is a combination of olanzapine, an atypical antipsychotic, and samidorphan, an opioid antagonist, indicated for the treatment of:

- Schizophrenia in adults (1)
- Bipolar I disorder in adults (1)
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

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

Indication	Recommended Starting Dose (olanzapine/samidorphan)	Recommended Dose (olanzapine/samidorphan)
Schizophrenia (2.2)	5 mg/10 mg or 10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder (manic or mixed episodes) (2.3)	10 mg/10 mg or 15 mg/10 mg	5 mg/10 mg 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder adjunct to lithium or valproate (2.3)	10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg

- See the full prescribing information for the recommended titration and maximum recommended dosage. (2.2, 2.3)
- Administer LYBALVI once daily with or without food. Do not divide tablets or combine strengths. (2.4)
- Recommended starting dosage is 5 mg/10 mg once daily in patients who have a predisposition to hypotensive reactions, have potential for slower metabolism of olanzapine, or may be more pharmacodynamically sensitive to olanzapine. (2.5)

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

Tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg. (3)

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

- Patients using opioids. (4)
- Patients undergoing acute opioid withdrawal. (4)
- If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for those products. (4)

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

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis*: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities). (5.2)
- *Precipitation of Opioid Withdrawal in Patients Who are Dependent on Opioids*: LYBALVI can precipitate opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids to avoid precipitation of opioid withdrawal. (2.1, 5.3)
- *Vulnerability to Life-Threatening Opioid Overdose*:
  - *Risk of Opioid Overdose from Attempts to Overcome LYBALVI Opioid Blockade:* Attempts to overcome LYBALVI opioid blockade with high or repeated doses of opioids may lead to fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued. (5.4)
  - *Risk of Resuming Opioids in Patients with Prior Opioid Use*: Patients with a history of chronic opioid use prior to LYBALVI treatment may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. (5.4)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring. (5.5)
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*: Discontinue if DRESS is suspected. (5.6)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.7)
- *Tardive Dyskinesia*: Discontinue if clinically appropriate. (5.8)
- *Orthostatic Hypotension and Syncope*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.9)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors. (5.11)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.13)
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery. (5.14)
- *Anticholinergic (Antimuscarinic) Effects:* Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. (5.16)
- *Hyperprolactinemia*: May elevate prolactin levels. (5.17)

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

Most common adverse reactions (incidence ≥5% and at least twice placebo):

- *Schizophrenia (LYBALVI):* weight increased, somnolence, dry mouth, and headache. (6.1)
- *Bipolar I Disorder, Manic or Mixed Episodes (olanzapine):* somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, tremor. (6.1)
- *Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine):* dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- *Strong CYP3A4 Inducers*: Not recommended. (7.1)
- *Strong CYP1A2 Inhibitors*: Consider dosage reduction of olanzapine component of LYBALVI. (7.1)
- *CYP1A2 Inducer*: Consider dosage increase of the olanzapine component of LYBALVI. (7.1)
- *CNS Acting Drugs*: May potentiate orthostatic hypotension. (7.1)
- *Anticholinergic Drugs:* Can increase risk for severe gastrointestinal adverse reactions. (7.1)
- *Antihypertensive Agents*: Monitor blood pressure. (7.2)
- *Levodopa and Dopamine Agonists*: Not recommended. (7.2)

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

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- *Renal Impairment:* Use is not recommended in patients with end-stage renal disease. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2025

Appendix 2: Current Preferred Drug List

Second Generation Antipsychotics

Generic	Brand	Form	PDL
aripiprazole	ABILIFY	TABLET	Y
aripiprazole	ARIPIPRAZOLE	TABLET	Y
asenapine maleate	ASENAPINE MALEATE	TAB SUBL	Y
asenapine maleate	SAPHRIS	TAB SUBL	Y
cariprazine HCl	VRAYLAR	CAPSULE	Y
clozapine	CLOZAPINE	TABLET	Y
clozapine	CLOZARIL	TABLET	Y
lurasidone HCl	LATUDA	TABLET	Y
lurasidone HCl	LURASIDONE HCL	TABLET	Y
olanzapine	OLANZAPINE	TABLET	Y
olanzapine	ZYPREXA	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE ER	TAB ER 24H	Y
quetiapine fumarate	SEROQUEL XR	TAB ER 24H	Y
quetiapine fumarate	SEROQUEL XR	TAB24HDSPK	Y
quetiapine fumarate	QUETIAPINE FUMARATE	TABLET	Y
quetiapine fumarate	SEROQUEL	TABLET	Y
risperidone	RISPERDAL	SOLUTION	Y
risperidone	RISPERIDONE	SOLUTION	Y
risperidone	RISPERDAL	TABLET	Y
risperidone	RISPERIDONE	TABLET	Y
ziprasidone HCl	GEODON	CAPSULE	Y
ziprasidone HCl	ZIPRASIDONE HCL	CAPSULE	Y
aripiprazole	OPIPZA	FILM	V
aripiprazole	ARIPIPRAZOLE	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	TABSENSSTR	V
aripiprazole	ABILIFY MYCITE	TABSENSTPD	V
asenapine	SECUADO	PATCH TD24	V
brexpiprazole	REXULTI	TAB DS PK	V
brexpiprazole	REXULTI	TABLET	V
clozapine	VERSACLOZ	ORAL SUSP	V
clozapine	CLOZAPINE ODT	TAB RAPDIS	V
iloperidone	FANAPT	TAB DS PK	V
iloperidone	FANAPT	TABLET	V
lumateperone tosylate	CAPLYTA	CAPSULE	V
olanzapine	OLANZAPINE ODT	TAB RAPDIS	V

olanzapine	ZYPREXA ZYDIS	TAB RAPDIS	V
olanzapine/samidorphan malate	LYBALVI	TABLET	V
paliperidone	INVEGA	TAB ER 24	V
paliperidone	PALIPERIDONE ER	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	CAPSULE	V
pimavanserin tartrate	NUPLAZID	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE	TABLET	V
risperidone	RISPERIDONE	SYRINGE	V
risperidone	RISPERIDONE ODT	TAB RAPDIS	V
xanomeline tart/trospium chlor	COBENFY STARTER PACK	CAP DS PK	V
xanomeline tart/trospium chlor	COBENFY	CAPSULE	V

Injectable Antipsychotics

Generic	Brand	Form	PDL
aripiprazole	ABILIFY ASIMTUFII	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	SUSER VIAL	Y
aripiprazole lauroxil	ARISTADA	SUSER SYR	Y
aripiprazole lauroxil, submicr.	ARISTADA INITIO	SUSER SYR	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	AMPUL	Y
chlorpromazine HCl	THORAZINE	AMPUL	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	VIAL	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	VIAL	Y
fluphenazine HCl	FLUPHENAZINE HCL	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALDOL DECANOATE 50	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	VIAL	Y
haloperidol lactate	HALOPERIDOL LACTATE	SYRINGE	Y
haloperidol lactate	HALOPERIDOL LACTATE	VIAL	Y
paliperidone palmitate	ERZOFRI	SYRINGE	Y
paliperidone palmitate	INVEGA HAFYERA	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	SYRINGE	Y
risperidone	PERSERIS	SUSER SYR	Y
risperidone	UZEDY	SUSER SYR	Y
risperidone microspheres	RISPERDAL CONSTA	VIAL	Y
risperidone microspheres	RISPERIDONE ER	VIAL	Y
risperidone microspheres	RYKINDO	VIAL	Y

trifluoperazine HCl	STELAZINE	VIAL	Y
olanzapine	OLANZAPINE	VIAL	V
olanzapine	ZYPREXA	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	VIAL	V
ziprasidone mesylate	GEODON	VIAL	V
ziprasidone mesylate	ZIPRASIDONE MESYLATE	VIAL	V

First Generation Antipsychotics

Generic	Brand	Form	PDL
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ELIXIR	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	TABLET	Y
fluphenazine HCl	PROLIXIN	TABLET	Y
haloperidol	HALOPERIDOL	TABLET	Y
haloperidol lactate	HALOPERIDOL LACTATE	ORAL CONC	Y
loxapine succinate	LOXAPINE	CAPSULE	Y
loxapine succinate	LOXAPINE SUCCINATE	CAPSULE	Y
perphenazine	PERPHENAZINE	TABLET	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL CONC	Y
thioridazine HCl	THIORIDAZINE HCL	TABLET	Y
thiothixene	THIOTHIXENE	CAPSULE	Y
thiothixene HCl	THIOTHIXENE HCL	ORAL CONC	Y
trifluoperazine HCl	STELAZINE	TABLET	Y
trifluoperazine HCl	TRIFLUOPERAZINE HCL	TABLET	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	TABLET	V
chlorpromazine HCl	THORAZINE	TABLET	V
loxapine	ADASUVE	AER POW BA	V
pimozide	PIMOZIDE	TABLET	V

Appendix 3: Diagnostic Criteria and Assessments in Select Mental Health Conditions

Table 17. Diagnostic Criteria for Major Depressive Disorder[28]

DSM-5 Criteria for MDD (must have all A-E below)
A. Depressive Symptoms: ≥5 symptoms during the same two-week period that are a change from previous functioning. Depressed mood (1) and/or loss of interest/pleasure (2) must be present. Exclude symptoms clearly attributable to another medical condition. 1. Depressed mood. Most of the day, nearly every day. May be subjective (e.g., feels sad, empty, hopeless) or observed by others (e.g., appears tearful). In children and adolescents, it can be irritable. 2. Loss of interest/pleasure. Markedly diminished interest/pleasure in all (or almost all) activities most of the day, nearly every day. May be subjective or observed by others. 3. Weight loss or gain. Significant weight loss (without dieting) or gain (change of >5% body weight in a month) or decrease or increase in appetite nearly every day. In children, it may be failure to gain weight as expected. 4. Insomnia or hypersomnia: Nearly every day. 5. Psychomotor agitation or retardation. Nearly every day and observable by others (not merely subjectively restless or slow). 6. Fatigue or loss of energy. Nearly every day. 7. Feeling worthless or excessive/inappropriate guilt. Nearly every day. Guilt may be delusional. Not merely self-reproach or guilt about being sick. 8. Decreased concentration. Nearly every day. May be indecisiveness. May be subjective or observed by others. 9. Thoughts of death/suicide. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, or suicide attempt, or a specific plan for suicide.
B. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. Episode not attributable to the physiological effects of a substance or another medical condition.
D. Episode not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. No history of manic or hypomanic episode (exclusion does not apply if all manic-like or hypomanic-like episodes are substance-induced or are attributable to physiological effects of another medical condition).
Abbreviations: DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MDD = major depressive disorder

Table 18. Categories of MDD Symptom Severity[33]

Instrument	None	Mild	Moderate	Severe/Very Severe
HAM-D17	0-7	8-13	14-19	20-25 or ≥26
HAM-D21	0-8	9-15	16-22	23-28 or ≥ 29
HAM-D24	0-9	10-18	19-26	27-34 or ≥ 35
MADRS	0-6	7-19	20-34	≥ 35
BDI	0-9	10-18	19-20	≥ 30
PHQ-9	0-4	5-9	10-19	20-27
QID-SR	0-5	6-10	11-15	16-20 or ≥ 21

Abbreviations: Abbreviations: BDI = Beck Depression Inventory; HAM-D = Hamilton Rating Scale for Depression (with 17, 21, or 24 items); MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = Major Depressive Disorder; PHQ-9 = Patient Health Questionnaire (9-item depression module); QID-SR = Quick Inventory of Depressive Symptomatology—Self-Report

Table 19. Assessments in Major Depressive Disorder[2]

Assessment	Description
Efficacy Scales	
Clinical Global Impressions-Severity (CGI-S) scale	Assesses overall severity of mental illness on a 7-point scale: • 1 = Not ill • 2 = Borderline ill • 3 = Mildly ill • 4 = Moderately ill • 5 = Markedly ill • 6 = Severely ill • 7 = Extremely severely ill
Clinical Global Impressions-Improvement (CGI-I) scale	Assesses overall improvement of condition on a 7-point scale, compared to baseline: • 1 = Very much improved • 2 = Much improved • 3 = Minimally improved • 4 = No change from baseline • 5 = Minimally worse • 6 = Much worse • 7 = Very much worse
Hamilton Depression Rating Scale (HAM-D17)	17-item scale; ratings cover symptom severity experienced over the past week. Items are scored from 0 (absent) to 4 (very severe) or 0 (absent) to 2 (definite), depending on the item. Total score of: • ≥ 23 = very severe depression • 19 to 22 = severe depression • 14 to 18 = moderate depression • 8 to 13 = mild depression • 0 to 7 = normal Total score ranges from 0 to 52. Minimal clinically important difference (MCID) = 3-to-7-point improvement
Hamilton Anxiety Rating Scale (HAM-A)	14-item scale; assesses the severity of anxiety symptoms. Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0 to 56. Scoring: • 1 to 17 = mild • 18 to 24 =mild to moderate

	• 25 to 30 = moderate to severe • Score < 7 = remission of condition
Montgomery-Åsberg Depression Rating Scale (MADRS)	65-item scale assesses 10 most commonly occurring symptoms in adult patients on a 0 to 6 scale, with higher scores indicating more severe symptoms: • Apparent sadness • Reported sadness • Inner tension • Reduced sleep • Reduced appetite • Concentration difficulty • Lassitude • Inability to feel • Pessimistic thoughts • Suicidal thoughts Minimal clinically important difference (MCID) = 2-point improvement
Adverse Event Scales	
Abnormal Involuntary Movement Scale (AIMS)	12-item scale; assesses abnormal movements in patients taking neuroleptic medications. Items are rated 0 to 4, with higher scores indicating more severe movements. Domains assessed include: • Facial and oral movements • Extremity movements • Trunk movements • Global judgements • Mental status
Barnes Akathisia Rating Scale (BARS)	4 item assessment to screen for akathisia (inability to remain still) with 0 = normal to 3 = severe. A low score indicates low levels of akathisia. • Objective akathisia: (scale 0 to 3) • Subjective akathisia: (scale 0 to 3) • Distress of patient (scale 0 to 3) • Global score (scale 0 to 5) with higher numbers associated with increased severity; ≥ 2 indicates presence of akathisia.

Table 20. Assessments in Schizophrenia, Psychosis, and Bipolar Disorder[1]

Assessment	Description
Efficacy Scales	
Brief Negative Symptom Scale (BNSS)	13-item scale with questions organized into 6 subscales for assessing: • Anhedonia (loss of interest or pleasure) • Distress • Asociality (social withdrawal or lack of interest in socializing) • Avolition (lack of motivation)

	• Blunted affect (reduced emotional expression) • Alogia (decreased speech or difficulty speaking) Items are scored on a 0 to 6 scale, with 0 indicating the symptom is absent and 6 indicating the symptom is severe. Items are summed. Total scores range between 0 and 78, with higher scores indicating more severe symptoms.
Brief Psychiatric Rating Scale (BPRS)	18 symptoms including hostility, suspiciousness, hallucination, and grandiosity are scored on a range from 1 (not present) to 7 (extremely severe). Clinical administered, based on patient's behavior over the previous 2-3 days. Final score ranges from o to 126. The higher the score, the more severe the pathology. Mildly ill = score of 31 Moderately ill = score of 41 Markedly ill = score of 53 "Minimally improved" interpretation was associated with a percentage BPRS reduction of 24, 27 and 30% at weeks 1, 2 and 4, respectively.
Calgary Depression Scale for Schizophrenia (CDSS)	9-item scale with questions assessing: • Depression • Hopelessness • Self-deprecation • Guilt • Sleep • Suicidal ideation Items are scored on a 0 to 3 scale with total scores ranging between 0 and 27. Higher scores indicate more severe depression.
Positive and Negative Symptom Scale (PANSS)	30-item scale cutoff scores do not clearly indicate the severity of illness. The range of possible scores is 30 to 210 (usual range is 60 to 150). A low score indicates less severity. • < 5 very low • 6 to 25 low • 26 to 74 moderate • 75 to 94 high • > 95 very high Subscales include positive, negative, and general psychopathology, rated on a scale of 1 (not present) to 7 (extremely severe).
Sheehan Disability Scale (SDS)	Assesses functional impairment in 3 main domains: • Work/school (scale 0 to 10) • Social life (scale 0 to 10) • Family life/home responsibilities (scale 0 to 10) Higher scores indicate more severe impairment.
Adverse Event Scales	
Columbia Suicide Severity Rating Scale (CSSRS)	6-item scale designed for all ages. Items are scored yes or no in reference to suicidal thoughts, actions, or plan. • Any score of yes designates the need for a referral • A score of yes on items 4, 5, or 6 designates need for immediate suicide precautions
Simpson Angus Scale (SAS)	10-item scale used to screen for extrapyramidal side effects (drug-induced movement). Items are rated on a continuum of 0 to 4:

	• 0 = absence • 4 = most extreme form of the condition Up to 3 is considered within normal range.

Appendix 4: Abstracts

Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression.[56]

Background: In treatment-resistant depression, commonly defined as a lack of response to two or more consecutive treatments during the current depressive episode, the percentage of patients with remission is low and the percentage with relapse is high. The efficacy and safety of esketamine nasal spray as compared with extended-release quetiapine augmentation therapy, both in combination with ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), in patients with treatment-resistant depression are unknown.

Methods: In an open-label, single-blind (with raters unaware of group assignments), multicenter, phase 3b, randomized, active-controlled trial, we assigned patients, in a 1:1 ratio, to receive flexible doses (according to the summary of product characteristics) of esketamine nasal spray (esketamine group) or extended-release quetiapine (quetiapine group), both in combination with an SSRI or SNRI. The primary end point was remission, defined as a score of 10 or less on the Montgomery-Åsberg Depression Rating Scale (MADRS), at week 8 (scores range from 0 to 60, with higher scores indicating more severe depression). The key secondary end point was no relapse through week 32 after remission at week 8. All patients were included in the analysis; patients who discontinued the trial treatment were considered as having had an unfavorable outcome (i.e., they were grouped with patients who did not have remission or who had a relapse). Analyses of the primary and key secondary end points were adjusted for age and number of treatment failures.

Results: Overall, 336 patients were assigned to the esketamine group and 340 to the quetiapine group. More patients in the esketamine group than in the quetiapine group had remission at week 8 (91 of 336 patients [27.1%] vs. 60 of 340 patients [17.6%]; P = 0.003) and had no relapse through week 32 after remission at week 8 (73 of 336 patients [21.7%] vs. 48 of 340 patients [14.1%]). Over 32 weeks of follow-up, the percentage of patients with remission, the percentage of patients with a treatment response, and the change in the MADRS score from baseline favored esketamine nasal spray. The adverse events were consistent with the established safety profiles of the trial treatments.

Conclusions: In patients with treatment-resistant depression, esketamine nasal spray plus an SSRI or SNRI was superior to extended-release quetiapine plus an SSRI or SNRI with respect to remission at week 8. (Funded by Janssen EMEA; ESCAPE-TRD ClinicalTrials.gov number, NCT04338321.).

Appendix 5: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to April 22, 2025>

1	Aripiprazole/tu [Therapeutic Use]	587
2	Antipsychotic Agents/tu [Therapeutic Use]	34269
3	asenapine.mp.	535
4	cariprazine.mp.	534
5	Clozapine/tu [Therapeutic Use]	4398
6	Lurasidone Hydrochloride/tu [Therapeutic Use]	146
7	Olanzapine/tu [Therapeutic Use]	507
8	Quetiapine Fumarate/tu [Therapeutic Use]	505
9	Risperidone/tu [Therapeutic Use]	4050
10	ziprasidone.mp.	2232
11	brexpiprazole.mp.	471
12	iloperidone.mp.	254
13	lumateperone.mp.	100
14	Paliperidone Palmitate/tu [Therapeutic Use]	256
15	pimavanserin.mp.	373
16	xanomeline.mp.	259
17	Chlorpromazine/tu [Therapeutic Use]	3876
18	Fluphenazine/tu [Therapeutic Use]	893
19	Haloperidol/tu [Therapeutic Use]	4093
20	Trifluoperazine/tu [Therapeutic Use]	465
21	Loxapine/tu [Therapeutic Use]	154
22	Perphenazine/tu [Therapeutic Use]	461
23	Thioridazine/tu [Therapeutic Use]	771
24	Thiothixene/tu [Therapeutic Use]	210
25	Pimozide/tu [Therapeutic Use]	466
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	46510
27	limit 26 to (english language and humans and yr="2020 -Current")	4826
28	limit 27 to (clinical trial, phase iii or guideline or meta-analysis or practice guideline or "systematic review")	571

Antipsychotics in Children

Goal(s):

- Ensure safe and appropriate use of antipsychotics in children
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Antipsychotic use beyond 60 days in children 3-6 years of age
- All antipsychotic use in children 2 years of age or younger
- For quetiapine requests in children ≥7 years of age, see criteria for Low Dose Quetiapine

Note: olanzapine can be automatically approved in patients with a recent cancer diagnosis

Covered Alternatives:

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

Table 1. FDA-Approved Indications and Ages for Oral Second-generation Antipsychotics in Children

FDA-Approved Indications and Ages				
Drug	**Schizophrenia**	**Bipolar I disorder**	**Major depressive disorder (adjunct)**	**Other**
aripiprazole	≥13 yrs	≥10 yrs	≥18 yrs	Irritability associated with Autistic Disorder ≥6 yrs Tourette's Disorder ≥6 yrs
asenapine maleate	≥18 yrs	≥10 yrs		
brexpiprazole	≥13 yrs			
lurasidone HCl	≥13 yrs	≥10 yrs		
olanzapine	≥13 yrs	≥13 yrs	≥18 yrs	
paliperidone	≥12 yrs			Schizoaffective disorder ≥18 yrs
quetiapine fumarate	≥13 yrs	≥10 yrs		Bipolar depression ≥18 yrs
risperidone	≥13 yrs	≥10 yrs		Irritability associated with Autistic Disorder ≥5 yrs

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for use of olanzapine as an antiemetic associated with cancer or chemotherapy?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Has the patient been screened for diabetes (blood glucose or A1C) within the last 12 months?	**Yes:** Go to #5	**No:** Go to #4
4. Is there documented clinical rationale for lack of metabolic monitoring (e.g. combative behaviors requiring sedation) OR documentation of patient weight before and after initiation of treatment? Note: Caregivers failing to take patients to the laboratory is not a clinical rationale for lack of monitoring.	**Yes:** Document rationale. Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Annual metabolic screening or consistent evaluation for rapid weight gain is required for chronic use of antipsychotics. Refer denied requests to the OHA for follow-up.
5. Is the patient engaged in, been referred for, or have documented inability to access evidence based first-line non-pharmacological therapy (e.g., applied behavior analysis therapy for autism, parent behavioral therapy, or parent child interaction therapy)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up.
6. Is the drug prescribed by or in consultation with a child psychiatrist or developmental pediatrician?	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Go to #7

Approval Criteria		
7. Is there detailed documentation regarding risk/benefit assessment and the decision to prescribe antipsychotic therapy? A thorough assessment should include ALL the following: a. Multidisciplinary review including a mental health specialist b. Mental health assessment including documentation of diagnoses, symptoms, and disease severity c. Discussion and consideration of first-line non-pharmacological therapies d. Assessment of antipsychotic risks and monitoring strategies e. Specific therapeutic goals of antipsychotic therapy, and for ongoing therapy, discussion of progress toward or achievement of therapeutic goals (or reasons for lack of progress and remediation strategies) f. Anticipated duration of therapy g. Detailed follow-up plan	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up.

P&T/DUR Review: 8/25; 2/24 (SS); 6/21(SS)
Implementation: 4/1/24; 10/1/22

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine, immediate- and extended-release

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- For any requests in children ≤6 years of age, see criteria for Antipsychotics in Children
- Auto-PA approvals for people 7 and older:
    - Patients with a claim for a second-generation antipsychotic in the last 6 months
    - Patients with prior claims evidence of schizophrenia or bipolar disorder
    - Prescriptions identified as being written by a mental health provider
    - Extended-release formulations in patients with claims for a selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor in the last 90 days

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

Table 1. Adults (age ≥18 years) with FDA-approved or Compendia-supported Indications

Bipolar Disorder	
Major Depressive Disorder (MDD)	Adjunctive therapy with antidepressants for MDD
Schizophrenia	
Bipolar Mania	
Bipolar Depression	
Generalized Anxiety Disorder (GAD)	Adjunctive therapy with SSRI/SNRI

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. Is the request for an evidence-supported diagnosis (Table 1 or Table 2)?	**Yes:** Go to #2	No: Pass to RPh. Deny; medical appropriateness.
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy (at ≤50 mg) longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *8/25; 6/23 (SS); 4/21 (SF); 8/20; 3/19; 9/18; 11/17; 9/15; 9/10; 5/10*
Implementation: *7/1/23; 1/1/18; 10/15; 1/1/11*

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

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 treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
4. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
5. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
6. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

P&T Review: *8/25; 8/20(SF); 3/19 (DM); 9/18; 3/18; 01/17*
Implementation: *4/1/17*

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

- Date of service or 12 months, depending on criteria

Requires PA:

Risperdal® Consta®

Approval Criteria		
1. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
2. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long-term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
3. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

P&T Review: *8/25; 10/23 (DM); 2/22 (DM); 9/18 (DM); 9/17; 9/16; 5/05*
Implementation: *10/13/16; 11/18/04*

Xanomeline-trospium (COBENFY) Safety Edit

Goal(s):

- Promote safe use of xanomeline-trospium in combination with other mental health drugs for schizophrenia.

Length of Authorization:

Up to 12 months

Requires PA:

- Xanomeline-trospium
- Auto-approval requests for people with a claim for xanomeline-trospium in the last 6 months

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 xanomeline-trospium prescribed for an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the intent to prescribe xanomeline-trospium in conjunction with another antipsychotic medication?	**Yes:** Go to #4	**No:** Go to #5
4. Is there documentation or provider attestation that the benefits of therapy (e.g. symptom improvement, social function, number of hospitalizations, etc.) outweigh potential risks of combination treatment (e.g. hepatic impairment, biliary disease, gastrointestinal and anticholinergic effects, etc.)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is there documentation or provider attestation that the patient does not have any of the following conditions? • Concurrent antidepressant that inhibits CYP2D6 (e.g., bupropion, fluoxetine, paroxetine, or duloxetine) • Urinary retention (e.g., benign prostatic hyperplasia, diabetic cystopathy) • Untreated narrow-angle glaucoma • Impaired gastric motility (e.g., gastrointestinal obstructive disorders) • Mild, moderate or severe hepatic impairment, biliary disease, or elevated liver function tests • Moderate or severe renal impairment or estimated glomerular filtration rate (eGFR) <60 mL/min	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/25; 2/2025 (SS)
Implementation: 3/10/25

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Drug Use Evaluation: Modafinil and Armodafinil

Plain Language Summary:

- Medicines called stimulants can help people who are very sleepy stay awake and alert. Examples of stimulants used for this purpose include modafinil and armodafinil.
- These medicines are prescribed for conditions like narcolepsy, which causes excessive daytime sleepiness and sudden sleep attacks. They can also be used in addition to other therapy for people with other health issues that can cause extreme tiredness. Examples of these conditions include cancer, depression, or obstructive sleep apnea.
- Providers must send the Oregon Health Authority (OHA) information to document why they are prescribing modafinil or armodafinil before the Oregon Health Plan (OHP) will pay for the medicine. This process is called prior authorization (PA).
- In an evaluation of this policy, we found that most members who were prescribed modafinil or armodafinil did not have claims paid by OHP (63%). About 14% of members had paid claims for modafinil or armodafinil, and prior authorization was denied in 23% of patients. About 26% of people had claims for a different type of stimulant.
- The most common reasons that the Oregon Health Plan did not pay for stimulants were:
    - No documentation of extreme tiredness before starting the medicine or symptom improvement after starting the medicine,
    - No documentation that the member had seen an expert who specialized in their condition, and
    - Prescription of a stimulant for a condition that is not covered by the Oregon Health Plan.
- We recommend that the Oregon Health Plan update their policy to automatically approve modafinil and armodafinil for people with narcolepsy because there is strong evidence to support use of these medicines as an initial treatment option.

Research Questions:

- For members starting treatment with modafinil or armodafinil, what proportion of members ultimately get a paid claim for the requested drug?
- How many members with a denied claim for modafinil or armodafinil have subsequent paid claims for a different stimulant?
- What types of stimulants are subsequently prescribed for members with denied claims for modafinil or armodafinil?
- Are there subgroups of members (e.g., based on diagnoses or denial reason) who are more likely to have subsequent paid claims for a different therapy?

Conclusions:

- Current prior authorization criteria for modafinil and armodafinil provide coverage for excessive sleepiness related to narcolepsy, obstructive sleep apnea (OSA), cancer, depression, and multiple sclerosis.
- Guidelines updated in 2021 from the American Academy of Sleep Medicine recommend either modafinil or armodafinil for narcolepsy, idiopathic hypersomnia, and for fatigue secondary to Lewy body dementia, Parkinson's disease, traumatic brain injury, myotonic dystrophy, or multiple sclerosis.[1] These stimulants are also recommended as adjunct treatments to positive airway pressure in obstructive sleep apnea (OSA)[2] and as an adjunct to antidepressants in people with treatment-resistant depression.[3]

- In an evaluation of this policy, 63% of members with an initial denied claim for modafinil or armodafinil did not have subsequent paid claims for any type of simulant or narcolepsy drug. About 14% of members had subsequent paid claims for modafinil or armodafinil (compared to 9% in the baseline period), and 23% of members had denied PAs. The most common reasons for denied PA requests included inadequate documentation for fatigue severity, no documentation of consultation with a relevant specialist, and unfunded diagnosis. About 26% of people had paid claims for a different type of stimulant indicated for attention deficit hyperactivity disorder (ADHD; compared to 19% in the baseline period).
- About 22% of members with denied claims were prescribed more than one tablet per day and 17% of denied PA requests appear to be for doses higher than recommended in the FDA-labeling. There is limited evidence to support improved efficacy of modafinil above 200 mg daily,[4] but also insufficient direct comparative evidence to show that higher doses of modafinil are less safe than other stimulants or other drugs for narcolepsy. All stimulants have similar warnings and precautions for cardiovascular adverse effects, psychiatric adverse events, and abuse or misuse.[4-8]
- The most common stimulants prescribed in the 6 months following a denied claim for modafinil or armodafinil were mixed amphetamine salts (17%), modafinil or armodafinil (14%), methylphenidate (9%), and lisdexamfetamine (3%).
- The proportion of people who switched from modafinil or armodafinil to an ADHD stimulant was generally small but occurred more commonly in people who had denials for modafinil or armodafinil. In people without ADHD stimulant claims in the baseline period, the proportion of people who switched to an ADHD stimulant was 14% in people with a denied modafinil/armodafinil claim compared to 8% of people who ultimately received a paid claim for modafinil or armodafinil.
- Members with an evidence-supported diagnosis (such as OSA, narcolepsy, or depression) were more likely to have subsequent paid claims for a stimulant or other narcolepsy drugs (42%) compared to members without an evidence-supported diagnosis (26%). Of the 147 members with subsequent paid claims for modafinil and armodafinil, 92% had an evidence-based and funded diagnosis present in the medical claims (n=135). However, a significant proportion of people with an evidence-supported diagnosis in medical claims did not have subsequent paid claims for a stimulant (n=423). In people without an evidence-supported diagnosis, ADHD stimulants were the most common type of drug prescribed following a denied claim for modafinil or armodafinil.

Recommendations:

- Automatically approve requests of modafinil or armodafinil for members with narcolepsy when prescribed for doses at or below 200 mg of modafinil or 250 mg of armodafinil daily.
- Continue to require PA for other indications and for higher doses.
- Update PA criteria to allow members to use higher doses of modafinil if lower doses are only partially effective.

Background

Modafinil and armodafinil are stimulants that have evidence for use in a variety of conditions. They are approved by the Food and Drug Administration (FDA) for excessive sleepiness associated with narcolepsy, OSA, and shift-work disorder. Modafinil has been studied for a variety of off-label conditions and current PA criteria include coverage for fatigue related to depression, cancer, and multiple sclerosis. Modafinil and armodafinil have also been studied in fatigue related to other neurologic disorders (such as Parkinson's Disease, traumatic brain injury, post-polio syndrome), cognitive enhancement, drug-related fatigue, and ADHD. In 2021, the American Academy of Sleep Medicine updated guidelines related to hypersomnia disorders and provided recommendations for the following therapies (**Table 1**).[1] There are strong recommendations for modafinil, pitolisant, sodium oxybate, and solriamfetol in adults with narcolepsy and for modafinil in people with idiopathic hypersomnia.[1] There are conditional recommendations based on lower quality evidence for modafinil and armodafinil related to a variety of other fatigue-related conditions.[1] These stimulants are also recommended as adjunct treatments to positive airway pressure in OSA[2] and as an adjunct to antidepressants in people with treatment-resistant depression.[3]

Table 1. American Academy of Sleep Medicine Recommendations for Central Disorders of Hypersomnia[1]

Condition	Treatment	Strength of evidence
Primary hypersomnia		
Narcolepsy (adults)	Modafinil, pitolisant, sodium oxybate, solriamfetol	Strong
	Armodafinil, dextroamphetamine, methylphenidate	Conditional
Narcolepsy (pediatric)	Modafinil, sodium oxybate	Conditional
Idiopathic hypersomnia	Modafinil	Strong
	Clarithromycin, methylphenidate, pitolisant, sodium oxybate	Conditional
Hypersomnia due to other medical conditions		
Lewy body dementia	Armodafinil	Conditional
Parkinson's disease	Modafinil, sodium oxybate	Conditional
Traumatic brain injury	Modafinil, armodafinil	Conditional
Myotonic dystrophy	Modafinil	Conditional
Multiple sclerosis	Modafinil	Conditional

FDA-labeling for stimulants like modafinil includes warnings and precautions for serious skin reactions (e.g., Stevens' Johnson Syndrome), psychiatric symptoms (e.g., delusions, mania, aggression, suicidal ideation), and cardiovascular events (e.g., chest pain, palpitations, electrocardiogram changes, increased blood pressure).[4,8] Stimulants for ADHD include similar warnings and precautions related to cardiac and psychiatric adverse events.[5-7] All stimulants have risk for abuse, misuse, and addiction. The Drug Enforcement Agency (DEA) categorizes modafinil and armodafinil as schedule IV substances and stimulants for ADHD as schedule II substances.[4-8] In addition, stimulants for ADHD may be associated with serotonin syndrome, seizures, motor and verbal tics, and peripheral vasculopathy including Raynaud's phenomenon.[5-7]

In the Oregon Health Plan, PA is required before the Oregon Health Authority will pay for modafinil or armodafinil. Current PA criteria requires the following:

- Diagnosis of a funded and evidence-supported condition (including narcolepsy, OSA, cancer, depression, or multiple sclerosis)
- Prescription by, or in consultation with, a relevant specialist for the condition
- Documentation of recent fatigue severity score
- When applicable, documentation of pregnancy risk assessment
- When applicable, use of first-line treatment for OSA

Approvals are limited to the FDA-recommended maintenance doses (200 mg daily for modafinil and 250 mg daily for armodafinil). In clinical trials, modafinil was studied for narcolepsy at doses of 100-600 mg daily, and up to 400 mg has been evaluated for other off-label conditions.[1,9] In clinical trials for narcolepsy, higher doses of modafinil were not associated with improved efficacy.[4] The most common adverse events occurring in more than 5% of patients included headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia.[4] Headache and anxiety occurred more commonly with higher doses.[4] Modafinil and armodafinil are rarely covered for shift work disorder and primary hypersomnia because these conditions are currently unfunded. However, other stimulants that are approved by the FDA for ADHD may have fewer utilization controls. For the FFS population, preferred stimulants for ADHD do not require PA if they are prescribed within FDA-approved doses and age limits. For members enrolled in a coordinated care organization (CCO), most simulants for ADHD are covered by the CCO. The purpose of this drug evaluation is to evaluate whether members are prescribed an alternative stimulant after receiving a denied claim for modafinil or armodafinil.

Methods:
The index event (IE) was defined as the first denied FFS pharmacy claim for modafinil or armodafinil during the claims evaluation window. If members had a paid and denied claim on the same day, the claim was classified as paid.

Time periods for review:

- The claims evaluation window was from 10/1/2023 to 09/30/2024
- The baseline period was defined as the 6 months before the IE (inclusive of the IE)
- The follow-up period was defined as the 6 months following the IE (exclusive of the IE)

Inclusion criteria:

- At least one denied FFS pharmacy claim for modafinil or armodafinil (defined based on HICL Sequence Numbers [HSNs]: 010865 and 034868) during the claim evaluation window. Denied claims were included if they were associated with an error code indicating PA was required or quantity limit was exceeded but were not associated with claims indicating errors in billing (**Appendix 1; Table A1**).

Exclusion criteria:

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

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

Population descriptors and definitions:

- CCO enrollment, age, sex at birth, and race were evaluated at the time of the IE.
- Patients were categorized as new starts if they had no paid claims for the IE drug in the baseline period.
- Stimulants for ADHD and other drugs for narcolepsy were defined based on HSNs in **Appendix 1, Table A2**.
- Sleep disorder diagnoses were evaluated during the baseline period (see **Appendix 1, Table A3**) and categorized as funded, unfunded, and evidence-supported.
- Denial reason codes were classified according to the error code on the claim. A single denied claim can be associated with multiple error codes.
- Denied PA requests were evaluated for key terms to determine the probable reason for the denial. The following terms were used to identify denial reasons:

Key Term	Probable Denial Reason
“Fatigue severity” or “Epworth”	- Inadequate documentation of baseline fatigue severity or improvement in symptoms
“Specialist”	- No documentation the drug was prescribed by or in consultation with a relevant specialist
“Funded” or “OHP-funded”	- No documentation the drug was prescribed for a funded condition
“Pregnancy” or “pregnant” or “teratogenic”	- No documentation of pregnancy risk assessment
“First-line” or “first line”	- No documentation for use or adherence to first-line treatment for OSA (e.g., CPAP or similar device)
“Dose” or “200mg” or “200 mg”	- Daily dose prescribed above recommended maintenance dose
“Covered indication”	- No documentation of an evidence-supported indication

A post-hoc subgroup analysis was conducted for people without claims for an ADHD stimulant in the baseline period. Members were categorized into the following groups:

- People who had subsequent paid claims for modafinil/armodafinil in the follow-up period (e.g., before any paid claims for an ADHD stimulant or in absence of an ADHD stimulant).
- Everyone else (including people without subsequent paid claims for modafinil/armodafinil and people with paid claims for an ADHD stimulant before the first paid claim for modafinil/armodafinil in the follow-up period).

Outcomes:

- Subsequent paid FFS or CCO claims in the follow-up period for stimulants (e.g., modafinil, armodafinil, or stimulants for ADHD) or other agents for narcolepsy (e.g., pitolisant, sodium oxybate, or solriamfetol).

Results:

This drug evaluation identified 1295 members with denied claims for modafinil or armodafinil over a 1-year period from 10/1/2023 to 09/30/2024. After exclusion of people with potentially incomplete claims data, 1080 people were included in the analysis (**Table 1**). The majority of participants identified as female (64%) and white (63%). Modafinil was prescribed in 84% of members (**Table 2**), and about 22% of members were prescribed more than one tablet per day which may be indicative of twice daily dosing or dosing above the FDA-recommended maintenance doses. The most common diagnoses identified in medical claims during the 6-month baseline period included depression (39%), OSA (29.3%), and narcolepsy (13.5%; **Table 3**). About 67% of members had a diagnosis that was both funded and evidence supported, 4% had an evidence-supported and unfunded diagnosis, and 29% of members did not have an evidence-supported diagnosis for modafinil or armodafinil identified in the 6-month baseline period.

Table 1. Included members

Exclusion Criteria	Denied IE #	Denied IE %
Members with FFS denied claims for modafinil or armodafinil	1,295	
After exclusion of members with Medicare, TPL, or limited drug benefit	1,151	88.9%
After exclusion of members with <75% eligibility in the baseline or follow-up period	1,080	83.4%
Total members included in the analysis	1,080	83.4%

Table 2. Baseline Demographics

	Denied IE	
	1,080	%
Age		
<18 years	0	0.0%
>=18 years	1,080	100.0%
Sex		
Male	392	36.3%
Female	688	63.7%
CCO enrollment at the time of the IE		
FFS	24	2.2%
CCO	1,056	97.8%
Race		
White	685	63.4%
Unknown	267	24.7%
Native American/Alaskan Native	54	5.0%
Other	74	6.9%
IE Drug		
Modafinil	908	84.1%
Armodafinil	172	15.9%
Daily Quantity (tablets per day)		
<1	49	4.5%
1	796	73.7%
>1 to 2	214	19.8%
>2	21	1.9%

Table 3. Diagnoses and claims in the baseline period

	Denied IE	
	1,080	%
Funded and evidence supported diagnoses	**725**	**67.1%**
Fatigue related to depression	423	39.2%
Obstructive sleep apnea	316	29.3%
Narcolepsy with or without cataplexy	146	13.5%
Fatigue related to multiple sclerosis	68	6.3%
Fatigue related to cancer	27	2.5%
Evidence-supported and unfunded diagnoses	**41**	**3.8%**
Idiopathic (primary) hypersomnia	28	2.6%
Shift work disorder	14	1.3%
No evidence supported diagnoses	**314**	**29.1%**
Other and chronic fatigue	65	6.0%
ADHD	65	6.0%
Other hypersomnia	24	2.2%
Insomnia	21	1.9%
Other and unspecified sleep disorders	12	1.1%
Other sleep apnea	12	1.1%
Other circadian rhythm sleep disorders	2	0.2%
Parasomnia	1	0.1%
Sleep-related movement disorders	1	0.1%

Of members with an initial denied claim for modafinil or armodafinil, most members (63%) did not have subsequent paid claims for any type of stimulant or narcolepsy drug (**Table 4**). PA was not submitted for 39% of members, and PA was denied for 23% of members. An evaluation of PA denial letters indicate that most PA requests had more than one reason for denial. The most common reasons for denial included inadequate documentation for fatigue severity (75%), no documentation of consultation with a relevant specialist (54%), and prescription for an unfunded diagnosis (49%; **Table 6**). Even for members with a funded and evidence-supported diagnosis present in the medical claims, about 40% of denied PA letters referenced unfunded conditions indicating that the diagnosis submitted on the PA request and in chart notes is often different than diagnoses present in medical claims.

Only 37% of people had a subsequent paid claim for a stimulant or other drug for narcolepsy (**Table 4**). The most common stimulants prescribed in the 6 months following a denied claim for modafinil or armodafinil were mixed amphetamine salts (17%), modafinil or armodafinil (14%), methylphenidate (9%), and lisdexamfetamine (3%). Utilization of both modafinil or armodafinil and ADHD stimulants increased from the 6-month baseline period to the 6-month follow-up period (**Table 5**). In the baseline period, 19% of members had paid claims for an ADHD stimulant compared to 26% of members in the 6-month follow-up period. ADHD stimulants were more frequently prescribed than modafinil or armodafinil (**Table 4**).

Table 4. Subsequent paid claims for stimulants or other narcolepsy drugs

	Denied IE	
	1,080	%
Subsequent paid claims in the follow-up period	398	36.9%
Modafinil or armodafinil	147	13.6%
Pitolisant, sodium oxybate, or solriamfetol	17	1.6%
ADHD stimulant	282	26.1%
Dextroamphetamine/amphetamine	184	17.0%
Methylphenidate	100	9.3%
Lisdexamphetamine	30	2.8%
Dexmethylphenidate	6	0.6%
No subsequent paid claims in the follow-up period	682	63.1%
PA never submitted	419	38.8%
PA submitted	263	24.4%
Denied	251	23.2%
Approved	12	1.1%

Table 5. Stimulant prescribing before and after a denied claim for modafinil/armodafinil

	Denied IE			
	1,080	%	1,080	%
	Baseline period		Follow-up period	
Paid FFS or CCO claims (not including the IE)				
Modafinil or armodafinil	101	9.4%	147	13.6%
ADHD stimulant	202	18.7%	282	26.1%
Pitolisant, sodium oxybate, or solriamfetol	14	1.3%	17	1.6%

Table 6. Denial reasons for prior authorization

	Evidence-supported & funded diagnosis		Evidence-supported & unfunded diagnosis		No evidence-supported diagnosis		Total	
	174	%	8	%	69	%	251	%
Denial related to inadequate documentation for:								
Fatigue severity score	135	77.6%	5	62.5%	49	71.0%	189	75%
Specialist involvement	86	49.4%	3	37.5%	47	68.1%	136	54%
Funded condition	70	40.2%	7	87.5%	46	66.7%	123	49%
Pregnancy risk assessment	52	29.9%	1	12.5%	16	23.2%	69	27%
First-line treatments for OSA	31	17.8%	1	12.5%	5	7.2%	37	15%
Appropriate dose	22	12.6%	2	25.0%	5	7.2%	32	13%
Evidence-supported indication	17	9.8%	1	12.5%	14	20.3%	29	12%
None of the above	2	1.1%	0	0.0%	1	1.4%	3	1%

The proportion of members with subsequent paid claims for stimulants or other drugs for narcolepsy was generally consistent across demographic groups (e.g., sex and race). Members with an evidence-supported diagnosis were more likely to have subsequent paid claims for a stimulant or other narcolepsy drug (42%) compared to members without an evidence-supported diagnosis (26%; **Table 7**). Of the 147 members with subsequent paid claims for modafinil and armodafinil, 92% had an evidence-based and funded diagnosis present in the medical claims (n=135). About 70% of people with claims for an ADHD stimulant had an evidence-supported diagnosis for modafinil or armodafinil. In members without an evidence-supported diagnosis, most (74%, n=233) did not have a subsequent claim for a stimulant. In people with subsequent claims but without an evidence-supported diagnosis, ADHD stimulants were the most common type of drug prescribed.

Table 7. Subsequent claims by subgroup for members with a denied IE

					Type of Subsequent Paid Claims*					
	No subsequent paid claim		Subsequent paid claim for any drug		Modafinil or armodafinil		ADHD stimulant		Pitolisant, sodium oxybate, or solriamfetol	
	682	63%	398	37%	147	%	282	%	17	%
CCO enrollment at the time of the IE										
FFS	18	75.0%	6	25%	1	0.7%	6	2.1%	0	0.0%
CCO	664	62.9%	392	37%	146	99.3%	276	97.9%	1	5.9%
IE Drug										
Modafinil	593	65.3%	315	35%	112	76.2%	224	79.4%	13	76.5%
Armodafinil	89	51.7%	83	48%	35	23.8%	58	20.6%	4	23.5%

Diagnoses in the baseline period										
Funded and evidence supported	423	58.3%	***302***	***42%***	135	91.8%	197	69.9%	15	88.2%
Unfunded and evidence-supported	26	63.4%	***15***	***37%***	1	0.7%	14	5.0%	1	5.9%
Not evidence-supported	233	74.2%	***81***	***26%***	11	7.5%	71	25.2%	1	5.9%
Paid claims in the baseline period										
Modafinil or armodafinil	19	18.8%	82	81%	72	49.0%	29	10.3%	8	47.1%
ADHD stimulant	34	16.8%	168	83%	27	18.4%	163	57.8%	8	47.1%
Pitolisant, sodium oxybate, or solriamfetol	1	7.1%	13	93%	7	4.8%	7	2.5%	12	70.6%

*Members may be categorized in more than one group if they had claims for more than one drug in the 6 months following the IE. For members with more than one type of paid claim in the follow-up period, this analysis did not evaluate if drugs were prescribed concurrently or sequentially.

Similar trends were observed in a subgroup of members who did not have claims for an ADHD stimulant in the baseline period (**Table 8**). Like the broader population, most members in this subgroup did not have subsequent paid claims for any type of stimulant (n=651; 75%). ADHD stimulants were prescribed for 9 members (8%) who had subsequent paid claims for modafinil or armodafinil. By comparison, in people with only denied claims for modafinil or armodafinil (n=775), use of ADHD stimulants was slightly more frequent (n=104; 14%).

Table 8. Subsequent stimulant use for members without an ADHD stimulant in the baseline period

	Subsequent paid claims for modafinil/armodafinil*		**No subsequent paid claims for modafinil/armodafinil**		**Total**	
	116	%	755	%	871	%
Subsequent ADHD stimulant in the follow-up period	9	7.8%	104	13.8%	113	13.0%
No subsequent ADHD stimulant in the follow-up period	107	92.2%	651	86.2%	758	87.0%

*Includes people with modafinil/armodafinil paid claims in the follow-up period before any ADHD stimulant **OR** those with modafinil/armodafinil paid claims in the follow-up period and no ADHD stimulant in the follow-up period

Discussion and Limitations:

The results of this analysis indicate that most people with a denied claim for modafinil or armodafinil do not have subsequent paid claims for a comparable medication. However, this analysis is based on claims data which has several inherent limitations.

First, we did not attempt to evaluate the proportion of people who may be paying cash for their prescriptions. Both modafinil and armodafinil are available as generic medications and are relatively inexpensive. Additionally, because most members are enrolled in a CCO, claims data on how many members may have received subsequent denied claims or had PA requests for an ADHD stimulant is lacking. ADHD stimulants are categorized as physical health drugs and are paid for by the CCOs. Policies for stimulants may vary between CCOs.

The proportion of people prescribed both modafinil or armodafinil and ADHD stimulants increased in the 6 months following a denied claim. In general, use of stimulants for ADHD has increased over time in the Oregon Medicaid population as a result of both increased prescribing and a larger Medicaid population. This analysis did not control for general trends over time. Notably, switching to an ADHD stimulant was slightly more common in people with only denied claims for modafinil or armodafinil (14%) compared to people with subsequent paid claims for modafinil or armodafinil (8%).

Diagnoses were only evaluated in the 6 months before the first denied claim for modafinil or armodafinil which may not accurately categorize members who have a chronic condition like OSA or narcolepsy. About 67% (n=725) of people had a funded and evidence-supported diagnosis in their medical claims. However, even in members with an evidence-supported indication in medical claims, 40% of denied PAs referenced unfunded indications and 10% referenced indications that are not currently covered under the OHP policy. Many diagnoses and medications can contribute to fatigue or excessive sleepiness, and not all of these diagnoses were included in this analysis. Based on low quality evidence, guidelines from the American Academy of Sleep Medicine include conditional recommendations for modafinil in fatigue related to Lewy body dementia, Parkinson's disease, traumatic brain injury, and myotonic dystrophy, and conditional recommendations for armodafinil in Lewy body dementia and traumatic brain injury. A more comprehensive review of both unfunded and off-label indications is currently planned for a future Pharmacy & Therapeutics meeting.

In practice, modafinil is often prescribed twice daily because patients report limited duration of effect which does not last the entire day. About 22% of members with denied claims were prescribed more than one tablet per day and 17% of denied PA requests appear to be for doses higher than recommended in the FDA-labeling. There is limited evidence to support improved efficacy of modafinil above 200 mg daily, but also very limited evidence to show that higher doses of modafinil are less safe than other stimulants or other drugs for narcolepsy. All stimulants have similar warnings and precautions for cardiovascular adverse effects, psychiatric adverse events, and abuse or misuse.

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Appendix 1: Drug Coding

Table A1. Error Codes associated with denied claims

Error Code	Error Status Description	
3002	NDC REQUIRES PA	**Include**
4167	DRUG QUANTITY PER DAY LIMIT EXCEEDED	**Include**
3000	UNITS EXCEED AUTHORIZED UNITS ON PA MASTER FILE	**Include**
3024	DRUG OPTIMAL DOSAGE EXCEEDED	**Include**
5001	EXACT DUPLICATE	Exclude
4002	Non-Covered Drug	Exclude
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)	Exclude
4890	Non covered drug class	Exclude
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE	Exclude
513	RECIPIENT NAME AND NUMBER DISAGREE	Exclude
4025	AGE IS NOT ALLOWED FOR NDC	Exclude
238	RECIPIENT NAME IS MISSING	Exclude
4891	Not covered drug class	Exclude
2017	RECIPIENT SERVICES COVERED BY HMO PLAN	Exclude
503	DATE DISPENSED AFTER BILLING DATE	Exclude
628	Other Coverage Reject Code Required for OCC 3	Exclude
209	DISPENSE AS WRITTEN CODE 02 NOT ALLOWED.	Exclude
221	DAYS SUPPLY MISSING	Exclude
268	BILLED AMOUNT MISSING	Exclude
270	HEADER TOTAL BILLED AMOUNT INVALID	Exclude
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER	Exclude

Table A2. Codes for stimulants and related drugs for narcolepsy

HSN	Generic Name	Category
002064	amphetamine sulfate	ADHD drug
043652	amphetamine	ADHD drug
013449	dextroamphetamine/amphetamine	ADHD drug
022987	dexmethylphenidate HCl	ADHD drug
002065	dextroamphetamine sulfate	ADHD drug
047926	dextroamphetamine	ADHD drug
034486	lisdexamfetamine dimesylate	ADHD drug
002067	methamphetamine HCl	ADHD drug
033556	methylphenidate	ADHD drug

001682	methylphenidate HCl	ADHD drug
047187	serdexmethylphen/dexmethylphen	ADHD drug
010865	modafinil	IE drug
034868	armodafinil	IE drug
012346	sodium oxybate	Other narcolepsy drug
046743	sodium,calcum,mag,pot oxybate	Other narcolepsy drug
045666	solriamfetol	Other narcolepsy drug
045575	pitolisant	Other narcolepsy drug

Table A3. Sleep Disorder Diagnoses

ICD-10 codes	Description	Category
G4733	Obstructive Sleep apnea	Funded and evidence-supported
G474x	Narcolepsy and cataplexy	
F32x-F33x	Depression (fatigue)	
G35x	Multiple sclerosis (fatigue)	
R530, C00x-C96x	Cancer (fatigue)	
G4711-G4712	Idiopathic (primary) hypersomnia	Unfunded and evidence-supported
G4726	Shift work disorder	
G4720-G4725, G4727-G4729	Other circadian rhythm sleep disorders	Not evidence supported
G4730-G4732, G4734-G4739	Other sleep apnea	
G4710, G4713-G4719	Other hypersomnia	
G470x	Insomnia	
G475x	Parasomnia	
G476x	Sleep-related movement disorders	
G478x-G479x	Other and unspecified sleep disorders	
R538x, G9332, G9339	Other and chronic fatigue	
F90x	ADHD	

Appendix 2: Proposed Prior Authorization Criteria

Sleep-Wake Medications

Goal(s):

- To promote safe use of drugs for obstructive sleep apnea and narcolepsy.
- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP. Accommodate individual review for individuals under the EPSDT program.

- Limit use to safe doses.

Length of Authorization:
- Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit

Requires PA:
- Modafinil or armodafinil without previous claims evidence of narcolepsy ~~or obstructive sleep apnea~~
- Solriamfetol
- Pitolisant

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. Funded and Evidence-Supported Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Solriamfetol (Sunosi™)	Pitolisant (Wakix™)
• Excessive daytime sleepiness in narcolepsy	X~~FDA approved for Adults 18 and older~~	X~~FDA approved for Adults 18 and older~~	X~~FDA approved for Adults 18 and older~~	X~~FDA approved for people 6 and older~~
• Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP	X ~~FDA approvedfor Adults 18 and older~~	X ~~FDA approvedfor Adults 18 and older~~	X~~FDA approved for Adults 18 and older~~	Not FDA approved; insufficient evidence
• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	X~~Not FDA approved; Low level evidence of inconsistent benefit~~	Not FDA approved; insufficient evidence		
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome)	Not FDA approved; insufficient evidence			

• ADHD • Cognition enhancement for any condition	

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
Armodafinil	18 years	250 mg
Modafinil	18 years	200 mg
Solriamfetol	18 years	150 mg
Pitolisant	6 years	17.8 mg (poor CYP2D6 metabolizers)

Table 3. Recommended safety assessments

Modafinil or Armodafinil	Solriamfetol	Pitolisant
For people of childbearing potential, documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant.	Renal assessment. Dose adjustment is recommended for moderate impairment (EGFR <60 mL/min) and use in end stage renal disease is not recommended.	Renal assessment. Dose adjustment is recommended for moderate renal (EGFR <60 mL/min) and use in end stage renal disease is not recommended.
	Recent cardiovascular risk assessment (including blood pressure) within the past 3 months. Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.	

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

Approval Criteria		
2. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) despite lifestyle modifications (e.g., strategic bright light receipt or avoidance, sleep hygiene, dietary changes, etc)?	**Yes:** Document symptom severity. Go to #4 Evidence supports modafinil and armodafinil in moderate-severe shift work disorder (e.g., sleep latency ≤ 6 minutes) and risks likely outweigh benefits in patients with mild symptoms.	**No:** Pass to RPh. Deny; medical necessity
~~2.~~4. Is the requested medication for an FDA-approved age (Table 2) and evidence-supported indication (Table 1)?	**Yes:** Go to #~~3~~5	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA-approved for narcolepsy in this age group.
~~3.~~5. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #~~4~~6
~~4.~~6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~5.~~7. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #8
~~6.~~8. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Go to #9	**No:** Go to #~~10~~11
9. Is the request for modafinil 200 mg twice daily (total daily dose of 400 mg) with documentation of inadequate symptom improvement with lower doses?	**Yes:** Go to #11	**No:** Go to #10
~~7.~~10. Is the request for pitolisant in a patient with documentation of all the following: • CYP2D6 testing which indicates the patient is not a poor metabolizer • Chart notes or provider attestation indicating lack of hepatic or renal impairment	**Yes:** Go to #~~10~~11 Max dose for pitolisant is 35.6 mg daily.	**No:** Pass to RPh. Deny; medical appropriateness.
~~8.~~11. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #~~11~~12 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
~~9.~~12. Is there documentation or provider attestation of recent safety assessments for the requested drug- (Table 3)~~request for solriamfetol or pitolisant~~?	**Yes:** Go to #~~12~~13	**No:** ~~Go to #16~~Pass to RPh. Deny; medical appropriateness
~~Does the patient have a diagnosis of end stage renal disease?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~	~~**No:** Go to #13~~
~~Is the request for solriamfetol?~~	~~**Yes:** Go to #14~~	~~**No:** Go to #16~~
~~Is the request for concurrent use with a monoamine oxidase inhibitor?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~	~~**No:** Go to #15~~

Approval Criteria		
~~Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?~~	~~**Yes:** Go to #19~~ ~~Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~ ~~Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.~~
~~Is the patient of childbearing potential?~~	~~**Yes:** Go to #17~~	~~**No:** Go to #19~~
~~Is the patient pregnant or actively trying to conceive?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~	~~**No:** Go to #18~~
~~Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?~~	~~**Yes:** Go to #19~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~10.~~13. Is the request for treatment of narcolepsy or fatigue secondary to major depression (MDD), MS, or cancer ~~a drug FDA-approved for the condition (Table 1)~~? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #~~20~~14
~~11.~~14. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) ~~for a drug FDA-approved for the condition (see Table 1)~~?	**Yes:** Go to #15	**No:** Go to #~~22~~16
~~12.~~15. Is the patient compliant with recommended first-line treatments (e.g., CPAP or other primary therapy)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Pass to RPh; Deny; medical appropriateness

Approval Criteria		
~~Is the request for off-label use of armodafinil, solriamfetol, or pitolisant (see Table 1)?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness.~~ ~~There is insufficient evidence for off-label use.~~	~~**No:** Go to #23~~
~~13. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue?~~ ~~Note: Methylphenidate is recommended first-line for cancer.~~	~~**Yes:** Inform prescriber of first-line options available without PA.~~ ~~May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.~~	~~**No:** Go to #24~~
~~24~~16. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for "medical appropriateness". • Evidence to support cognition enhancement is insufficient and should be denied for "medical appropriateness". If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Renewal Criteria		
1. Is the request for solriamfetol?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #4	**No:** Go to #5
4. Is the patient adherent to primary OSA treatment (e.g.,CPAP) based on chart notes?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
5. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness (EDS), fatigue secondary to MS and/or cancer, major depressive disorder (MDD) is recommended to document clinical benefit. For Epworth Sleepiness Scale, and improvement of at least 3 points is considered clinically significant.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *4/23; 10/20 (DE); 2/20; 7/19; 03/16; 09/15*
Implementation: *5/1/23; 11/1/20; 3/1/2020; 8/19/19; 8/16, 1/1/16*

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Drug Class Update: Hepatitis B

Date of Review: August 2025

Date of Last Review: March 2017
Dates of Literature Search: 01/01/2017 – 03/19/2025

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

Purpose for Class Update:
To identify and evaluate new comparative evidence for the safety and efficacy of medications used in the treatment of chronic hepatitis B infection published since the previous class review.

Plain Language Summary:

- Hepatitis B is an infection caused by the hepatitis B virus that affects the liver. This virus is very contagious and spreads through contact with blood or other body fluids from a person infected with the virus. The infection happens within 6 months of exposure to the virus.
- Most people with hepatitis B infection do not have symptoms and do not know they are infected. The viral infection can be short-term (acute) lasting a few weeks, or long-term (chronic), lasting for many years. If not treated, chronic hepatitis B infection can lead to liver damage, liver cancer, or death.
- The best way to prevent hepatitis B infection is to get vaccinated with a hepatitis B vaccine. Most babies born in the United States (U.S.) receive the first dose of the hepatitis B vaccination series 24 hours after birth. Two or three additional doses of the vaccine (depending on which vaccine is being used) must be given to provide full protection against the virus.
- Chronic hepatitis B infection is treated with oral antiviral medicines. These medicines prevent the virus from reproducing which decreases damage to the liver. All of the antiviral medicines (lamivudine, adefovir, entecavir, and tenofovir), are taken by mouth every day and are continued indefinitely to prevent reactivating the virus.
- Another medicine used to treat chronic hepatitis B infection, peginterferon, is injected under the skin once a week. Peginterferon boosts the infected person's immune system to help fight the virus. Unlike the oral medicines, peginterferon is only taken for 2 years. However, peginterferon has many side effects that may it make it difficult for people to continue taking it. Side effects reported with peginterferon include: flu-like symptoms, fatigue, mood disturbances, and weight loss in children. People that complete a course of peginterferon do not need to use the oral medicines to treat hepatitis B infection.
- Providers must explain to the Oregon Health Authority why someone needs oral medicine to treat chronic hepatitis B infection. This process is called prior authorization. Requests for peginterferon do not need prior authorization from the provider.

Research Questions:

1. Is there new evidence demonstrating differences in efficacy between oral antivirals for the management and prophylaxis of chronic hepatitis B virus (HBV) infection?
2. Is there new evidence demonstrating differences in the safety of oral antivirals for the management and prophylaxis of HBV infection?
3. Are there specific populations (e.g., pregnancy) in which one antiviral may be more effective or safer for the treatment or prophylaxis of HBV infection?

Conclusions:

Efficacy and Safety

- Since the last review, 1 systematic review[1] and 4 clinical practice guidelines[2-5] have been updated to guide management of HBV infection and prophylaxis.
- In 2022, Canada's Drug Agency published a health technology review on antiviral prophylaxis in patients with a history of HBV receiving immunosuppressive therapy.[1] One randomized controlled trial (RCT) and 2 retrospective cohort studies found no statistically significant differences between the 2 tenofovir formulations and entecavir administered over 24 weeks to 18 months for prophylaxis of hepatitis B virus reactivation (HBVr) in patients receiving chemotherapy or immunosuppressive therapy.[1] There were no statistically significant differences between tenofovir products and entecavir regarding renal function and other side effects.[1] Four guidelines included in this review strongly recommend the use of tenofovir or entecavir as antiviral prophylaxis in all patients with high risk of HBVr who are receiving chemotherapy or immunosuppressive therapy.[1]
- The American Association for the Study of Liver Diseases (AASLD) updated guidance for management of chronic HBV in 2018.[6] Updated recommendations for the treatment of patients with chronic HBV include:
    - The AASLD recommends antiviral therapy for adults with immune-active chronic hepatitis B (hepatitis B e-antigen [HBeAg] negative or HBeAg positive) to decrease the risk of liver-related complications (Strong Recommendation. Moderate-Quality Evidence).[6]
    - The AASLD recommends peginterferon (peg-IFN), entecavir, or tenofovir dipivoxil fumarate as preferred initial therapy for adults with immune-active chronic hepatitis B. (Strong Recommendation. Low-Quality Evidence).[6] Note: Tenofovir alafenamide is also preferred initial therapy for adults with immune-active chronic hepatitis B. Consider tenofovir alafenamide in patients at risk for renal dysfunction or bone disease. Tenofovir alafenamide is not recommended in patients with creatinine clearance (CrCl) less than 15 mL/min.[6]
- In 2024, the World Health Organization (WHO) published updated guidance for management of chronic hepatitis B infection.[3] The updated recommendations include guidance for first- and second-line antiviral treatment, inclusion of treatment criteria for adolescents, and use of antiviral prophylaxis in pregnancy.

    First-line antiviral therapies for chronic hepatitis B:

    - Antivirals with a low genetic barrier to resistance (i.e., lamivudine, adefovir) can lead to drug resistance and are not recommended (Strong Recommendation, Moderate-Certainty Evidence).[3]
    - For all adults, adolescents and children (2 years or older) for whom antiviral therapy is indicated, the antivirals that have a high genetic barrier to drug resistance, tenofovir disoproxil fumarate or entecavir, are recommended as preferred regimens. (Strong Recommendation, Moderate-Certainty Evidence).[3]
    - Entecavir or tenofovir alafenamide are recommended for people with established osteoporosis and/or impaired kidney function, and for children (entecavir for those aged two years or older) or adolescents (tenofovir alafenamide for those aged 12 years or older)* as an alternative regimen, for whom antiviral therapy is indicated. (Strong Recommendation, Moderate-Certainty Evidence).[3] *The Food and Drug Administration (FDA) expanded the use of tenofovir alafenamide to children 6 years of age and older in 2024.[7]

    Second-line antiviral therapies for chronic hepatitis B:

- Among people with evidence of treatment failure* due to confirmed or suspected antiviral resistance (based on history of previous exposure or primary non-response) to lamivudine, entecavir, or adefovir, switching to tenofovir disoproxil fumarate is recommended. Tenofovir alafenamide may be considered as an alternate regimen. (Strong Recommendation, Low-Certainty Evidence). *Treatment adherence should be reinforced for all people with confirmed or suspected antiviral resistance.[3]

Preventing mother-to-child transmission of HBV and use of antiviral prophylaxis:

- Prophylaxis with tenofovir disoproxil fumarate* is recommended for all HBV positive pregnant women with HBV DNA ≥ 200,000 IU/mL or positive HBeAg (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission of HBV. (Strong Recommendation, Moderate-Certainty Evidence). *Tenofovir disoproxil fumarate may be considered for people (including pregnant women) with impaired kidney function or osteoporosis but is not FDA-approved for HBV treatment in pregnancy.[3]

- The American Gastroenterology Association (AGA) updated guidance for prevention and treatment of HBVr in 2025.[4] Reactivation of the HBV is generally a result of chronic immunosuppression, induced either by drug therapy or by pathologic immunosuppression.[4]
  - For individuals at high risk of HBVr, the AGA recommends antiviral prophylaxis over monitoring alone. (Strong Recommendation, Moderate Certainty Evidence).[4]
  - For individuals at moderate risk of HBVr, the AGA suggests antiviral prophylaxis over monitoring alone. (Conditional Recommendation, Moderate Certainty Evidence).[4]
  - For individual at low risk of HBVr, the AGA suggests monitoring alone over using antiviral prophylaxis. (Conditional Recommendation, Moderate Certainty Evidence)**.[4]**
  - For individuals at risk of HBVr, the AGA recommends testing for HBV (Strong Recommendation, Moderate Certainty Evidence).[4]
- In 2025, the Office of AIDS Research Advisory Council (OARAC) guidelines were updated by a panel of representatives from the National Institutes of Health (NIH), HIV Medicine Association (HIVMA), and Infectious Diseases Society of America (IDSA) to provide recommendations for treatment of opportunistic infections in adults and adolescents with human immunodeficiency virus (HIV).[5] Specific guidance for co-infection with HBV includes a new section on use of oral antiviral regimens in people with past HBV, chronic HBV, and isolated hepatitis B core antibody positivity.[5] The use of peginterferon was changed from preferred therapy to an alternative treatment used only in rare cases.[5] HBV-active antiretroviral treatment (ART) (i.e., tenofovir with lamivudine or emtricitabine) decreases the risk for acute HBV infection, but it does not eliminate the risk, so taking ART alone is not a recommended strategy to prevent HBV infection.[5] The specific oral antiviral recommendations based on renal function are presented below in the clinical guideline section.

Guidance for Specific Populations

- There are specific populations (e.g., pregnancy, people with HIV coinfection, and people receiving chemotherapy) in which one antiviral may be more effective or safer for the treatment of HBV. WHO guidance provides specific recommendations for use of tenofovir disoproxil fumarate prophylaxis in patients that are positive for HBV infection during pregnancy to prevent maternal transmission to the fetus.[3] The AGA recommends antiviral prophylaxis with tenofovir or entecavir in patients at moderate to high risk for reactivation of the HBV who are receiving immunosuppressive therapy.[4] Preferred treatment recommendations issued by 2025 ORAC guidance for patients coinfected with HBV and HIV are tenofovir with lamivudine or emtricitabine adjusted for renal function as needed.[5]

Expanded Indications and Market Removals

- An expanded age range was approved by the FDA for VIREAD (tenofovir disoproxil fumarate) oral tablets in December 2018.[8] This approval extended the use of tenofovir disoproxil fumarate to pediatric patients aged 2 years of age and older weighing at least 10 kg for the treatment of chronic HBV infection.[8] Prior to this expanded indication, tenofovir disoproxil fumarate was approved for use in pediatric patients aged 12 years and older.

- In March 2024, an expanded age range was FDA-approved for VEMLIDY (tenofovir alafenamide) oral tablets.[7] This approval extended the use of tenofovir alafenamide to pediatric patients aged 6 years and older weighing at least 25 kg for the treatment of chronic HBV infection with compensated liver disease.[7] Prior to this expanded indication, the drug was approved for use in pediatric patients aged 12 years and older.
- TYZEKA (telbivudine) was removed from the United States (U.S.) market in 2016 by Novartis based on business factors, not safety or efficacy issues.

Recommendations:
- Based on recent guidelines, make entecavir tablets preferred on the preferred drug list (PDL). Due to viral resistance patterns with lamivudine, make this product nonpreferred on the PDL.
- Revise prior authorization (PA) criteria to include only nonpreferred hepatitis B antiviral agents.
- Review medication costs in executive session.

Summary of Prior Reviews and Current Policy:
- The Pharmacy and Therapeutics (P & T) Committee reviewed hepatitis B antiviral agents at the March 2017 meeting. No differences were reported in terms of efficacy or safety between entecavir and tenofovir disoproxil fumarate. Both antiviral agents are recommended as first-line treatments by clinical practice guidelines. One randomized trial showed tenofovir dipivoxil fumarate had favorable outcomes in treatment of HBV in known-lamivudine resistant patients. Switching to tenofovir disoproxil fumarate is recommended by guidelines in cases of known resistance to other antiviral agents. There is insufficient evidence of improved efficacy or effectiveness or safety of tenofovir alafenamide compared to other antivirals for the treatment of HBV. The recommendation to add tenofovir alafenamide to the PDL as a non-preferred antiviral was approved by the Committee.
- The PDL status of the hepatitis B antiviral agents is presented in **Appendix 1**. Preferred products are tenofovir disoproxil fumarate and lamivudine. Nonpreferred products include entecavir, adefovir, and tenofovir alafenamide. All antivirals require PA. PA criteria are included in **Appendix 4**. In the first quarter of 2025 (January 1, 2025-April 30, 2025), there were 4 claims for oral hepatitis B antivirals. Three claims were for entecavir, and one claim was for tenofovir disoproxil fumarate.

Background:
The HBV is a partially double-stranded deoxyribonucleic acid (DNA) virus that causes an infection in hepatic tissue, which is the primary site of HBV replication.[9] Once the hepatic cells get infected by the HBV, the viral DNA remains permanently inside the host cells and serves as a template for future viral replication.[10] Transmission of HBV occurs through perinatal, percutaneous or mucosal contact with blood, semen, or other bodily fluids.[6] The virus remains infectious on environmental surfaces for at least 7 days.[9] Symptoms of acute HBV infection can include abdominal pain, nausea, vomiting, dark urine, fatigue, fever, jaundice, and joint pain, although 70% of people with HBV are asymptomatic.[11] People at higher risk of HBV infection include infants born to people with hepatitis B; people born in countries where hepatitis B is more common; and people born in the United States (U.S.) who were not vaccinated as infants and whose parents were born in areas with high rates of hepatitis B (e.g., Africa, Asia, the Pacific Islands, the Caribbean, parts of South America, and Eastern Europe).[11] Other risk factors include people who have hepatitis C; those who have sexually transmitted infections such as HIV; people who are receiving dialysis; people receiving immunosuppressive therapy; and people with liver damage or inflammation.[11] In addition, people who have been incarcerated, those who inject drugs or share needles, sexual partners of people with hepatitis B, men who have sex with men, people who live with someone with hepatitis B, and health care workers exposed to blood and body fluids are at increased risk of contracting the virus.[11] The Advisory Committee on Immunization Practices (ACIP) recommends hepatitis B vaccination for all medically stable infants weighing 2,000 grams or more within 24 hours of birth, unvaccinated infants and children, and unvaccinated adults requesting protection from hepatitis B or who are at increased risk of infection.[9]

In humans, there are 8 major HBV genotypes (A-H).[10] In North America and Africa, the HBV infections are primarily genotype A. Genotype C is almost as common in the U.S. as genotype A. HBV infections in East Asia are most commonly genotypes B and C and infections in Southern Europe and India are genotype D.[10] The HBV genotype A responds most favorably to interferon-based therapy relative to other genotypes, and the genotype C is associated with more advanced liver fibrosis and an increased risk of hepatocellular carcinoma.[10] Commercial testing for HBV genotype is not required for clinical care except when interferon-based therapy is considered, or when knowledge of the HBV genotype may aid risk stratification of disease progression.[10]

The risk of developing chronic hepatitis B depends on the age at which the individual becomes infected, with the majority of chronic infection developing in people initially exposed in infancy and childhood.[11] Approximately 90% of infants infected with the HBV in the perinatal period will develop chronic hepatitis B, whereas only 5% of adults acutely infected will develop chronic hepatitis B.[11] Recognition of the virus as a foreign antigen activates the host immunity to target and destroy infected liver cells, resulting in inflammation and necrosis of liver tissue.[10] The HBV does not directly kill hepatic cells.[10] People with chronic HBV infection are at increased risk for liver cancer and cirrhosis and are 70%–85% more likely to die prematurely than the general population, if not treated.[11] An estimated 580,000 to 2.4 million persons are living with chronic HBV in the U.S., two thirds of whom may be unaware of their infection.[11] Chronic HBV infection disproportionately affects persons born outside the United States; non-U.S.–born persons account for 14% of the general population, but account for 69% of the U.S. population living with chronic HBV infection.[11] The Centers for Disease Control and Prevention (CDC) estimates that about 640,000 adults in the U.S. have chronic HBV.[11] In 2022, the rate of newly reported chronic HBV cases was 11 times higher among non-Hispanic, Asian/Pacific Islander persons than among non-Hispanic, White people.[11]

Individuals with chronic HBV infection are typically asymptomatic and are diagnosed during routine health maintenance or screening (e.g., blood donation or an evaluation for an elevated level of liver enzymes).[10] Evaluation of individuals with chronic HBV includes a complete history, examination, and serologic testing.[2] There should be an emphasis on signs and symptoms of cirrhosis, evaluation of alcohol intake and metabolic risk factors, family history of hepatocellular carcinoma (HCC), and hepatitis A and B vaccination status.[2] The presence of Hepatitis B surface antigen (HBsAG) in the blood provides a definitive diagnosis of hepatitis B infection.[11] Chronic hepatitis B infection is defined by the presence of HBsAG on two occasions at least 6 months apart.[6] Screening for HBV includes testing for HBsAg and, if positive, testing for antibodies to HBsAg (anti-HBs) and hepatitis B core antigen (anti-HBc) to distinguish between infection and immunity.[2] Interpretation of viral markers to diagnosis acute or chronic HBV is presented in **Table 1**.

Routine assessment of additional serologic markers, such as HBV DNA, hepatitis B e-antigen (HBeAg), and alanine aminotransferase (ALT) levels, should be performed in order to guide the management of HBV infection.[2] The assessment of HBV DNA is a measure of viral load and reflects viral replication.[9] Hepatitis B e-antigen can be detected in persons with acute or chronic HBV infection; the presence of HBeAg correlates with viral replication and high infectivity; antibody to HBeAg (anti-HBe) correlates with the loss of replicating virus, although reversion to HBeAg positivity can occur.[9] Additional testing to determine the advancement of liver fibrosis through non-invasive tests such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), transient elastography (FibroScan) or FibroTest is also recommended.[2]

Table 1. Diagnosis of Acute and Chronic HBV Infection[10]

Interpretation	HBsAg	Anti-HBs	Anti-HBc	HBV DNA Detected	Interpretation Details
HBV Infection	Positive	Negative	Positive	Positive	• Presence of HBsAg for > 6 months defines chronic infection • In acute infection, Anti-HBc is in the form of IgM

Resolved Infection	Negative	Positive	Positive	Negative	• Adults infected with HBV will resolve the acute infection within 6 months • HBsAg is no longer detected (termed HBsAg loss) • 80% of adults will develop anti-HBs (termed anti-HBs seroconversion) • Anti-HBc is present in the form of IgG
Immunity	Negative	Positive	Negative	Negative	• Immunity gained through vaccination
Isolated Core	Negative	Negative	Positive	Negative or Positive	• Undetectable HBV DNA: previous infection without anti-HBs or level of anti-HBs is below the level of detection by serological test. May indicate individuals at risk of disease reactivation and should be identified prior to immunosuppressive therapy. • Detectable HBV DNA: occult HBV infection. May indicate individuals at risk of disease reactivation and should be identified prior to immunosuppressive therapy. • Period during acute infection either immediately after infection and before the appearance of HBsAg or during the resolution of infection after HBsAg loss and before appearance of anti-HBs. • False-positive test result
Abbreviations: Anti-HBc = antibodies to hepatitis B core antigen; Anti-HBs = antibodies to hepatitis B surface antigen; DNA = deoxyribonucleic acid; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M					

The CDC recommends all adults aged 18 years and older should be screened for the presence of the HBsAg at least once in their lifetime.[11] All pregnant patients should be tested for the HBsAg during an early prenatal visit for each pregnancy and all infants born to antigen-positive people should be tested.[11] The following populations, activities, exposures, or conditions associated with increased risk for HBV infection should also be tested for the HBsAg: persons incarcerated or formerly incarcerated in a jail, prison, or other detention setting; persons with a history of sexually transmitted infections or multiple sex partners; and persons with a history of hepatitis C virus infection.[11] In addition, to provide increased access to testing, anyone who requests HBV testing should receive it, regardless of disclosure of risk, because many persons may be reluctant to disclose stigmatizing risks.[11]

Although most patients with chronic HBV infection will not develop liver-related complications, the 5-year incidence of cirrhosis is approximately 8-20%, with relatively few of these cases developing HCC (2-5%).[5] Additional risk factors for developing cirrhosis and HCC in patients with chronic HBV infection include high serum HBV DNA (>2,000 IU/mL), elevated ALT levels, prolonged time to HBeAg seroconversion and development of HBeAg-negative chronic HBV.[5] In 2022, a total of 2,126 cases of acute HBV infection were reported in the U.S. but experts estimate the actual number is much higher, and likely around 13,800.[11] In 2022, HBV-related death rates among non-Hispanic, Asian/Pacific Islander people and non-Hispanic, Black people were 8.5 times and 2.6 times as high as the rate among non-Hispanic, White people, respectively.[11]

Although antiviral treatment is not considered curative, antiviral treatment, monitoring, and liver cancer surveillance can reduce morbidity and mortality associated with chronic HBV infection.[11] Current antiviral therapy for chronic HBV does not eradicate the virus and is not considered curative, but can produce an

immunological cure, defined as loss of HBsAg from the serum and sustained HBV DNA suppression.[2] There is no evidence that antiviral treatment is effective for managing acute HBV infection.[2] The goal of chronic HBV antiviral therapy is to reduce the incidence of liver-related complications including cirrhosis and HCC.[6] Treatment is indicated during the immunoactive phase of chronic HBV infection when liver injury and fibrosis occur.[10] The immunoactive phase is when a patient has an ALT level greater than the upper limit of normal in combination with a high HBV DNA level (>2,000 IU/mL if negative for HBeAg or >20,000 IU/mL if positive for HBeAg), or if a patient has evidence of at least moderate liver inflammation or fibrosis.[10]

The available treatment options for chronic HBV infection include pegylated interferon (peginterferon) and oral nucleoside/nucleotide analogs (NAs).[5] Peginterferon activates the host immune system to combat the infection but it does not kill the virus.[10] The primary drawback of peginterferon is tolerability because it is associated with frequent adverse effects (i.e., flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders in adults, and anorexia and weight loss in children).[2] The preferred formulation is peginterferon alfa-2a, which should be administered as 180 mcg once weekly via subcutaneous injection for 48 weeks for HBeAg-positive or HBeAg-negative chronic HBV infection.[2] The finite duration of therapy may be advantageous for women positive for the HBeAg with high HBV DNA levels planning on getting pregnant in the future.[10] However, peginterferon is contraindicated during pregnancy.[10] No viral resistance has been reported with peginterferon.[10]

The oral NAs target the HBV by inhibiting viral polymerase.[2] They have excellent tolerability profiles; however, the duration of their use is often indefinite because of frequent relapses or reactivation of HBV after cessation of treatment.[2] The cure rates (defined as hepatitis B surface antigen loss with undetectable viral DNA) after treatment remain low (3%-7% with peginterferon and 1%-12% with NA therapy).[10] The 5 FDA-approved NAs are described in **Table 2.** The 2024 WHO guidance recommends tenofovir disoproxil fumarate or entecavir, the 2 NAs with a high genetic barrier to resistance, as preferred first-line regimens.[3] Lamivudine, adefovir, entecavir, and tenofovir disoproxil fumarate require dose adjustment for CrCl less than 50 mL/min.[10] Tenofovir alafenamide is not recommended in patients with CrCl less than 15 mL/min.[7] All NAs carry a black box warning for the risk of lactic acidosis and severe hepatomegaly.[10] Efficacy of antiviral therapy should be assessed by serologic testing every 6 months.[10]

Table 2. Nucleoside/Nucleotide Analogs (NAs) FDA-Approved for Treatment of Chronic Hepatitis B[6,10]

Drug (BRAND NAME)	Adult Dose (all oral)	Pediatric Dose (all oral)	Development of Resistance	Pregnancy Category*
Adefovir dipivoxil (HEPSERA)	10 mg once daily	Age ≥ 12 years: 10 mg once daily	Resistance among 20% to 29% after 5 years	C
Entecavir (BARACLUDE)	Age ≥ 16 years: 0.5 mg once daily. 1 mg once daily in known lamivudine-resistance or decompensated cirrhosis.	Age ≥ 2 years and weight ≥10 kg: weight-based dosing up to 30 kg. Weight > 30 kg: 0.5 mg once daily	Resistance among 1.2% after 5 years in NA-naïve patients. Resistance increased to > 50% among patients with resistance to lamivudine.	C
Lamivudine (EPIVIR-HBV)	100 mg once daily	Age ≥ 2 years: 3 mg/kg once daily up to maximum dose of 100 mg per day	Resistance among 24% to 30% after 1 year and 70% after 5 years	C
Tenofovir alafenamide (VEMLIDY)	25 mg once daily	Age ≥ 6 years and weight ≥ 25 kg: 25 mg once daily with food	No resistance reported through 8 years of treatment.	Insufficient data for use in pregnancy

Tenofovir dipivoxil fumarate (VIREAD)	300 mg once daily	Age ≥ 2 years and weight ≥ 10 kg: 8 mg/kg once daily, maximum dose of 300 mg once daily	No resistance reported for up to 7 years.	B
*Pregnancy Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. *Pregnancy Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.				
Abbreviations: FDA = Food and Drug Administration; kg = kilograms; mg = milligrams				

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:
Canada's Drug Agency: Antiviral Prophylaxis with Tenofovir for Patients with History of HBV Receiving Oncology Treatment
In 2022, Canada's Drug Agency published a health technology review for antiviral prophylaxis in patients with a history of HBV receiving immunosuppressive therapy for hematologic and solid tumor malginancies.[1] Literature was searched through July 2022.[1] Two RCTs, 2 observational studies, and 8 evidence-based guidelines met inclusion criteria.[1] One RCT and 2 retrospective cohort studies found no statistically significant differences between either tenofovir formulation and entecavir administered from 24 weeks to 18 months for prophylaxis of HBV reactivation in patients who were hepatitis B surface antigen positive and/or hepatitis B core antibody positive receiving chemotherapy or immunosuppressive therapy.[1] There were no statistically significant differences between these 3 antivirals renal function and other side effects.[1] Guidelines focused on antiviral prophylaxis in patients receiving immunosuppressive therapy were published in Australia, Germany, Brazil, India, Italy, the U.S., and Canada from 2017 through 2022.[1] All 8 included guidelines strongly recommend the use of tenofovir or entecavir as antiviral prophylaxis in all patients with high risk of HBV reactivation (hepatitis B surface antigen positive and/or hepatitis B core antibody positive) during chemotherapy or immunosuppressive therapy.[1]

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria),[12,13] wrong study design of included trials (e.g., observational),[14-16] comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

American Association For The Study Of Liver Diseases: Update On Prevention, Diagnosis, and Treatment Of Chronic HBV Infection

The AASLD updated guidance for management of chronic HBV infection in 2018.[6] Tenofovir alafenamide received FDA-approval for treatment of chronic HBV infection in adults, after the publication of the 2016 AASLD HBV treatment guideline, so the guideline was updated to include the new tenofovir formulation.[6] Head-to-head comparisons of antiviral therapies failed to show superiority of one therapy over another in achieving risk reduction in liver-related complications.[6] However, in recommending pegylated interferon (peg-IFN), tenofovir, and entecavir as preferred therapies, the most important factor considered by the AALD panel was the lack of viral resistance with long-term use.[6] Patient-specific factors that should be considered in choosing therapeutic options include:

- the anticipated tolerability of treatment side effects,
- comorbidities (interferon is contraindicated in people with autoimmune disease, uncontrolled psychiatric disease, cytopenia, severe cardiac disease, uncontrolled seizures, and decompensated cirrhosis),
- previous history of lamivudine resistance (entecavir is preferred in this setting),
- family planning: finite therapy with peg-IFN pre-pregnancy or use of an oral antiviral that is safe in pregnancy (preferably tenofovir dipivoxil fumarate),
- HBV genotype: A and B genotypes are likely to achieve HBeAg and HBsAg loss with peg-IFN than non-A or non-B genotypes, and
- medication costs.[6]

Additional guidance:

- Peg-IFN is preferred over nonpegylated forms for simplicity.[6]
- For patients treated with peg-IFN, 48 weeks duration is used in most studies and is preferred. This treatment duration yields HBeAg seroconversion rates of 20% to 31% and sustained off-treatment HBV DNA suppression of less than 2,000 IU/mL in 65% of persons who achieve HBeAg to anti-HBe seroconversion. The combination of peg-IFN and NAs has not yielded higher rates of off-treatment serological or virological responses and is not recommended.[6]
- Duration of therapy for NA-based therapy is variable and influenced by HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis and/or decompensation. All NAs except tenofovir alafenamide require dose adjustment in persons with CrCl less than 50 mL/min.[6]
- Evaluation for cirrhosis using noninvasive methods or a liver biopsy is useful to guide treatment decisions, including duration of therapy.[6]
- Treatment with antivirals does not eliminate the risk of HCC, and surveillance for HCC should continue in persons who are at risk.[6]

Updated recommendations on the treatment of patients with chronic HBV infection:

- The AASLD recommends antiviral therapy for adults with immune-active chronic HBV infection (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications (Quality and Certainty of Evidence: Moderate*;* Strength of Recommendation: Strong*).*[6]
- The AASLD recommends peg-IFN, entecavir, or tenofovir dipivoxil fumarate as preferred initial therapy for adults with immune-active chronic hepatitis B. (Quality and Certainty of Evidence: Low; Strength of Recommendation: Strong).[6] Note: Tenofovir alafenamide is also preferred initial therapy for adults with immune-active chronic HBV infection. Consider tenofovir alafenamide in patients at risk for renal dysfunction or bone disease. Tenofovir alafenamide is not recommended in patients with creatinine clearance less than 15 mL/min.[6]

World Health Organization: Guidelines For the Prevention, Diagnosis, Care and Treatment for People with Chronic HBV Infection

In 2024, WHO published updated guidance for management of chronic HBV infection.[3] Updated recommendations include guidance for who should be treated, inclusion of treatment criteria for adolescents, first- and second-line antiviral treatment use of antiviral prophylaxis in pregnancy, and monitoring for people receiving treatment.

Treatment is recommended for all adults and adolescents (aged ≥ 12 years with chronic HBV infection (including pregnant women and girls and women of reproductive age) with:

- Evidence of significant fibrosis (≥ F2) based on an APRI score of > 0.5 or transient elastography value of > 7 kPa or evidence of cirrhosis (F4) based on clinical criteria (or an APRI score of >1 or transient elastography value of > 12.5 kPa), regardless of HBV DNA or ALT levels. (Adults: Strong Recommendation, Moderate-Certainty Evidence; Adolescents: Strong Recommendation, Low-Certainty Evidence).
  OR
- HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least 2 occasions in a 6- to 12-month period. (Adults: Strong Recommendation, High-Certainty Evidence [HBV DNA >20 000 IU/mL] and low-certainty evidence [HBV DNA 2000–20 000 IU/mL]; Adolescents: Conditional Recommendation, Low-Certainty Evidence).
  OR
- Presence of coinfections (such as HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroid use, solid organ or stem cell transplant); comorbidities (such as diabetes or metabolic dysfunction-associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of the APRI score or HBV DNA or ALT levels. (Adults: Strong Recommendation, Moderate-Certainty Evidence; Adolescents: Conditional Recommendation, Low-Certainty Evidence).
  OR
- In the absence of access to an HBV DNA assay: Persistently abnormal ALT levels alone (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score. (Adults And Adolescents: Conditional Recommendation, Very-Low Certainty Evidence).[3]

First-line antiviral therapies for chronic hepatitis B:

- NAs with a low genetic barrier to resistance (lamivudine, adefovir) can lead to drug resistance and are not recommended (Strong Recommendation, Moderate-Certainty Evidence).[3]
- For all adults, adolescents and children (2 years or older) for whom antiviral therapy is indicated, the NAs that have a high genetic barrier to drug resistance, monotherapy with tenofovir disoproxil fumarate or entecavir are recommended as preferred regimens. Tenofovir disoproxil fumarate plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine are recommended as alternative regimens (where tenofovir disoproxil fumarate monotherapy is not available) (Strong Recommendation, Moderate-Certainty Evidence).[3]
- Entecavir or tenofovir alafenamide (if available) are recommended for people with established osteoporosis and/or impaired kidney function, and for children (entecavir for those aged two years or older) or adolescents (for those aged 12 years or older) as alternative regimen, for whom antiviral therapy is indicated (Strong Recommendation, Moderate-Certainty Evidence).[3]

Second-line antiviral therapies for chronic hepatitis B:

- Among people with evidence of treatment failure* due to confirmed or suspected antiviral resistance (based on history of previous exposure or primary non-response) to lamivudine, entecavir, or adefovir, switching to tenofovir disoproxil fumarate is recommended. Tenofovir alafenamide may be considered as an alternate regimen, if available (Strong Recommendation, Low-Certainty Evidence).
  *Treatment adherence should be reinforced for all people with confirmed or suspected antiviral resistance.[3]

Preventing mother-to-child transmission of hepatitis B and use of antiviral prophylaxis:

- In settings where HBV DNA or HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate* is recommended for all HBV positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission of HBV. (Strong Recommendation, Moderate-Certainty Evidence).
  *Tenofovir disoproxil fumarate may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not approved for HBV treatment in pregnancy.[3]

For people receiving treatment, the following are recommended to be monitored at least annually:

- Non-invasive tests (APRI score or transient elastography) to assess stage of disease and progression of fibrosis or cirrhosis; and
  ALT levels (and AST for APRI), HBV DNA levels (when HBV DNA testing is available), HBsAg and HBeAg/anti-Hb (Strong Recommendation, Moderate-Certainty Evidence).[3]
- Treatment adherence should be monitored regularly and at each visit (Strong Recommendation, Moderate-Certainty Evidence).[3]

Office of AIDS Research Advisory Council: Clinical Guideline for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

In 2025 OARAC guidelines were updated by a panel of representatives from the NIH, HIVMA, and IDSA to provide recommendations for treatment of opportunistic infections in adults and adolescents with HIV.[5] Globally and in North America, approximately 8% of people with HIV have evidence of chronic HBV infection, but this varies by region of the world.[5] Compared with people with HBV mono-infection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[17] People with HIV/HBV are also more likely to have detectable HBeAg,[18] lower rates of seroconversion to anti-HBe, and increased risk of HCC and liver-related mortality and morbidity.[19] In HIV/HBV coinfection, monitoring and treatment are focused on the simultaneous and immediate treatment of both viruses regardless of HBV phase.[5]

Waning immunity is typically seen in people with low CD4 cell counts (<350 cells/mm^3) and may be a consequence of the height of the initial antibody response after immunization.[3] In a study of people with HIV who had antibody titers assessed 4 weeks after completing the three-dose hepatitis B vaccine series, those who had a titer less than 100 mIU/mL were significantly more likely to have waning immunity over the next 5 years compared with individuals who had higher titers after vaccination.[20] HBV-active ART (i.e., tenofovir with lamivudine or emtricitabine) decreases the risk for acute HBV infection, but it does not eliminate the risk, so taking ART alone is not a recommended strategy to prevent HBV infection.[5] Therefore, hepatitis B vaccination is recommended even if receiving an HBV-active ART regimen.[5]

Specific guidance for co-infection with HBV includes a new section on use of NA regimens in people with past HBV, chronic HBV, and isolated hepatitis B core antibody positivity.[5] The use of peginterferon was changed from preferred to an alternative treatment used only in rare cases.[5] The rating system for OARRAC recommendations is presented in **Table 3**.

Table 3. Rating System for Office of AIDs Research Advisory Council Recommendations[3]

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Weak recommendation for the statement	**I**: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints. **II**: One or more well-designed, non-randomized trials or observational cohort studies with long clinical outcomes. **III**: Expert Opinion

Strength of Recommendations and Quality of Evidence are **bolded** at the end of each statement based on definitions in **Table 3**.

Indication for Therapy

- All people with HIV/HBV coinfection (HBsAg positive), including pregnant people, regardless of CD4 count and HBV DNA level**,** should be treated with an ART regimen that includes drugs active against both HIV and HBV infections **(AII).**
- Tenofovir, entecavir, lamivudine, and emtricitabine should not be used alone in the absence of a fully HIV-suppressive ART regimen because of the potential for development of HIV drug**-**resistance mutations **(AI).[5]**

Preferred Therapy (CrCl ≥60 mL/min)

- The ART regimen should include two oral drugs active against HBV, preferably with:
  - tenofovir alafenamide (10 or 25 mg)* plus emtricitabine 200 mg OR tenofovir alafenamide 25 mg plus lamivudine 300 mg once daily (**AII**), or
  - tenofovir disoproxil fumarate 300 mg plus (emtricitabine 200 mg or lamivudine 300 mg) once daily (**AII**).[5]

  *Tenofovir alafenamide 10 mg dose is in the fixed-dose combination tablets of elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine and darunavir/cobicistat/tenofovir alafenamide/emtricitabine when tenofovir alafenamide is used with other antiretrovirals, the dose is 25 mg.[5]

Preferred Therapy (CrCl 30–59 mL/min)

- The ART regimen should include two oral drugs active against HBV, preferably with tenofovir alafenamide (10 or 25 mg) plus emtricitabine 200 mg once daily (**AII**).[5]

Preferred Therapy (CrCl <30 mL/min, Not Receiving Hemodialysis)

- Renally dosed entecavir (in place of tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate/lamivudine or tenofovir alafenamide/lamivudine, with a fully suppressive antiretroviral regimen), (**AIII**) or
- ART with renally dose-adjusted tenofovir disoproxil fumarate and (emtricitabine or lamivudine) when recovery of renal function is unlikely (**AIII**).[5]
- If CrCl ≥ 15 to 29 mL/min, then ART with tenofovir alafenamide (10 or 25 mg) once daily plus renally dose-adjusted emtricitabine or lamivudine is an option (**AIII**).
- Some clinicians may choose to continue full-dose emtricitabine or lamivudine to allow for people with CrCl 15–29 mL/min to remain on fixed-dose tenofovir alafenamide/emtricitabine products.[5]

Preferred Therapy (Receiving Hemodialysis)

- ART with renally dose-adjusted tenofovir disoproxil fumarate plus (emtricitabine 200 mg or lamivudine 300 mg once daily) (**AII**) or
- ART with tenofovir alafenamide (10 or 25 mg)* plus emtricitabine 200 mg PO once daily (given after HD on dialysis days) (**AII**).[5]
  *Tenofovir alafenamide and emtricitabine do not require renal dose adjustment in people receiving HD; therefore, fixed dose tenofovir alafenamide and emtricitabine products may be continued.[5]

Duration of Therapy/Monitoring During Therapy

- People on treatment for HBV and HIV should receive therapy indefinitely (**AIII**).
- HBV DNA should be monitored at 6-month intervals (**AII**).
- HBsAg should be monitored yearly (**AIII**).

The American Gastroenterology Association: Prevention and Treatment of HBV Reactivation in At-Risk Individuals

The AGA updated guidance for prevention and treatment of HBVr in 2025.[4] HBV reactivation is characterized by a loss of immunologic suppression of HBV activity in patients who are either positive for HBsAg or HB core antibody.[4] Reactivation of the HBV is generally a consequence of chronic immunosuppression, induced either by drug therapy or by pathologic immunosuppression.[4] Rituximab, and other B cell–depleting agents, are traditionally associated with a notably high risk of HBVr.[4] The current update provides guidance on the prevention and management of HBVr in individuals taking immune checkpoint inhibitors, anti-interleukin therapies, chimeric antigen receptor T cell (CAR-T) therapies, cytokine/integrin inhibitor therapies, tyrosine kinase inhibitors, anti T-cell therapies, and Janus kinase inhibitors, and updated the guidance provided for anti–tumor necrosis factor (TNF) therapies in light of new evidence.[4] The updated guideline also provides guidance on the prevention and management of HBVr among individuals undergoing transcatheter arterial chemoembolization (TACE) for HCC, and individuals who are co-infected with hepatitis C virus (HCV) and undergoing direct-acting antiviral (DAA) treatment.[4]

In keeping with the definitions established in the 2014 guideline, the AGA panel defined HBVr as either the de novo appearance of HBV-DNA in a patient with previously undetectable HBV-DNA or at least a 10-fold increase in HBV-DNA value compared with their baseline.[4] Permissible surrogates were new detection of HBsAg or HBeAg.[4] Hepatitis flare due to HBVr is defined as an elevation in serum ALT level at least 3-times the baseline level that, at a minimum, is beyond the reference range. Additional outcomes of interest were interruption of treatment (e.g., chemotherapy) and adverse events from antiviral prophylaxis against HBVr.[4]

To date, 3 RCTs have compared the duration of antiviral prophylaxis after withdrawal of the exposure of interest. When comparing a longer with a shorter duration of prophylaxis (3 months after withdrawal of exposure in 1 study; 6 months in 2 studies), a relative risk (RR) of 0.99 (95% CI, 0.76–1.28) for HBVr and a RR 1.24 (95% CI, 0.46–3.39) for hepatitis flare from HBVr were found on pooled analysis of these trials.[4] The certainty in these effect estimates was downgraded to low due to concerns regarding very serious imprecision.[4] On subgroup analysis, 2 RCTs comparing 12 months of antiviral continuation after cessation of exposure with 6 months found a RR of 1.07 (95% CI, 0.68–1.68) for HBVr and a RR of 1.35 (95% CI, 0.45–3.99) for hepatitis flare from HBVr.[4] These findings suggest that the current body of evidence suffers from imprecision.[4] The panel concluded that antiviral prophylaxis should be continued for at least 6 months after cessation of exposure of interest.[4] However, in cases when the risk of HBVr is considered high, extension of antiviral therapy to 12 months is reasonable.[4] In cases of exposure to B cell–depleting agents, antiviral prophylaxis should be extended to at least 12 months after end of exposure to B cell–depleting agents, given several case reports of delayed HBVr beyond 12 months.[4]

The undesirable consequences of antiviral therapy were considered small when prescribing antiviral prophylaxis.[4] With use of tenofovir disoproxil fumarate, there can be concern regarding its impact on renal function and bone mineral density, although the overall effect remains small.[4] Tenofovir alafenamide does not adversely impact renal function or bone mineral density compared with tenofovir disoproxil fumarate.[4]

- For individuals at high risk of HBVr, the AGA recommends antiviral prophylaxis over monitoring alone (strong recommendation, moderate certainty evidence).[4] This recommendation assumes the use of antivirals with a high barrier to resistance. Antiviral prophylaxis should be started before medications that impose risk of HBVr and should be continued for at least 6 months after discontinuation of risk-imposing therapy (at least 12 months for B cell–depleting agents).[4]

- For individuals at moderate risk of HBVr, the AGA suggests antiviral prophylaxis over monitoring alone (conditional recommendation, moderate certainty evidence).[4] This recommendation assumes the use of antivirals with a high barrier to resistance. Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use, and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative) may reasonably select active monitoring over antiviral prophylaxis, with careful consideration of feasibility and likelihood of adherence to long-term monitoring. Monitoring should be performed at 1- to 3-month intervals, and must include assessment of hepatitis B viral load in addition to assessment of ALT.[4]

- For individual at low risk of HBVr, the AGA suggests monitoring alone over using antiviral prophylaxis (conditional recommendation, moderate certainty evidence)**.**[4] This recommendation assumes regular and sufficient follow-up that ensures continued monitoring. Patients who place a higher value on avoiding the small risk of reactivation (particularly those who may be on more than 1 low-risk immunosuppressive medication) and a lower value on the burden and cost of antiviral therapy may reasonably select antiviral therapy.[4]

- For individuals at risk of HBVr, the AGA recommends testing for hepatitis B (strong recommendation, moderate certainty evidence).[4] Given universal CDC screening guidance for hepatitis B for all adults by testing for HBsAg, anti-HBs, and total anti-HBc, stratifying screening practices by magnitude of HBVr risk is no longer needed. It is reasonable to test initially for serologic markers alone (at minimum for HBsAg, anti-HBc) followed by viral load testing (HBV-DNA) if HBsAg and/or anti-HBc is positive.[4]

New Indications or Market Removals:

- December 2018: An expanded age range was approved for VIREAD (tenofovir disoproxil fumarate) oral tablets.[8] This approval extended the use of tenofovir disoproxil fumarate to pediatric patients aged 2 years of age and older weighing at least 10 kg for the treatment of chronic HBV infection or in combination with other antiretroviral agents for the treatment of HIV infection.[8] The recommended pediatric dose for both indications is 8 mg/kg up to a maximum of 300 mg taken once daily.[8] Prior to this expanded indication, tenofovir disoproxil fumarate was approved for use in pediatric patients aged 12 years and older. The safety and efficacy of tenofovir in children aged 2 to 12 years with chronic hepatitis B was evaluated in a placebo-controlled, double blind RCT (NCT01651403).[8] Eighty-nine children were enrolled and 60 were assigned to weight-based tenofovir 8 mg/kg once daily, while 29 were assigned to receive placebo once daily over 48 weeks.[8] At week 48, 77% (46/60) of tenofovir-treated patients had achieved serum hepatitis B DNA < 400 copies/mL (60 IU/mL) compared with 7% (2/29) of placebo-treated patients who achieved this primary endpoint.[8] The adverse reactions observed in pediatric subjects who received treatment with tenofovir were consistent with those observed with tenofovir in clinical trials in adults.[8]

- March 2024: An expanded age range was approved for VEMLIDY (tenofovir alafenamide) oral tablets.[7] This approval extended the use of tenofovir alafenamide to pediatric patients aged 6 years and older weighing at least 25 kg for the treatment of chronic HBV infection with compensated liver disease.[7] Prior to this expanded indication, the drug was approved for use in pediatric patients aged 12 years and older. The pediatric dose is the same as adults, 25 mg taken orally once daily with food.[7] The safety and efficacy of tenofovir alafenamide in pediatric patients was evaluated in an ongoing phase 2 trial (NCT02932150), which enrolled 88 patients with chronic hepatitis B infection aged 6 years to 18 years. Fifty-nine patients received tenofovir alafenamide and 29 patients received placebo once daily over 24 weeks in the double-blind RCT.[7] The study met its primary endpoint of percentage of patients with HBV DNA levels below 20 IU/mL at 24 weeks of therapy.[7] In total, 19% (11/59)of patients who received the treatment achieved the reduction in HBV DNA levels, compared to 0% (0/29) in the placebo group.[7] The safety profile of tenofovir alafenamide in pediatric patients was similar to that observed in adults.[7]

- Telbivudine (TYZEKA) was removed from the United States (U.S.) market in 2016 by the manufacturer based on business factors, not safety or efficacy issues.

Randomized Controlled Trials:
A total of 116 citations were manually reviewed from the initial literature search. After further review, 116 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).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
tenofovir disoproxil fumarate	VIREAD	ORAL	POWDER	N
entecavir	BARACLUDE	ORAL	SOLUTION	N
adefovir dipivoxil	ADEFOVIR DIPIVOXIL	ORAL	TABLET	N
entecavir	BARACLUDE	ORAL	TABLET	N
entecavir	ENTECAVIR	ORAL	TABLET	N
lamivudine	LAMIVUDINE HBV	ORAL	TABLET	Y
tenofovir disoproxil fumarate	TENOFOVIR DISOPROXIL FUMARATE	ORAL	TABLET	Y
tenofovir alafenamide	VEMLIDY	ORAL	TABLET	N
tenofovir disoproxil fumarate	VIREAD	ORAL	TABLET	Y

Appendix 2: Medline Search Strategy

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

1	Tenofovir/	5785
2	Antiviral Agents/ or entecavir.mp.	107790
3	Antiviral Agents/ or adefovir.mp. or HBV/	134262
4	Lamivudine/	7058
5	Hepatitis B/th [Therapy]	1983
6	1 or 2 or 3 or 4	41896
7	5 and 6	809
8	limit 7 to (english language and humans and yr="2017 -Current")	116

Appendix 3: Key Inclusion Criteria

Population	People with chronic HBV infection
Intervention	Peginterferon or oral antiviral agents (tenofovir disoproxil fumarate, tenofovir alafenamide, lamivudine, adefovir, entecavir)
Comparator	Other antiviral agents or peginterferon
Outcomes	Progression to cirrhosis or hepatocellular carcinoma
Timing	5 to 10 years
Setting	Outpatient

Hepatitis B Antivirals

Goal(s):
- Approve treatment supported by medical evidence and consensus guidelines
- Cover preferred products when feasible for covered diagnosis

Length of Authorization:
- Up to 12 months; quantity limited to a 30-day supply per dispensing.

Requires PA:
- All nonpreferred Hepatitis B antivirals

Covered Alternatives:
- Preferred alternatives listed at http://www.orpdl.org/drugs/

Pediatric Age Restrictions:
- lamivudine (Epivir HBV) – ≥ 2 years ~~2-17 years~~
- ~~teblivdine (Tyzkea) – 16 years~~
- adefovir dipivoxil (Hepsera) – ≥ 12 years
- entecavir (Baraclude) – ≥ 2 years
- tenofovir disoproxil fumarate (Viread) – ≥ 2 years and weight ≥ 10 kg ~~safety and effectiveness not established in pediatrics~~
- tenofovir alafenamide (Vemlidy) – ≥ 6 years and ≥ 25 kg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for an antiviral for the treatment of HIV/AIDS?	**Yes:** Approve for up to 12 months	**No:** Go to #3
3. Is the request for treatment of chronic Hepatitis B Virus infection?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the request for a pediatric patient?	**Yes**: Go to #5	**No:** Go to #6
5. Does the pediatric patient meet the age and weight requirements for the requested drug (see Pediatric Age Restrictions above).	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is this a continuation of current therapy previously approved by the FFS program (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims. ~~***If request is for Pegasys, refer to PA criteria "Pegylated Interferon and Ribavirin".***~~	**Yes:** Go to Renewal Criteria	**No:** Go to #7
7. Has the client tried and is intolerant to, resistant to, or has a contraindication to the preferred products?	**Yes:** Document intolerance, resistance, or contraindication. Approve requested treatment for 6 months with monthly quantity limit of 30-day supply.	**No:** Go to #8
8. Will the prescriber consider a change to a preferred product?	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve requested treatment for 6 months with monthly quantity limit of 30-day supply

Renewal Criteria		
1. Is the patient adherent with the requested treatment (see refill history)?	**Yes:** Go to #2	No: Deny; Pass to RPh for provider consult

Renewal Criteria		
2. Is HBV DNA undetectable (below 10 IU/mL by real time PCR) or the patient has evidence of cirrhosis? Note: Antiviral treatment is indicated irrespective of HBV DNA level in patients with cirrhosis to prevent reactivation.	**Yes:** Approve for up to 1 year with monthly quantity limit of 30-day supply	No: Deny; pass to RPh for provider consult

P&T Review: *8/25 (DM); 3/17(MH); 3/12*
Implementation: *TBD; 4/1/17; 5/29/14; 1/13*

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New Drug Evaluations: gepotidacin, pivmecillinam, and sulopenem etzadroxil/probenecid

Date of Review: August 2025
Generic Name: gepotidacin
Generic Name: pivmecillinam
Generic Name: sulopenem etzadroxil/probenecid

End Date of Literature Search: 06/01/2025
Brand Name (Manufacturer): Blujepa (GSK)
Brand Name (Manufacturer): Pivya (Utility therapeutics)
Brand Name (Manufacturer): Orlynvah (Iterum Therapeutics)
Dossier Received: No (applies to all 3 drugs)

Plain Language Summary:

- This review looks at the evidence for 3 new medicines used for the treatment of urinary tract infections (UTIs), caused by bacteria, which affect the bladder. Medicines used to treat infections are called antibiotics. The new antibiotics are ORLYNVAH (sulopenem/probenecid), BLUJEPA (gepotidacin) and PIVYA (pivmecillinam).
- Antibiotics are used to treat UTIs because they reduce symptoms such as painful urination (i.e. peeing), how often people must urinate, and burning associated with urinating. How well they work is measured by reducing the bacteria, also called germs, in the urine that cause UTIs. If a UTI is not treated with an antibiotic it could spread elsewhere in the body, such as the kidney.
- The antibiotic used most often to treat UTIs is nitrofurantoin.
- Some antibiotics do not work in all patients as bacteria become resistant to the effects of the antibiotic.
- The new antibiotics approved for UTIs are to be used in patients who are known to have infections caused by certain bacteria that can be identified by a lab test called a urine culture.
- A study of sulopenem/probenecid found that it worked better than ciprofloxacin, another antibiotic used for UTIs, for the treatment of UTI by reducing symptoms and bacteria in the urine in patients who had infections caused by bacteria that were resistant to ciprofloxacin.
- Two studies found that the antibiotic gepotidacin was no different than slow-release nitrofurantoin for reducing symptoms of UTI and bacteria in the urine.
- Pivmecillinam was found to be more effective than a sugar pill (placebo) for the treatment of UTI for reducing symptoms and bacteria in the urine.
- The most common adverse reactions experienced with the 3 new antibiotics used for UTIs are nausea, vomiting and diarrhea.
- Providers must request the new antibiotics for patients if other antibiotics are not an option through a process called prior authorization.

Research Questions:

1. What is the evidence for efficacy of the new drugs for uncomplicated urinary tract infection (uUTI), sulopenem/probenecid, gepotidacin, and pivmecillinam?
2. What is the evidence for the safety of the new drugs for uUTI, sulopenem/probenecid, gepotidacin, and pivmecillinam?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender, disease severity), for whom the new drugs for uUTI are more effective or associated with less harm?

Author: Kathy Sentena, PharmD

Conclusions:

- The evidence for sulopenem/probenecid, gepotidacin, and pivmecillinam are presented and reviewed in the following 6 studies.

Sulopenem/probenecid

- A double-blind, double-dummy randomized controlled trial (RCT) compared 5 days of therapy with sulopenem/probenecid to ciprofloxacin in females with uUTI.[1] For the primary endpoint of overall response of the combined clinical and microbiologic response at day 12, there is moderate quality evidence that sulopenem/probenecid was noninferior to ciprofloxacin in the modified intent to treat (mITT) population. The Food and Drug Administration (FDA) also recommended that the primary endpoint be analyzed in 2 subsets of the population; patients with baseline pathogens susceptible to ciprofloxacin and in patients who had ciprofloxacin resistant organisms at baseline. There is moderate quality evidence that sulopenem/probenecid is superior to ciprofloxacin in patients with ciprofloxacin resistant organisms for the outcome of overall response, which combined clinical (e.g., resolution of patient reported UTI symptoms and no new UTI symptoms) and microbiological response (e.g., reduction of all baseline uropathogens to less than 10^3 colony forming units (CFU)/mL in the urine). The combination of sulopenem/probenecid was not noninferior to ciprofloxacin in patients who had ciprofloxacin susceptible organism.[1] Additional study details are presented in **Table 4.**
- The most frequent adverse events associated with sulopenem/probenecid after 5 days of treatment were diarrhea, nausea, vulvovaginal mycotic infections, headache and vomiting. Sulopenem/probenecid inhibits organic anion transporters 1 and 3 (OAT1/3) and can interfere with medications using this enzyme system for metabolism.[2] See **Table 2** for a list of drug interactions.
- Sulopenem/probenecid was studied in patients with complicated UTIs and complicated intraabdominal infections and found to not be effective for these indications and should not be used in these conditions.[2]

Gepotidacin

- Gepotidacin was studied in females with uUTI in 2, methodologically similar, double-blind, double-dummy, noninferiority RCTs (EAGLE-2 and EAGLE-3).[3] Both trials compared gepotidacin to slow release nitrofurantoin for 5 days. For the primary outcome of clinical and microbiological cure, there was moderate quality evidence that gepotidacin was noninferior to nitrofurantoin in both studies for the prespecified population of nitrofurantoin susceptible organisms. In EAGLE-3, gepotidacin was superior to nitrofurantoin (treatment difference [TD] 14.6%; 95% confidence interval [CI], 6.4 to 22.8; p=0.003).[3] Additional outcome information is presented in **Table 7**.
- The most common adverse events occurring in people treated with gepotidacin are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting and vulvovaginal candiasis.[4] See **Table 5** for adverse events compared to nitrofurantoin. Gepotidacin may prolong the QT interval and also is prone to drug interactions as it is metabolized by the CYP3A4 enzyme system.[4]

Pivmecillinam

- Pivmecillinam was studied in 3 trials in women with uUTI. There is low quality evidence that pivmecillinam is not noninferior to ibuprofen for symptom relief; however, for the secondary endpoint of positive urine culture at day 14, pivmecillinam treated patients had fewer positive cultures compared to ibuprofen (risk difference [RD] -16%; 95% CI, -26% to -7%; p<0.001; absolute risk reduction [ARR] 18%/number needed to treat [NNT] 6).[5] Pivmecillinam was not superior to cephalexin based on the outcome of clinical cure (odds ratio [OR] 1.40; 95% CI, 0.4 to 4.6; P=0.58) or microbiological cure (OR 1.96; 95% CI, 0.9 to 4.3; p=0.09) (low quality evidence) (noninferiority not assessed).[6] There is low quality evidence that pivmecillinam is superior to placebo for the treatment of uUTI (ARR 52%/NNT 2).[7]
- The most common adverse events associated with pivmecillinam use in clinical trials were nausea and diarrhea (see **Table 8**).[8]
- There is no evidence available for the use of the new antibiotics for uUTI specifically in the Medicaid population or in specific subgroups.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the evidence for the new drugs for uUTI. Nonpreferred antibiotics are subject to the non-preferred prior authorization (PA) criteria.
- Maintain sulopenem/probenecid, pivmecillinam and gepotidacin as nonpreferred.

Background:

Urinary tract infections are more common and more likely to occur in women than in men.[9] The incidence of UTI is at least one infection per year in 10-20% of adult women in the United States (US). Urinary tract infections are designated as uncomplicated or complicated based on infection location. Uncomplicated infections are confined to the bladder and occur in healthy, non-pregnant women or men.[9] A complicated UTI is a systemic infection extending beyond the bladder to the kidneys (e.g., pyelonephritis). The European Association of Urology (EAU) has recommended new nomenclature for the definitions of UTI which are localized (i.e., cystitis without any signs of systemic infection in either sex) and systemic UTI (i.e., an infection with signs and symptoms of systemic infection with or without localized symptoms that may originate from any site in the urinary tract of either sex, including pyelonephritis and prostatitis).[9] Asymptomatic bacteriuria occurs in individuals without symptoms. Asymptomatic bacteriuria is more common in the elderly and usually does not require treatment. The exception is those that are pregnant, renal transplant or undergoing a urological procedure in which treatment recommendations are similar to uUTI.[10] The focus of this review will be on the uUTIs related to the approval of 3 new antibiotics used for the treatment of uUTI. Symptoms of uUTI are: frequency, urgency, dysuria and suprapubic pain.[9] Risk factors for development of an uUTI are prior UTI, recent sexual intercourse and use of spermicides.

Patients presenting with uUTI are most often treated empirically. Most uUTIs are caused by *Escherichia coli (E. coli)*, accounting for approximately 75%-95% of infections.[11] Less common bacteria associated with uUTIs are *Proteus mirabilis (P. mirabilis), Klebsiella pneumonia* (*K. pneumonia*) and *Staphylococcus saprophyticus (S. saprophyticus)*.[11] Resistant uropathogens are more commonly seen in women 50 years and older, patients with recurrent uUTI, and patients with diabetes.[3] The most recent guidelines from the Infectious Disease Society of America (IDSA), published in 2011, recommend treatment options for women based on resistance patterns and the likely causative organisms.[11] Patient allergy, compliance, availability and cost should be considered. Empirical treatment with nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) , trimethoprim-sulfamethoxazole (TMP/SMX) (160/800 mg twice daily for 3 days), fosfomycin (3 gm single dose) or pivmecillinam (400 mg twice daily for 5 days) are all recommended as treatment options (pivmecillinam was approved in Europe prior to US approval).[11] The 2025 EAU guidelines recommend that TMP/SMX only be used empirically if resistance rates in the area of use are <20% for *E. coli*.[9] Fluoroquinolones (i.e., ofloxacin, ciprofloxacin and levofloxacin) can be considered as an option but are associated with adverse events and resistance. The Food and Drug Administration (FDA) put out a 2016 Safety Announcement advising against the use of fluoroquinolones for uUTIs who have other treatment options, due to the serious side effects associated with their use.[12] Guidance by the EAU enacted stringent regulatory actions recommending against the use of fluoroquinolones due to disabling and long-lasting adverse events associated with use.[9] The EAU guidance recommends fluoroquinolones only be used when it is inappropriate to use other antibiotics. Beta-lactam antibiotics (e.g., amoxicillin/clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil) may also be considered as an alternative, with consideration of high *E. coli* resistance rates with these medications. Resistant rates seen with TMP/SMX are approximately 25%, followed by approximately 21% being fluoroquinolone resistant. Beta-lactam antibiotics can have resistant rates up to 15% in the US.

Important outcomes in the study of uUTI are resolution of symptoms and microbiological cure to prevent the progression of the infection to pyelonephritis. The Food and Drug Administration (FDA) requires therapeutic success to be based on combined clinical success (i.e., symptom resolution) and microbiological success (i.e., reduction of qualifying uropathogens to $<10^3$ CFU/mL).[13]

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

Sulopenem/probenecid (ORLYMVAH)

Clinical Efficacy:
Sulopenem/probenecid is a combination tablet approved for the treatment of uUTI due to *E. coli, K. pneumoniae or P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.[2] Sulopenem/probenecid is a penem antibacterial, specifically a broad-spectrum thiopenem ß-lactam antibiotic with efficacy against multi-drug resistant bacteria.[2] Penem antibiotics differ from carbapenems because they have different chemical structures which confers a wider spectrum of action, especially against Gram-negative bacteria, associated with carbapenems. Sulopenem inhibits cell wall synthesis and is mediated through sulopenem binding to penicillin binding proteins (PBPs). Probenecid is a renal tubular transporter inhibitor, which increases sulopenem serum concentrations and extends the half-life of sulopenem. The dose is sulopenem 500 mg/probenecid 500 mg as one tablet twice daily for 5 days, with food if possible.[2] Sulopenem/probenecid is not indicated for treatment of complicated UTIs or as step-down treatment after intravenous (IV) antibacterial treatment of complicated UTI or for complicated intra-abdominal infections or as step-down treatment after IV antibacterial treatment of complicated intra-abdominal infections.

There is one published RCT that was used for the Food and Drug Administration (FDA) approval, which compared sulopenem/probenecid to ciprofloxacin .[1] Women, 18 years of age and older with a urinalysis positive for nitrite and either leukocyte esterase or microscopic evidence of white blood cells (WBC) indicating uUTI were included in the study (n=1,579). Samples were taken between 24 and 96 hours of onset of urinary symptoms. Culture and susceptibility testing was collected at each visit. Patients also had to have 2 or more signs or symptoms of uUTI (e.g., urinary frequency, urgency, dysuria, or suprapubic pain) for inclusion into the study.[1] Patients were excluded if they had fever, chills, costovertebral angle tenderness, flank pain, nausea, vomiting or fever. The modified intention to treat (mITT) population was studied. There were 785 (73.3%) women who had ciprofloxacin susceptible organisms (mITT-S) compared to those who had ciprofloxacin resistant organisms (mITT-R).[1] Those with non-susceptible organisms were more likely to have diabetes or those with a creatinine clearance <72 mL/minute. *E. coli* was the most common causative organism, present in approximately 85% patients in both the mITT-S and mITT-R groups. *K. pneumoniae* was the second most common organism (~11%) and *P. mirabilis* was the third most common (~5%).[1] In 53 (4.9%) of patients, pathogens were resistant to all 4 commonly used antibacterials (e.g., nitrofurantoin, quinolones, TMP-SMX, and ß-lactam). Thirty percent of patients had negative urine cultures but were still included in the MITT population.

The primary endpoint was overall response, which combined clinical (e.g., resolution of patient reported UTI symptoms and no new UTI symptoms) and microbiological response (e.g., reduction of all baseline uropathogens to less than 10^3 CFU/mL in the urine) on day 12.[1] The overall response was to be compared in 2 subsets by testing ciprofloxacin susceptible microbiological MITT (mMITT-S) and non-susceptible ciprofloxacin microbiological MITT (mMITT-R) patient samples from the mITT population. In the overall mITT group combined response was 65.6% in the sulopenem/probenecid group and 67.9% in the ciprofloxacin group. In the sulopenem group 28% were mITT-R and 72% were mMITT-S. In the ciprofloxacin group 25% of the samples were mITT-R and 75% were mITT-S. Superiority of sulopenem/probenecid to ciprofloxacin was based on the mMITT-R population and noninferiority was based on the comparison of sulopenem/probenecid to ciprofloxacin in the mMITT-S population.[1]

Results for the primary endpoint of clinical and microbiologic response demonstrated superiority of sulopenem/probenecid at 12 days compared to ciprofloxacin in the subset of patients in the mMITT-R group with an absolute difference of 26.6% (95% CI, 15.1 to 37.4; p-value not reported) (**Table 4**).[1] Sulopenem/probenecid was not noninferior to ciprofloxacin in the mMITT-S subset; however, sulopenem/probenecid was noninferior to ciprofloxacin in the full mMITT population.

Sulopenem/probenecid was also studied in a non-published, phase 3, double-dummy, double-blind, multi-center RCT.[14] Details are available via the FDA Other Reviews supplemental material.[14] The trial included 2,222 adult women with uUTI. Pyelonephritis, urinary tract abnormalities, and poorly controlled diabetes were all reasons for trial exclusion. Patients received sulopenem 500 mg/probenecid 500 mg twice daily for 5 days or 2 capsules of amoxicillin 875 mg/clavulanate 125 mg for 5 days.[14] The primary outcome was the overall treatment response, the clinical (e.g., urinary frequency,/urgency, pain/burning on micturition, suprapubic pain) and microbiological (e.g., quantitative culture results and sensitivity) on the test of cure (TOC) visit on day 12 for the mITT-R and mITT-S populations. For the mMITT-S population the success rate was 61.7% in the sulopenem/probenecid group compared to 55% in the amoxicillin/clavulanate group (TD 6.7% ; 95% CI, 0.3 to 13).[14] For the mMITT-R group success occurred in 22 (52.4%) of patients in the sulopenem/probenecid group versus 17 (68%) amoxicillin/clavulanate group (TD -15.6%; 95% CI, -37.5 to 9.1).[14] Success rates were higher in the amoxicillin/clavulanate group despite being labeled as resistant.

Sulopenem/probenecid was also studied in two additional studies as stepdown treatment following complicated UTI and complicated intrabdominal infection. Sulopenem/probenecid was inferior to comparative therapies and should not be used for these conditions as described in the labeling.[2]

Clinical Safety:
The most common adverse events associated with sulopenem/probenecid were diarrhea, nausea, vulvovaginal mycotic infections, headache and vomiting.[2] Individuals with hypersensitivity, blood dyscrasias, uric acid kidney stones, or taking ketorolac should not receive sulopenem/probenecid. Sulopenem/probenecid is contraindicated in patients with a history of hypersensitivity reactions to either component. Serious adverse reactions are hypersensitivity reactions and risk of clostridium difficile-associated diarrhea, which is associated with all antibiotics.[2] Probenecid has been associated with hepatic necrosis, anaphylaxis, aplastic anemia, leukopenia and hemolytic anemia.[2] It was noted several times in the FDA review that the tablets were large and patients had difficulty swallowing them.[14] Sulopenem/probenecid inhibits OAT1/3 which can increase drug concentrations of medications that use this enzyme system for elimination (**Table 2**). Sulopenem/probenecid should be taken with food to minimize gastrointestinal adverse reactions and increase the bioavailability of sulopenem. Use of sulopenem/probenecid in pregnant women has not been evaluated.[2]

Table 1. Adverse Events with Sulopenem/probenecid Occurring in >1% of Patients[2]

Adverse Reactions	Sulopenem/probenecid N=1,932	Amoxicillin/Clavulanate N=1,107	Ciprofloxacin N=822
Diarrhea	194 (10%)	45 (4%)	21 (3%)
Nausea	80 (4%)	32 (3%)	30 (4%)
Vulvovaginal mycotic infection	46 (2%)	13 (1%)	7 (1%)
Headache	42 (2%)	17 (2%)	18 (2%)
Vomiting	29 (2%)	4 (0.4%)	11 (1%)
Abdominal Pain	22 (1%)	11 (1%)	9 (1%)

Table 2. Clinically Significant Drug Interactions with Sulopenem/probenecid[2]

Concomitant Drug /Drug Class	Effect on Drug Concentration	Recommendation
Ketorolac tromethamine	Increased ketorolac tromethamine	Contraindicated
Ketoprofen	Increased ketoprofen	Concomitant use not recommended
Indomethacin	Increased indomethacin	May increase risk of adverse reactions
Naproxen	Increased naproxen	May increase the risk of adverse reactions
Methotrexate	Increased methotrexate	Monitor frequently for adverse events if concomitant use cannot be avoided
Rifampin	Increased rifampin	Monitor for adverse reactions more frequently
Lorazepam	Increased lorazepam	Follow lorazepam prescribing dosage modifications
Oral sulfonylureas	Increased sulfonylurea	Monitor for hypoglycemia. Follow dosage recommendations.

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

Comparative Endpoints:

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

Primary Study Endpoint:
1) Clinical and microbiological response

Table 3. Pharmacology and Pharmacokinetic Properties for Sulopenem/probenecid.[2]

Parameter	
Mechanism of Action	Sulopenem etzadroxil is a penem antibacterial and probenecid is a renal tubular inhibitor (used as pharmacokinetic booster to increase plasma concentrations of sulopenem and extend the half-life)
Oral Bioavailability	Sulopenem: 40-64%, probenecid: unknown
Distribution and Protein Binding	Volume of Distribution - sulopenem distribution: 92-134 L, probenecid: 8.81 to 11.94 L Protein binding: sulopenem: 11%, probenecid: unknown
Elimination	Sulopenem: 50.55-77.6 L/hour, probenecid: 2.06 to 2.22 L/hour
Half-Life	Sulopenem: 1.18 – 1.28 hours, probenecid: 2.93 to 3.83 hours
Metabolism	Sulopenem: hydrolyzed by esterases to active sulopenem then metabolized by hydrolysis followed by dehydrogenation in the kidneys Probenecid: hepatic metabolism via glucuronidation

Abbreviations: L=liter

Table 4. Comparative Evidence Table for Sulopenem/probenecid.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Dunne, et al[1] DB, DD, MC, RCT	1. Sulopenem 500 mg /probenecid 500 mg orally twice daily for 5 days 2. Ciprofloxacin 250 mg orally twice daily for 3 days	Demographics: Age: 53 years White: 90% Diabetic: 15% Ciprofloxacin susceptible: 73.3% *E. coli* organism: 85% Key Inclusion Criteria: - Female - 18 years and older - uUTI diagnosis - 2 or more signs/symptoms of UTI Key Exclusion Criteria: - Acute pyelonephritis - Treatment with antibacterial within the prior 7 days for uUTI - Concurrent use of non-study medications with potential to effect outcome (e.g., NSAIDs, aspirin, acetaminophen, phenazopyridine)	mITT:‡ 1. 785 2. 794 mITT-R: 1. 147 (28%) 2. 139 (25%) mITT-S: 1. 370 (72%) 2. 415 (75%) PP: 1. 517 2. 554 Attrition: 1. 268 (34%) 2. 240 (30%)	**Primary Endpoint:** Combined clinical and microbiologic response at day 12: mMITT* Sulopenem/probenecid: 339 (65.6%) Ciprofloxacin: 376 (67.9%) AD -2.3 (95% CI, -7.9 to 3.3) Noninferiority criteria met mMITT-R† Sulopenem/probenecid: 92 (62.6%) Ciprofloxacin: 50 (36.0%) AD 26.6 (95% CI, 15.1 to 37.4) p-value not reported mMITT-S* Sulopenem/probenecid: 247 (66.8%) Ciprofloxacin: 326 (78.6%) AD -11.8 (95% CI, -18.0 to -5.6) Noninferiority criteria not met **Secondary Endpoint:** Combined clinical and microbiologic response at day 5 (end of treatment): mMITT Sulopenem/probenecid: 335 (64.8%) Ciprofloxacin: 313 (56.5%) AD 8.3 (95% CI, 2.4.0 to 14.1) p-value not reported mMITT-R Sulopenem/probenecid: 95 (64.6%) Ciprofloxacin: 42 (30.2%) AD 34.3 (95% CI, 23.1.0 to 44.8) p-value not reported mMITT-S Sulopenem/probenecid: 240 (64.6%) Ciprofloxacin: 271 (65.3%) AD -0.4 (95% CI, -7.1 to 6.2) p-value not reported	NA ARR 26.6/ NNT 4 NA NA NA NA	Drug related adverse event: Sulopenem/ probenecid: 207 (24.8%) Ciprofloxacin: 115 (13.9%) Serious adverse reaction: Sulopenem/ probenecid: 6 (0.7%) Ciprofloxacin: 2 (0.2%) Diarrhea: Sulopenem/ probenecid: 103 (12.4%) Ciprofloxacin: 21 (2.5%) Nausea: Sulopenem/ probenecid: 32 (3.8%) Ciprofloxacin: 30 (3.6%) Headache: Sulopenem/ probenecid: 18 (2.2%) Ciprofloxacin: 18 (2.2%) p-value and CI not reported	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized by a centralized interactive web randomization system. There were more patients with diabetes in the mITT-R group by a difference of 6.9%. Performance Bias: Low. Patients received matched placebos to maintain blinding. Investigators were blinded to susceptibility results until after TOC assessments. Detection Bias: Unclear. Interim analysis performed by independent data monitoring committee. Methodology for analyzing results was not described. Attrition Bias: High. High attrition rates in both groups due primarily to negative urine cultures in both groups. Reporting Bias: Low. Results reported as outlined in protocol. Other Bias: High. Manufactured funded. **Applicability**: Patient: The patient population is representative of those most likely to get UTIs and from the most causative common organism which is *E. coli.* Intervention: The dose and duration of sulopenem/probenecid is appropriate. Comparator: The dose of ciprofloxacin is the recognized dose for the treatment of female UTIs; however, the use of cipro is not recommended first-line for uUTIs due to adverse events. Outcomes: Clinical and microbiologic response are appropriate endpoints for the evaluation of antibiotic efficacy. Setting: Multicenter (142 sites) in 4 countries (specifics not provided).

Key: † Superiority comparison; * Noninferiority comparison; ‡Urine negative cultures excluded from mITT analysis
Abbreviations: AD = absolute difference; ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind. DD = double-dummy; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; mITT-R = modified intention to treat in ciprofloxacin resistant organisms; mITT-S = modified intention to treat in ciprofloxacin susceptible organisms; N = number of subjects; NA = not applicable; NI = noninferiority; NNT = number needed to treat; NSAIDs = nonsteroidal anti-inflammatory drugs; PP = per protocol; RCT = randomized controlled trial; TD = treatment difference; TOC = test of cure; UTI = urinary tract infection; uUTI = uncomplicated urinary tract infection.

Gepotidacin (BLUJEPA)

Clinical Efficacy:

Gepotidacin is a triazaacenaphtheylene bacterial type II topoisomerase inhibitor.[4] Gepotidacin blocks DNA replication by the inhibition of DNA gyrase and topoisomerase IV. Gepotidacin is indicated for the treatment of uUTI infections in female adult and pediatric patients 12 years of age and older who are at least 40 kg with the following susceptible organisms: *E. coli, K. pneumoniae, C. freundii* complex, *S. saphrophyticus*, and *E. faecalis*.[4] Gepotidacin is given as two 750 mg (1500 mg) tablets twice daily for 5 days, to be taken after a meal.[4]

Gepotidacin was studied in 2 similar methodologically designed studies to determine efficacy.[3] Both studies were randomized, double-blind, double-dummy, phase 3, non-inferiority studies comparing gepotidacin 1500 mg twice daily for 5 days to nitrofurantoin 100 mg (slow release formulation) twice daily for 5 days (EAGLE-2 and EAGLE-3).[3] Patients were randomized 1:1 and stratified by age and history of recurrent uUTI. Symptoms were accessed at baseline, on-treatment (day 2-4), TOC (day 10-13) and follow-up (day 25-31) and scored from 0-3 with 0 being none and 3 being severe. Symptoms were assessed by a provider or trained medical staff.[3] Urine samples were taken at each visit and underwent culture and susceptibility testing. Patients could have one or 2 identified pathogens. Qualifying uropathogens were: gram-negative bacilli, *S. saphrophyticus* or *Enterococcus* species at concentrations of $\geq 10^5$ CFU/mL.[3] The average of age of participant was 52 years and 50 years in EAGLE-2 and EAGLE-3, respectively. There was only 1 patient under the age of 18 years randomized to gepotidacin included in EAGLE-3 and none in EAGLE-2.[3] There were 4 nitrofurantoin patients under the age of 18 enrolled between the 2 studies. The majority of patients in both studies were positive for *E. coli*.[3]

The primary endpoint was therapeutic response at TOC, which combined clinical (e.g., symptom score of 0) and microbiological response (e.g., reduction of qualifying uropathogens to less than 10^3 CFU/mL in the urine). Uropathogens had to be susceptible to nitrofurantoin to be included in the microbiological intention to treat (ITT) nitrofurantoin (NTF-S) population.[3] Both studies were stopped early due to efficacy after interim analysis. The primary analysis population included patients at the time of the interim analysis cutoff, had the opportunity to reach the TOC visit or who were known to have achieved therapeutic success before the TOC visit.

Results are for described for the microbiological ITT NTF-S unless specifically stated. Gepotidacin was non-inferior to nitrofurantoin in both studies. Gepotidacin achieved therapeutic success with 50.6% of gepotidacin patients compared to 47.0% for nitrofurantoin (TD 4.3%; 95% CI, -3.6 to 12.1) in EAGLE-2.[3] In EAGLE-3, gepotidacin was noninferior and superior to nitrofurantoin (TD 14.6%; 95% CI, 6.4 to 22.8; p=0.003). Statistical superiority for gepotidacin was most likely due to a higher microbiological failure in the nitrofurantoin group and less discordance between clinical and microbiological response in the gepotidacin group. More women used another antibiotic concurrently for uUTI in those taking nitrofurantoin (4.2%) compared to gepotidacin (1.6%) in EAGLE-2 and 6.5% for gepotidacin and 5.3% for nitrofurantoin in EAGLE-3.[3] In EAGLE-2 clinical success was the same between groups (65%) and higher in the gepotidacin group (67.9%) compared to nitrofurantoin (63.3%) in EAGLE-3. Gepotidacin resulted in a higher percentage of microbiological cure compared to nitrofurantoin in EAGLE-2, 72.5% versus 67.6% (TD 5.2%, 95% CI, -2.1 to 12.5).[3] In EAGLE-3 microbiological cure was higher with gepotidacin compare to nitrofurantoin, 72.2% versus 57.2% (TD 15.0%, 95% CI, 7.2 to 22.9). Microbiological failure was due to missing cultures or taking other antibiotic in the gepotidacin group and microbiological recurrence with

nitrofurantoin. Therapeutic success rates for those with *E. coli* was higher in gepotidacin treated patients compared to nitrofurantoin in both studies; EAGLE-2, 51.1% and 45.9% and EAGLE-3, 59.8% and 44.0%.[3]

The scoring of uUTI symptoms was subjective. There was discordance in clinical and microbiologic failure rates that can influence results but is not uncommon in trials studying antibiotics for uUTI.

Clinical Safety:
The most common adverse events associated with the use of gepotidacin are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting and vulvovaginal candidiasis.[4] See **Table 5** for specific adverse event rates.

Table 5. Adverse Events with Gepotidacin Occurring in 1% or More Patients than Nitrofurantoin[4]

Adverse Event	Gepotidacin (N=1,570)	Nitrofurantoin (N=1,558)
Diarrhea	258 (16%)	51 (3%)
Nausea	146 (9%)	64 (4%)
Adnominal pain	60 (4%)	34 (2%)
Flatulence	43 (3%)	8 (<1%)
Headache	38 (2%)	40 (3%)
Soft feces	37 (2%)	8 (<1%)
Dizziness	29 (2%)	19 (1%)
Vomiting	28 (2%)	10 (<1%)
Vulvovaginal candidiasis	20 (1%)	18 (1%)

Gepotidacin may prolong the QT interval and should be avoided in patients with a history of QT prolongation, those with relevant cardiovascular (CV) disease or taking other drugs that may prolong the QT interval.[4] Gepotidacin should not be taken with drugs that cause CYP3A4 inhibition and in those with severe hepatic (Child-Pugh Class C) or renal (estimated glomerular filtration rate [eGFR] <30 ml/min) impairment due to the risk of increased concentrations of gepotidacin.[4] Reports of dysarthria (i.e., slurred speech) have been reported with gepotidacin. Use of gepotidacin with anticholinesterase inhibitors, succinylcholine-type neuromuscular blocking agents, systemic anticholinergic medications or non-depolarizing neuromuscular blocking agents may exacerbate underlying medical conditions.[4] As with all antibiotics there is a risk of *C. difficile* infection.

Look-alike / Sound-alike Error Risk Potential: may be confused with gentamicin.

Comparative Endpoints:

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

Primary Study Endpoint:
1) Clinical and microbiological response

Table 6. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	Triazaacenaphthylene antibacterial that inhibits Type II topoisomerases including bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, thereby inhibiting DNA replication
Oral Bioavailability	45%
Distribution and Protein Binding	172.9 L 25-41%
Elimination	33.4 L/hr
Half-Life	9.3 hours
Metabolism	Oxidative metabolism mediated by CYP3A4, producing several circulating metabolites

Abbreviations: CYP = cytochrome P450 enzymes; DNA = deoxyribonucleic acid; hr = hour; L = Liters

Table 7. Comparative Evidence Table for Gepotidacin.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Wagenlehner, et al[3] EAGLE-2, DB, DD, MC, NI, Phase 3, RCT	1. Gepotidacin orally 1500 mg twice daily for 5 days 2. Nitrofurantoin slow-release formulation orally 100 mg twice daily for 5 days	Demographics: Age: 52 years White: 84% BMI: 26.9 History of recurrent UTI: 40% Total symptom score: 7.2 *E coli* organism: 90% Key Inclusion Criteria: - Female - 12 years and older - Nonpregnant - ≥ 40 kg - ≥ 2 signs/symptoms of UTI - Urinary nitrite, pyuria or both Key Exclusion Criteria: - Uncontrolled diabetes - Symptoms known to be caused by another disease process - Anatomical or physiological anomaly that might predispose patient to UTI - Complicated UTI - CrCl <60 mL/min	ITT: 1. 320 2. 287	Primary Endpoint: Combined clinical and microbiologic response at day 10 to 13 (nitrofurantoin-susceptible qualifying uropathogen): 1. Gepotidacin: 162 (50.6%) 2. Nitrofurantoin: 135 (47.0%) TD -4.3% (95% CI, -3.6 to 12.1) Noninferiority criteria met Secondary Endpoint: Clinical Success: 1. Gepotidacin: 210 (65.6%) 2. Nitrofurantoin: 187 (65.2%) TD 1.2% (95% CI, -6.3 to 8.7) Noninferiority criteria met Microbiological Success: 1. Gepotidacin: 232 (72.5%) 2. Nitrofurantoin: 194 (67.6%) TD 5.2% (95% CI, -2.1 to 12.5) Noninferiority criteria met	NA NA NA	Drug related adverse event: Gepotidacin: 197 (26%) Nitrofurantoin: 93 (12%) Diarrhea: Gepotidacin: 258 (16%) Nitrofurantoin: 51 (3%) Nausea: Gepotidacin: 146 (9%) Nitrofurantoin: 64 (4%) Serious adverse reaction: Gepotidacin: 2 (<1%) Nitrofurantoin: 3 (<1%) Adverse events leading to discontinuation: Gepotidacin: 27 (4%) Nitrofurantoin: 18 (2%) Safety population: Gepotidacin n=766 Nitrofurantoin n=760	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized 1:1 by a centralized by interactive response technology. Baseline demographics were well matched. Performance Bias: Low. Patients received matched placebos to maintain blinding. Patients, investigators and sponsor study team were blinded to treatment assignment. Detection Bias: Unclear. Scoring of symptoms was subjective and could increase risk of bias. Gastrointestinal adverse events were more common with gepotidacin and could result in unblinding. Attrition Bias: Unclear. Analysis of interim data and no data on per protocol population numbers provided for this interim set. Reporting Bias: Unclear. Results were analyzed on the interim ITT set for the primary endpoint because the trial was stopped early due to efficacy. Other Bias: High. Manufactured funded. Authors were employees, shareholders and/or advisors with GSK.

								Applicability: Patient: The patient population is representative of those most likely to get UTIs and from the most causative common organism which is *E. coli.* Intervention: The dose and duration of gepotidacin is appropriate. Comparator: Nitrofurantoin is a first-line treatment option for uUTI and is an appropriate comparator at the study dose. The dose and treatment duration were appropriate. Outcomes: Clinical and microbiologic response are appropriate endpoints for the evaluation of antibiotic efficacy. Setting: Multicenter (219 sites) in 15 countries for both studies.
2. Wagenlehner, et al[3] EAGLE 3 DB, DD, MC, NI, Phase 3, RCT	1. Gepotidacin 1500 mg twice daily for 5 days 2. Nitrofurantoin slow-release formulation 100 mg twice daily for 5 days	Demographics: Age: 50 years White: 85% BMI: 27.2 History of recurrent UTI: 41% Total symptom score: 7.4 *E coli* organism: 90% Key Inclusion Criteria: - See above Key Exclusion Criteria: - See above	ITT: 1. 277 2. 264	**Primary Endpoint:** Combined clinical and microbiologic response at day 10 to 13 (nitrofurantoin-susceptible qualifying uropathogen): 1. Gepotidacin: 162 (58.5%) 2. Nitrofurantoin: 115 (43.6%) TD -14.6% (95% CI, 6.4 to 22.8) P=0.0003 Noninferiority criteria met, and superiority was confirmed in sequential testing **Secondary Endpoint:** Clinical Success: 1. Gepotidacin: 188 (67.9%) 2. Nitrofurantoin: 167 (63.3%) TD 4.4% (95% CI, -3.5 to 12.3) Noninferiority criteria met Microbiological Success: 1. Gepotidacin: 200 (72.2%) 2. Nitrofurantoin: 151 (57.2%) TD 15.0% (95% CI, 7.2 to 22.9) Noninferiority criteria met	ARR 14.6/ NNT 7 NA NA	Drug related adverse event: Gepotidacin: 221 (27%) Nitrofurantoin: 108 (14%) Serious adverse reaction: Gepotidacin: 5 (<1%) Nitrofurantoin: 5 (<1%) Adverse events leading to discontinuation: Gepotidacin: 52 (6%) Nitrofurantoin: 12 (2%) Safety population: Gepotidacin n=804 Nitrofurantoin n=798	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: See above. Performance Bias: See above. Detection Bias: See above. Attrition Bias: See above. Reporting Bias: See above. Other Bias: See above. **Applicability**: Patient: See above. Intervention: See above. Comparator: See above. Outcomes: See above. Setting: See above.

Abbreviations: ARR = absolute risk reduction; BMI = body max index; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind. DD = double-dummy; ITT = intention to treat; kg = kilogram; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = noninferiority; NNT = number needed to treat; PP = per protocol; RCT = randomized controlled trial; TD = treatment difference; UTI = urinary tract infection.

Pivmecillinam (PIVYA)

Clinical Efficacy:

Pivmecillinam is a penicillin antibacterial used for the treatment of uUTI in female patients 18 years old and older caused by susceptible isolates of *E. coli, P. mirabilis and S. saprophyticus.*[8] Pivmecillinam is given as a single 185 mg tablet by mouth 3 times a day for 3-7 days as clinically indicated.

Pivmecillinam was studied in 3, phase 3, clinical trials for evidence for FDA approval. The first trial was a dosing study in Sweden.[7] The second trial compared pivmecillinam to cephalexin and the third trial was a trial comparing pivmecillinam to ibuprofen.[5,6]

In a 2007 study, pivmecillinam was compared to placebo in adult women (n=1162) with symptoms of uUTI in a multi-center, randomized, double-blind study in Sweden.[7] Women took pivmecillinam 185 mg (package insert states 185 mg and published study states 200 mg) three times daily for 7 days, 185 mg twice daily for 7 days (not approved regimen) or 370 mg twice daily for 3 days (not an approved regimen) or placebo three times a day for 7 days.[7] The primary outcome was to compare 4 different treatment regimens based on symptoms and bacterial counts after 8-10 days and at 1 month follow-up (days 35-49). Clinical and microbiological cure was similar between the all the doses (**Table 10**). Overall, the combined clinical and microbiological endpoint was achieved in 62% of patients in the combined pivmecillinam group compared to 10% of placebo treated patients (TD 52%; 95% CI, 41 to 62).[8] At one month the percentage of clinical cure was similar between pivmecillinam and placebo (87-88%). Microbiological cure was higher at the one month follow up in the pivmecillinam groups compared to placebo.[7] The seven day regimens were found to be more effective than the 3 day regimen. Few details were provided on study methodology which prevented strong conclusions. The study was considered low quality. One patient in each group developed pyelonephritis.

The second trial compared the use of pivmecillinam 185 mg (package insert states 185 mg and published study states 200 mg) three times daily for 3 days compared to cephalexin 250 mg four times daily for 7 days in a multi-center, double-blind, superiority RCT in the U.S.[6] Women 18 years with uUTI were included. Patients were seen at entry day, day 10 and day 14. The composite endpoint was clinical and microbiological cure. Symptoms were monitored and recorded by investigators. Clinical cure was based no symptoms that persisted during treatment or post treatment. Microbiological cure was a negative urine culture on day 10 for presenting pathogen.[6] Microbiological cure and clinical cure was not significantly different between pivmecillinam compared to cephalexin.[6] The composite endpoint was achieved in 72% of those treated with pivmecillinam compared to 76% of patients treated with cephalexin (TD -4%; 95% CI, -16 to 7; p>0.05).[8]

In a third trial, pivmecillinam 185 mg three times daily was compared to ibuprofen 600 mg daily three times daily.[5] Both regimens were given for 3 days. Ibuprofen was chosen as a comparator to see if symptomatic uUTI treatment could reduce antibiotic use since uUTIs are often self-limiting. The trial was a double-blind, double dummy, noninferiority trial. Patients were asked to record symptoms daily, including if they felt cured, in a provided diary that had been validated. Adverse events and information on adherence were also requested. Patients were contacted on day 14 and 28 to ask about symptoms and if the patient felt they were cured. A baseline urine dipstick (leukocytes, protein, nitrates and blood) was obtained and again at 2 weeks. Results of the dipstick testing were not used for inclusion but included for additional analysis. The main outcome was proportion of patients who felt cured by day 4, as recorded in their diary.[5] Missing cure data was obtained by telephone follow-up. A key secondary outcome was the proportion of patients with a positive second urine culture at 14 days for primary pathogen.

Pivmecillinam was found to be associated with a higher number of patients who felt cured by day 4 of treatment compared to those randomized to ibuprofen (RD 35%; 95% CI, 27% to 43%; noninferiority not met).[5] There were fewer patients in the pivmecillinam group that experienced a positive bacterial culture at 14 days compared to ibuprofen (RD -16%; 95% CI, -26% to -7%; p<0.001; ARR 18%/NNT 6).

Limitations to the evidence are efficacy evidence based on subjective patient reported symptoms. Resistance to *E. coli* was not studied or reported. The number of previous uUTIs at baseline was not reported. Methodology was not well described for the first 2 trials resulting in an unclear risk of bias for many domains.

Clinical Safety:
The most common adverse reactions with pivmecillinam are nausea and diarrhea.[8] Contraindications to treatment are history of serious hypersensitivity reactions to pivmecillinam or other beta-lactam antibacterial drugs, primary or secondary carnitine deficiency , or acute porphyria. Serious adverse events were rare in clinical trials. See **Table 8** for specific adverse event rates.

Table 8. Adverse Reactions in Patients Receiving Pivmecillinam Compared to Placebo Occurring in ≥1% of Patients[8]

Adverse Event	Pivmecillinam (N=282)	Placebo (N=288)
Nausea	12 (4.3%)	6 (2.1%)
Diarrhea	6 (2.1%)	2 (0.7%)
Vulvovaginal candidiasis	5 (1.8%)	0
Genital pruritus	5 (1.8%)	4 (1.4%)
Headache	4 (1.4%)	1 (0.3%)

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

Comparative Endpoints:
Clinically Meaningful Endpoints:
1) Microbiological eradication
2) Symptom improvement
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical and microbiological response

Table 9. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	A pro-drug containing pivaloxyloxymethylester of the amidinopenicillanic acid, mecillinam. Pivmecillinam is hydrolyzed to mecillinam to the active antibacterial agent. Mecillinam is a beta-lactam antibacterial drug. Majority of activity is against gram-negative bacteria by interfering with the biosynthesis of the bacterial cell wall. There is high specificity against the penicillin-binding protein-2 (PBP-2) in the gram-negative cell wall.
Oral Bioavailability	25-35%
Distribution and Protein Binding	51 L <25%
Elimination	Renal: 580 mL/min
Half-Life	61 minutes
Metabolism	Pivmecillinam converted to mecillinam and pivalic acid by non-specific esterases. Mecillinam undergoes minimal metabolism.

Abbreviations: L = Liters; mL = milliliters

Table 10. Comparative Evidence Table for Pivmecillinam.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Ferry, et al[7] DB, MC, PC, RCT, Phase 3	1. Pivmecillinam 200 mg orally three times daily for 7 days† 2. Pivmecillinam 200 mg orally two times daily for 7 days† 3. Pivmecillinam 400 mg orally two times daily for 3 days 4. Placebo	Demographics: Mean age: 43 years Mean symptom duration: 10 days Mean baseline symptom score: 5.3 points *E. coli* as baseline pathogen: 62.1% Key Inclusion Criteria: - Females - 18 years and older - Clinical symptoms of lower UTI (terminology used in 2007) - Symptom score of 2 or greater Key Exclusion Criteria: - Antibiotic therapy in the last month	ITT: 1. 281 2. 289 3. 285 4. 288 PP: 1. 172 2. 187 3. 164 4. 94 Attrition: 1. 109 (39%) 2. 94 (33%) 3. 121 (42%) 4. 194 (67%)	Primary Endpoint (m-ITT population): Clinical Cure day 8-10: 1. 62 (29%) 2. 64 (29%) 3. 55 (25%) 4. 25 (11%) P<0.001 for all pivmecillinam groups compared to placebo Microbiological Cure day 8-10: 1. 93 (43%) 2. 94 (43%) 3. 38 (25%) 4. 34 (15%) P<0.001 for all pivmecillinam groups compared to placebo Composite Response Rate at day 8-10: Combined pivmecillinam groups: 85 (62%)	ARR 52%/	Adverse reactions: 1. 48 (17%) 2. 35 (12%) 3. 40 (14%) 4. 35 (12%) p-value not reported Gastrointestinal: Pivmecillinam (pooled doses reported): 5-8% Placebo: 4% p-value not reported Severe adverse events were not reported.	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Not described. Performance Bias: Low. Stated that it was a double-blind, double-dummy trial design. Detection Bias: High. There was no detail on how symptoms were tracked and recorded. Attrition Bias: High. Attrition was high in all groups. Study duration went out to 49 days follow-up contributing to high attrition rates. Reporting Bias: High. There was insufficient reporting of study details to assess. Other Bias: High. Manufacture funded. **Applicability**: Patient: Patients had a lower incidence of pathogens caused by *E. coli* than seen in the community. Intervention: It is the appropriate dose of pivmecillinam. Comparator: An active comparison would be more appropriate in quantifying efficacy. Outcomes: Microbiological cure and clinical cure are appropriate outcomes. Reporting of resistance patters would be helpful. Setting: Eighteen primary healthcare centers in Sweden.

		- Participation in a study within the last 3 months - Penicillin allergy - Genital infection - Signs of upper UTI - Diabetes - Pregnancy		Placebo: 14 (10%) TD 52% (95% CI, 41 to 62)	NNT 2			
3. Menday, et al[6] DB, DD, MC, NI, RCT	1. Pivmecillinam 200 mg orally three times daily for 3 days† 2. Cephalexin 250 mg four times daily for 7 days	Demographics: Females: 2% Age: 32 years *E coli* as baseline pathogen: 92% Key Inclusion Criteria: - Females and males - 18 years and older - Uncomplicated UTI - No more than 2 symptomatic episodes within the last year - No history of obstructive uropathy Key Exclusion Criteria: - Pregnant - Febrile - Allergy to study drugs - Signs of upper UTI	ITT: 1. 219 2. 221 PP: 1. 107 2. 109 Attrition: 1. 112 (51%) 2. 112 (51%)	Primary Endpoint: Clinical cure: Pivmecillinam: 102 (95.3%) Cephalexin: 102 (93.6%) OR 1.40 (95% CI, 0.4 to 4.6) P=0.58 Microbiological cure: Pivmecillinam: 96 (89.7%) Cephalexin: 89 (81.7%) OR 1.96 (95% CI, 0.9 to 4.3) P=0.09	NA NA	Adverse event: Pivmecillinam: 13 (5.9%) Cephalexin: 16 (7.2%) Gastrointestinal: Pivmecillinam: 11 (5%) Cephalexin: 5 (2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Not described. Performance Bias: Low. Medications were packaged with a double dummy design and patients and investigators were blinded to treatment. Detection Bias: Unclear. Limited detail on symptom and outcome assessment. Attrition Bias: High. Attrition was high in both groups primarily due to not having adequate bacteria in the urine and inadequate cultures. Reporting Bias: High. There was a lack of detail on study methodology. Other Bias: High. Manufacture funded. **Applicability**: Patient: Patients were representative of those presenting with uUTI. Intervention: It is the appropriate dose of pivmecillinam. Comparator: Cephalexin is not a first line treatment and is considered an alternate therapy. Outcomes: The combined outcome of microbiological and clinical response is recommended by the FDA. Setting: Twenty-eight centers in the United States.
3. Vik, et al[5] DB, MC, NI, RCT	1. Pivmecillinam 185 mg orally three times daily for 3 days 2. Ibuprofen 600 mg three times daily for 3 days	Demographics: Age: 29 years Dysuria: 96% Urinary urgency: 98% Urinary frequency: 99% *E coli* as baseline pathogen: 80% History of 0-2 UTIs in last 12 months: 92% Key Inclusion Criteria: - Females - 18-60 years	ITT: 1. 181 2. 178 PP: 1. 150 2. 154 Attrition: 1. 31 (17%) 2. 24 (13%)	Primary Endpoint: Proportion of patients who felt cured (i.e. no symptoms) by day 4: Pivmecillinam: 131 (73.6%) Ibuprofen: 70 (38.7%) RD 35% (95% CI, 27% to 43%) Noninferiority criteria not met Secondary Endpoint: Positive Urine Culture at day 14:	NA	Adverse event: Pivmecillinam: 38 (21%) Ibuprofen: 32 (18%) Serious adverse reaction: Pivmecillinam: 1 (<1%) Ibuprofen: 6 (3%)		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized in a 1:1 ratio by computer-generated randomization list. Performance Bias: Low. The medications were formulated to be identical in appearance, weight, and taste. Providers and patients were blinded to drug assignment. Detection Bias: Unclear. Patients recorded symptoms in diary. Subjective outcome reporting may increase the risk of bias. Attrition Bias: High. Attrition was high in both groups primarily due to dropouts and lost to follow-up. Reporting Bias: Unclear. The primary outcome was done on the ITT population which can bias results in noninferiority

		- Clinical symptoms of uUTI* Key Exclusion Criteria: - Pregnant - Symptoms more than 7 days - Allergy to study drugs - Signs of upper UTI - Diabetes - Kidney disease -Immunosuppressants or blood thinners - Previous pyelonephritis		Pivmecillinam: 16 (10%) Ibuprofen: 43 (28%) RD -16% (95% CI, -26% to -7%; p<0.001) Patients without symptoms by day 4: Pivmecillinam: 112 (73%) Ibuprofen: 60 (40%) RD -33% (95% CI, -22% to -43%)	ARR 18%/ NNT 6 ARR 33%/ NNT 3	Gastrointestinal adverse reactions: Pivmecillinam: 27 (15%) Ibuprofen: 20 (11%)		studies. Analysis of the per protocol population is recommended. This was a secondary endpoint and results were similar. Other Bias: High. Manufacture funded. **Applicability**: Patient: Patients had a lower incidence of pathogens caused by *E. coli* than seen in the community. There is no data on resistance patterns so it is unknown if pivmecillinam would be effective in this population. Intervention: It is the appropriate dose of pivmecillinam. Comparator: Ibuprofen has no antibacterial properties and is not standard of care for the treatment of symptomatic uUTI. Comparative efficacy to another antibiotic would be more appropriate in assessing efficacy. Outcomes: The combined outcome of microbiological and clinical response is recommended by the FDA. Setting: Centers in Norway (2 sites), Denmark (7 sites), Sweden (7 sites) from accident and emergency outpatient clinics (AEOCs).
Key: * Dysuria with either increased urinary frequency or urinary urgency or both; † Package insert states 185 mg and published study states 200 mg Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind. DD = double-dummy; FDA = Food and Drug Administration; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = noninferiority; NNT = number needed to treat; OR = odds ratio; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; UTI = urinary tract infection.								

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Appendix 1: Prescribing Information Highlights

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

BLUJEPA (gepotidacin) tablets, for oral use
Initial U.S. Approval: 2025

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

BLUJEPA is a triazaacenaphthylene bacterial type II topoisomerase inhibitor indicated for the treatment of female adult and pediatric patients 12 years of age and older weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTI) caused by the following susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii* complex, *Staphylococcus saprophyticus,* and *Enterococcus faecalis*. (1.1)

Usage to Reduce Development of Drug-Resistant Bacteria
To reduce the development of drug-resistant bacteria and maintain the effectiveness of BLUJEPA and other antibacterial drugs, BLUJEPA should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. (1.2)

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

- The recommended dosage of BLUJEPA is 1,500 mg (two 750 mg tablets) taken orally, twice daily (approximately 12 hours apart), for 5 days. (2.1)
- Administer BLUJEPA tablets after a meal to reduce the possibility of gastrointestinal intolerance. (2.1)

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

Tablets: 750 mg of gepotidacin. (3)

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

A history of severe hypersensitivity to BLUJEPA. (4)

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

- QTc Prolongation: Avoid use of BLUJEPA in patients with a history of QTc prolongation, or with relevant pre-existing cardiac disease, and in patients receiving drugs that prolong the QTc interval. Due to an increase in BLUJEPA exposure, avoid concomitant administration of BLUJEPA with strong CYP3A4 inhibitors and in patients with severe hepatic impairment (Child-Pugh Class C) and in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min). (5.1)
- Acetylcholinesterase inhibition: Dysarthria and other adverse reactions have been reported in patients receiving BLUJEPA. Monitor patients with underlying medical conditions that may be exacerbated by acetylcholinesterase inhibition and patients receiving succinylcholine-type neuromuscular blocking agents, systemic anticholinergic medications, or non-depolarizing neuromuscular blocking agents. (5.2)
- Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving BLUJEPA. If an allergic reaction to BLUJEPA occurs, discontinue the drug and institute appropriate supportive measures. (5.3)
- *Clostridioides difficile* Infection (CDI): CDI has been reported with nearly all systemic antibacterial agents, including BLUJEPA. Evaluate patients who develop diarrhea. (5.4)

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

The most common adverse reactions occurring in ≥1% of patients are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting, and vulvovaginal candidiasis. (6.1)

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

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

- CYP3A4 Inhibitors: Avoid coadministration of BLUJEPA with strong CYP3A4 inhibitors. (7.1)
- CYP3A4 Inducers: Avoid coadministration of BLUJEPA with strong CYP3A4 inducers (7.1)
- CYP3A4 Substrates: Avoid coadministration of BLUJEPA with drugs that are extensively metabolized by CYP3A4 and have a narrow therapeutic window. (7.2)
- Digoxin: Due to an increase in digoxin exposures, consider monitoring digoxin serum concentration, as appropriate, with concomitant administration of BLUJEPA. (7.2)

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

- Renal Impairment: Avoid use of BLUJEPA in patients with severe renal impairment with eGFR <30 mL/min, including those receiving dialysis. (8.6)
- Hepatic Impairment: Avoid use of BLUJEPA in patients with severe hepatic impairment (Child-Pugh Class C). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

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

PIVYA (pivmecillinam) tablets, for oral use
Initial U.S. Approval: 2024

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

PIVYA is a penicillin class antibacterial indicated for the treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus saprophyticus*. (1.1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PIVYA and other antibacterial drugs, PIVYA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)

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

- The recommended dosage of PIVYA is one 185 mg tablet orally 3 times a day for 3 to 7 days as clinically indicated. (2.1)
- Administer PIVYA with or without food. (2.1)

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

Tablets: 185 mg pivmecillinam. (3)

---------- **CONTRAINDICATIONS** ----------

- Serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to PIVYA or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins). (4.1)
- Primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, and other inborn errors of metabolism (e.g., methylmalonic aciduria, or propionic acidemia). (4.2)
- Acute porphyria. (4.3)

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

- Hypersensitivity Reactions: Serious hypersensitivity reactions including anaphylaxis have been reported in patients treated with PIVYA. If hypersensitivity reactions occur, discontinue treatment with PIVYA and institute appropriate therapy. (5.1)
- Severe Cutaneous Adverse Reactions (SCAR): Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with PIVYA. Monitor patients closely and discontinue PIVYA at the first signs or symptoms of SCAR or other signs of hypersensitivity. (5.2)
- Carnitine Depletion: Clinically significant hypocarnitinemia has been observed in patients at risk for reductions in serum carnitine. In patients with significant renal impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment, consider alternative antibacterial therapies. PIVYA is not recommended when prolonged antibacterial treatment is necessary. Avoid concurrent treatment with valproic acid, valproate or other pivalate-generating drugs due to increased risk of carnitine depletion. (5.3)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): This has been reported for nearly all systemic antibacterial agents, including PIVYA. Evaluate if diarrhea occurs (5.5)
- Interference with Newborn Screening Test: Treatment of a pregnant individual with PIVYA prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening. Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended. (5.7)

---------- **ADVERSE REACTIONS** ----------

The most common adverse reactions observed in ≥2% of the patients receiving PIVYA in clinical trials are nausea and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UTILITY therapeutics Ltd at 1-888-353-3180 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2024

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

ORLYNVAH™ (sulopenem etzadroxil and probenecid) tablets, for oral use
Initial U.S. Approval: 2024

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

ORLYNVAH a combination of sulopenem etzadroxil, a penem antibacterial, and probenecid, a renal tubular transport inhibitor, is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options. (1.1)

Limitations of Use

ORLYNVAH is not indicated for the treatment of:

- Complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI. (1.1, 14.2)
- Complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI. (1.1, 14.3)

Usage to Reduce Development of Drug-Resistant Bacteria

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORLYNVAH and other antibacterial drugs, ORLYNVAH should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy. (1.2, 5.5)

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

- The recommended dosage of ORLYNVAH is one tablet orally twice daily for 5 days. (2.1)
- Administration of ORLYNVAH with food is recommended. (2.1)

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

- ORLYNVAH Tablets: 500 mg sulopenem etzadroxil and 500 mg probenecid. (3)

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

- Patients with a history of hypersensitivity to the components of ORLYNVAH (sulopenem etzadroxil and probenecid) or other beta-lactam antibacterial drugs. (4)
- Patients with known blood dyscrasias. (4)
- Patients with known uric acid kidney stones. (4)
- Concomitant use of ORLYNVAH and ketorolac tromethamine is contraindicated. (4)

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

- Hypersensitivity Reactions: Hypersensitivity reactions have been reported in patients treated with ORLYNVAH. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, have been reported with beta-lactam antibacterial drugs. Severe allergic reactions and anaphylaxis have been reported with the use of probenecid (a component of ORLYNVAH). If an allergic reaction to ORLYNVAH occurs, discontinue the drug and institute appropriate therapy. (5.1)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): This has been reported with nearly all systemicantibacterial agents. Evaluate if diarrhea occurs. (5.2)
- Exacerbation of Gout: When prescribing ORLYNVAH to patients with a known history of gout, ensure appropriate therapy of gout is instituted. (5.4)

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

The most common adverse reactions (≥2%) in patients treated with ORLYNVAH were diarrhea, nausea, vulvovaginal mycotic infection, headache, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Iterum Therapeutics. at 1-866-414-SULO or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Ketoprofen: Concomitant use is not recommended (7.1)
- See full prescribing information for additional clinically significant drug interactions with ORLYNVAH (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2025

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

New Drug Evaluation: diazoxide choline, oral

Date of Review: August 2025
Generic Name: diazoxide choline

End Date of Literature Search: 05/21/2025
Brand Name (Manufacturer): Vykat XR (Soleno Therapeutics, Inc.)

Dossier Received: No

Plain Language Summary:

- Prader-Willi Syndrome is a rare genetic condition that affects the body's metabolism and affects childhood development and behavior.
- Vykat XR (diazoxide choline extended-release) are tablets taken by mouth to treat a condition called hyperphagia, which is an unusually strong feeling of hunger that can lead to overeating in people with Prader-Willi syndrome.
- One study compared diazoxide choline to placebo pills and found that caregivers did not notice a difference in overeating with people who got the medicine. A second study was conducted that did seem to show a small difference with the medicine, with less food-seeking behaviors compared to people who got placebo.
- Side effects seen with diazoxide choline included high blood sugar, fluid in the legs or ankles, increased hair growth, and rash.
- Prescribers of diazoxide choline for a patient on the Oregon Health Plan will need to receive prior authorization from the Oregon Health Authority before it will be covered. This process is meant to ensure appropriate prescribing of the medicine.

Research Questions:

1. What is the evidence for the efficacy of diazoxide choline extended-release tablets in managing hyperphagia in people with Prader-Willi syndrome (PWS)?
2. What are the harms of diazoxide choline extended-release tablets in people with PWS?
3. Are there specific subpopulations for which diazoxide choline is better tolerated, more effective, or safer when used for hyperphagia in people with PWS?

Conclusions:

- VYKAT XR (diazoxide choline) extended-release tablets are Food and Drug Administration (FDA)-approved for the treatment of hyperphagia in adults and pediatric patients aged 4 years and older with PWS.[1] The safety and efficacy of diazoxide choline was studied in a phase 3, randomized controlled trial (RCT) and an extension trial with different methods and varying results.
- The phase 3 RCT was conducted in 124 patients aged 4 years and older with hyperphagia and PWS (DESTINY PWS).[2] The primary endpoint was the change in the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) from baseline to Week 13.[2] A change from baseline of 7 points was considered clinically significant.[2] At 13 weeks there was no difference in the HQ-CT score between diazoxide choline and placebo (least-square mean [LSM] −5.94 vs −4.27; mean difference [MD], -1.67; 95% confidence interval [CI] -4.24 to 0.89; P=0.193; low-quality evidence).[2]

Author: Deanna Moretz, PharmD

- In an open-label extension trial, all patients initially received diazoxide choline. At the end of the open-label period, 77 patients were randomized 1:1 to continue receiving diazoxide or switch to placebo. At 16 weeks, the LSM change from baseline in HQ-CT score was worse in the placebo-treated patients than those who continued diazoxide choline (7.6 vs. 2.6; LSM difference -5.0; 95% CI -8.1 to -1.8; very low-quality evidence).[1] The results of this phase of the trial have not been published and they are only reported in the manufacturer's prescribing information.
- The most common adverse events reported with diazoxide choline in clinical trials included hypertrichosis, edema, hyperglycemia, and rash.[1] Adverse events leading to discontinuation in diazoxide-treated patients included aggression, diabetes mellitus, fluid retention, hirsutism, hyperglycemia, lower respiratory tract infection, peripheral edema, pulmonary edema, and papular rash.[1]
- Hyperglycemia, including severe adverse events associated with diabetic ketoacidosis, occurred in diazoxide choline-treated patients.[1] Fasting glucose should be monitored more frequently for the first few weeks of treatment in patients with risk factors for hyperglycemia, such as obesity, elevated fasting plasma glucose (FPG), hemoglobin A1c (HbA1c) at the upper limit of normal or above, concomitant use of growth hormone, or concomitant use of systemic corticosteroids.[1]
- Severe adverse events associated with fluid overload, including pulmonary edema, were reported in diazoxide choline-treated patients during clinical trials.[1] Diazoxide choline has not been studied in patients with compromised cardiac reserve and should be used with caution in these patients.[1] Patients should be monitored for signs or symptoms of edema or fluid overload, and if clinically significant, the diazoxide choline dose should be reduced or the drug discontinued.[1]

Recommendations:

- Designate diazoxide choline extended-release tablets as non-preferred on the Preferred Drug List (PDL) with prior authorization (PA) criteria to ensure appropriate utilization in patients with hyperphagia due to PWS.

Background:

Prader-Willi syndrome is a rare neurodevelopmental condition due to errors in genomic imprinting involving chromosome 15.[3] This leads to the loss of expression of paternally derived genes caused by paternal deletion, maternal disomy, or an imprinting center defect.[3] Prader-Willi syndrome is associated with intellectual disability, low muscle mass, neuroendocrine abnormalities including growth hormone and gonadotropin deficiency, behavioral problems including aggression, anxiety and compulsivity, and hyperphagia resulting in severe obesity if not controlled.[4] It is the most common genetic cause of life-threatening obesity in humans.[3] The estimated prevalence of PWS is 1 in 10,000 to 20,000 individuals with a reported range of 1 in 8,000 to 1 in 30,000.[3] The number of individuals worldwide with PWS is estimated at 400,000 and about 20,000 individuals in the United States.[3] All ethnic groups are represented, but PWS is reported disproportionately more in White people with a 1:1 gender ratio.[3] Approximately 89 people enrolled in the Oregon Health Plan (OHP) have a diagnosis of PWS, with about 20 people enrolled in fee-for-service (FFS).

The clinical presentation of PWS has historically been divided into 2 distinct clinical stages with failure-to-thrive and feeding problems representing the first stage and onset of obesity representing the second stage.[3] Hypotonia and poor feeding in infancy almost always requires some type of assisted feeding for a period of time.[5] Hyperphagia, which occurs at a median age of 8 years, presents as food obsession, aggressive food seeking, and lack of satiety, with progression to severe obesity if energy intake is not restricted.[4] The etiology of the switch from the stage of poor feeding/failure-to-thrive to obesity/hyperphagia stage has yet to be determined, but is thought to be associated with abnormalities in the hypothalamic circuitry or peripheral satiety signals.[5] Individuals with PWS have differences in various gut hormones, including high levels of obestatin (an appetite suppressant hormone) in infancy, with markedly elevated levels of ghrelin (an appetite stimulant hormone) in childhood and adulthood.[5] These shifts in gut hormones may possibly correspond to the change between the poor feeding and

failure to thrive stage and the hyperphagia and obesity stage of PWS.[5] Individuals with PWS have also been shown to have structural brain abnormalities which may contribute to appetite aberrations.[5]

In PWS, weight control and diet restriction are key management issues.[3] Caloric restrictions of 6–8 calories/cm of height will usually allow for weight loss and 10–12 calories/cm of height may be required to maintain weight in PWS subjects.[3] This calorie requirement to maintain weight is about 60% of normal.[3] Medications to suppress appetite have met with little success in PWS individuals.[3] Growth hormone therapy helps to increase stature and muscle mass in patients with PWS but is not effective in managing hyperphagia.[3]

The primary endpoint in the placebo-controlled diazoxide choline trials was improvement in the HQ-CT score. The HQ-CT is a care-giver reported questionnaire that focuses on food-seeking behaviors in people with PWS during the previous 2 weeks.[6] It consists of 9 questions with responses ranging from 0-4 units each (possible total score range: 0-36).[1] A score of 0 indicates an absence of behaviors and a score of 4 indicating the most frequent or severe behaviors.[1] Higher scores indicate greater overall severity of hyperphagic and food-related behaviors.[1] There is no established threshold for hyperphagia severity based on the HQ-CT score and a minimal clinically effective difference (MCID) has not been developed for this assessment.

VYKAT XR (diazoxide choline) extended-release tablets are FDA-approved for the treatment of hyperphagia in adults and pediatric patients aged 4 years and older with PWS.[1] The exact mechanism of action of diazoxide in the treatment of hyperphagia is unknown.[1] Diazoxide is a potent activator of the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel that is capable of crossing the blood-brain barrier.[7] Activation of the K_{ATP} channel in neuropeptide Y (NPY)/Agouti related-protein (AgRP) neurons has the potential to reduce secretion of NPY and AgRP, potent endogenous appetite stimulatory neuropeptides, which may contribute to a reduction in hyperphagia.[7] This medication is designated as an orphan drug by FDA.[1] Dosing is weight-based and maintenance dosing ranges from 225 mg once daily (40 to 64 kg) to 525 mg once daily (≥ 135 kg) after the initial titration over 6 weeks.[1] Diazoxide choline is available in 25 mg, 75 mg, and 150 mg tablets.

PROGLYCEM (diazoxide) oral suspension received initial FDA approval in 1976 for treatment of adults with hyperinsulinemia and hypoglycemia associated with inoperable islet cell adenoma or extra pancreatic malignancy.[8] In pediatric patients, diazoxide oral suspension is indicated for management of hypoglycemia due to hyperinsulinism associated with leucine sensitivity, islet cell hyperplasia, nesidioblastosis, extrapancreatic malignancy, islet cell adenoma, or adenomatosis.[8] If other specific medical therapy or surgical management has either been unsuccessful or is not feasible, treatment with diazoxide should be considered.[8]

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

Clinical Efficacy:
The efficacy of diazoxide choline in patients with hyperphagia due to PWS was first evaluated in a 13-week, multicenter, double-blind, phase 3 RCT (DESTINY PWS).[2] The study enrolled males and females with genetically confirmed PWS, aged 4 years and older with moderate to severe hyperphagia (defined by the investigators as an HQ-CT score ≥ 13), weighing between 20 and 135 kg.[2] The enrolled participants who continued to meet the inclusion criteria at the end of a 2-week single-blind, placebo run-in were randomly assigned 2:1 to treatment with diazoxide choline or matching placebo stratified by growth hormone treatment (currently treated, not currently treated) and baseline HQ-CT score (scores from 13-19 and from 20-36).[2] A total of 181 people with PWS were screened for the study, 158 of whom were enrolled; among these, 31 were not eligible for randomization because of failure to continue to meet inclusion criteria after the

placebo run-in, and 127 were randomly assigned.[2] Patients were titrated to target dose of diazoxide choline 3.3 to 5.8 mg/kg within 6 weeks.[2] The daily dose ranged from 100 to 450 mg.[2] The primary endpoint was decreased hyperphagia based upon changes in the HQ-CT score from baseline to week 13.[2] A decrease of 7 points from baseline represented clinical improvement.[2] The mean age of patients in the study was 13.5 years, most of the patients were White (85%) and 56% were female.[2] The median baseline HQ-CT score was 22.6 points and 84% of enrolled patients were being treated with growth hormone.[2] Additional study details that contribute to the efficacy data for this indication are described and evaluated below in **Table 2**.

At 13 weeks there was no statistically significant difference in the LSM HQ-CT score between diazoxide choline and placebo (−5.94 vs −4.27; MD = -1.67; 95% CI -4.24 to 0.89; P=0.198).[2] However, in a prespecified analysis focused on patients with severe hyperphagia with a baseline HQ-CT score 22 points or higher (40 patients received diazoxide and 19 patients received placebo), diazoxide choline-treated patients had a LSM improvement of -9.67 compared to the -4.26 change seen in placebo-treated patients (95% CI not reported [NR]; p=0.012).[2] Secondary endpoints included Clinical Global Impression of Improvement (CGI-I), Caregiver Global Impression of Change (CGI-C) and body fat measured using dual energy x-ray absorptiometry (DEXA).[2] If the primary end point was statistically significant, then each of the secondary end points was tested in order, with each subsequent analysis reported as significant only if the preceding analysis was significant.[2] Two of 3 secondary end points were improved when diazoxide was compared to placebo (CGI-I: 3.7 vs. 4.0; 95% CI NR; p=0.029 and Fat Mass: -0.80 kg vs. 0.25 kg 95% CI NR; p=0.023).[2]

Eligible patients were subsequently enrolled in 52-week open-label study in which all patients received diazoxide choline. After completion of the open-label extension study, 77 patients participated in a 16-week randomized medication withdrawal phase.[1] This group of patients was randomized 1:1 to continue their current weight-based diazoxide choline regimen or switch to placebo.[1] The mean baseline HQ-CT score at the beginning of the withdrawal period was 9.0 points for diazoxide choline-treated patients and 8.1 points for placebo-treated patients. At 16 weeks, the LSM change from baseline in HQ-CT score was less in the placebo-treated patients than those who continued diazoxide choline (7.6 vs. 2.6; LSM difference -5; 95% CI -8.1 to -1.8).[1] The results of this phase of the trial have not been published and are only reported in the manufacturer's prescribing information.

Clinical Safety: Adverse events leading to discontinuation in diazoxide choline-treated patients in clinical trials included aggression, diabetes mellitus, fluid retention, hirsutism, hyperglycemia, lower respiratory tract infection, peripheral edema, pulmonary edema, and papular rash.[1] The most common adverse events were hypertrichosis, edema, hyperglycemia, and rash.[1] **Table 1** presents adverse reactions that occurred in at least 5% of patients in the DESTINY PWS trial who received diazoxide choline compared with placebo.

Table 1. Adverse Reactions Reported with Diazoxide and Placebo[1]

Adverse Reaction	**Diazoxide Choline Extended Release N=84**	**Placebo N=42**
Hypertrichosis	36%	14%
Edema	27%	12%
Hyperglycemia	17%	5%
Rash	12%	2%
Pyrexia	6%	0%
Arthralgia	5%	2%
Influenza	5%	2%

Nasopharyngitis	5%	2%

Warnings and Precautions
Diazoxide choline increases blood glucose, due primarily to an inhibition of insulin release from the pancreas.[1] Hyperglycemia, including severe adverse reactions associated with diabetic ketoacidosis, occurred in diazoxide-treated patients during clinical trials.[1] Before initiating diazoxide choline, the manufacturer recommends obtaining an FPG and HbA1c.[1] After initiating treatment with diazoxide choline, FPG and HbA1c should be routinely monitored.[1] Fasting glucose should be monitored more frequently for the first few weeks of treatment in patients with risk factors for hyperglycemia, such as obesity, elevated FPG, HbA1c at the upper limit of normal or above, concomitant use of growth hormone, or concomitant use of systemic corticosteroids.[1]

Severe adverse reactions associated with fluid overload, including pulmonary edema, were reported in diazoxide choline-treated patients during clinical trials.[1] The antidiuretic property of diazoxide may lead to significant fluid retention, which may precipitate congestive heart failure in patients with compromised cardiac reserve.[1] Diazoxide choline has not been studied in patients with compromised cardiac reserve and should be used with caution in these patients.[1] Patients should be monitored for signs or symptoms of edema or fluid overload and if clinically significant should be managed with either diazoxide choline dosage reduction or treatment interruption.[1]

Drug Interactions
Diazoxide choline is a substrate of CYP3A4 and CYP1A2.[1] Concomitant use of diazoxide choline and CYP1A2 substrates (e.g., fluvoxamine) is not recommended.[1] Concomitant use of diazoxide with strong CYP3A4 inhibitors (e.g., itraconazole) increases exposure of diazoxide, which may increase the frequency and/or severity of adverse reactions from diazoxide choline.[1] Concomitant use of diazoxide choline with strong CYP3A4/moderate 1A2 inducers (e.g., rifampin) may decrease exposure of diazoxide and may decrease the efficacy of diazoxide.[1]

Diazoxide choline is highly bound to serum proteins.[1] Diazoxide choline may displace other drugs which are also highly bound to protein resulting in higher or lower blood levels of the concomitantly used drugs.[1] The impact of protein binding displacement is expected to be clinically important for drugs with narrow therapeutic range such as coumadin or phenytoin.[1] Protein binding displacement may result in an increased risk of adverse reactions due to higher blood levels of coumadin or loss of efficacy due to lower exposures of phenytoin.[1]

Look-alike / Sound-alike Error Risk Potential: Diazepam, Dyazide

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduction in the HQ-CT score
2) Improvements in provider assessments (CGI-I and CGI-C)
3) Reduction in body weight and body fat
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in the HQ-CT score

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1.Miller, et al[2] DESTINY PWS NCT03714373 DB, PC, MC, Phase 3 RCT	1. DCCR 100 to 450 mg (weight-based) po once daily 2. Placebo po once daily	Demographics: -Mean age: 13.4 y -Female: 56% -Hispanic/Latino: 10% White: 85% Black: 5% Asian: 1% Other: 2% -Baseline HQ-CT score: 22.6 -Treated with growth hormone: 84% Key Inclusion Criteria: -Genetically confirmed PWS w/ hyperphagia -Age ≥4 y -Stable care setting for ≥ 6 months -HQ-CT score ≥ 13 -Weight 20-135 kg Key Exclusion Criteria: -Pregnancy	ITT: 1. 82 2. 42 PP: 1. 73 2. 40 Attrition: 1. 9 (11%) 2. 2 (5%)	Primary Endpoint: LSM change in HQ-CT from baseline to Week 13 (ITT) 1. -5.94 2. -4.27 MD = -1.67 95% CI -4.24 to 0.89 P=0.198 Secondary Endpoints: LSM CGI-I change from baseline to Week 13 (ITT) 1. 3.7 2. 4.0 MD = 0.3 95% CI NR P=0.029 LSM CGI-C change from baseline to Week 13 (ITT) 1. 3.7 2. 4.0 MD = 0.3 P=0.41 LSM change in body fat mass change from baseline to Week 13 in ITT analysis 1. -0.80 kg 2. 0.25 kg MD = -1.05 95% CI NR P=0.023 LSM change from baseline in HQ-CT in a prespecified subgroup analysis of patients with severe hyperphagia (HQ-CT ≥22) 1.-9.67 (n=40) 2.-4.26 (n=19) MD = -5.41 95% CI NR	NS NA NS NA NA	Hypertrichosis 1. n=30 (36%) 2. n=6 (14%) Edema 1. n=17 (20%) 2. n=4 (10% Hyperglycemia: 1. n=10 (12%) 2. n=0 (0%) Adverse Events 1. n= 70 (83.3%) 2. n=31 (73.8%) Serious Adverse Events: 1. n=6 (7%) 2. n=0 p-value and 95% CI NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 via a centralized generator, stratified by GH treatment and baseline HQ-CT score. Baseline characteristics balanced between groups. Performance Bias: High. Patients, caregivers, investigators blinded. Placebo tablets were matched to appearance of DCCR tablets. Side effects observed with DCCR may have resulted in unmasking of treatment assignment. Detection Bias: Unclear. Method of blinding not described for outcome assessors. Primary endpoint was a care-giver assessment of changes in hyperphagia. Attrition Bias: High. More discontinuations in treatment arm compared with placebo arm., due to adverse events. Not clear how missing data was handled. Reporting Bias: Unclear. Only p-values were reported for study results. Confidence intervals not reported in the publication – found some results at clinicaltrials.gov Study protocol available on-line. Other Bias: High: Sponsored by manufacturer. Several authors received financial support from the manufacturer. **Applicability**: Patient: Two-week run-in period resulted in exclusion of 17% of potential participants. Reasons for exclusion not clearly explained. Intervention: Dosing determined in Phase 2 RCT. Comparator: Placebo is an appropriate comparator as no other drugs are approved for hyperphagia in PWS. Outcomes: HQ-CT questionnaire may be subject to caregiver bias. Exploratory endpoints included parameters of body composition. Setting: 29 sites in the United States (80%) and United Kingdom (20%)

				P=0.012				

Abbreviations: ARR = absolute risk reduction; CGI-I = Clinical Global Impression of Improvement; CI = confidence interval; double-blind; DCCR = diazoxide choline controlled release; GH =growth hormone; HQ-CT = Hyperphagia Questionnaire; kg = kilogram; ITT = intention-to-treat; LSM = least-square mean; MC = multi-center; MD = mean difference: mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PC = placebo controlled; po = oral route; PP = per protocol; PWS = Prader-Willi Syndrome; RCT = randomized controlled trial; y = years.

References:

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Appendix 1: Prescribing Information Highlights

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

VYKAT™ XR (diazoxide choline) extended-release tablets, for oral use
Initial U.S. Approval: 1973

----------INDICATIONS AND USAGE----------
VYKAT XR is indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS). (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Prior to initiation, test fasting plasma glucose and HbA1c; optimize blood glucose in patients who have hyperglycemia. (2.1)
- Do not substitute with diazoxide oral suspension. (2.1)
- Administer orally once daily. (2.2)
- Recommended starting dosage and titration schedule is based on patient's body weight. (2.2)

Weight	Starting Dosage	Titration Dosage	Titration Dosage	Target Maintenance Dosage
	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	
20 to <30 kg	25 mg	50 mg	75 mg	100 mg
30 to <40 kg	75 mg	150 mg	150 mg	150 mg
40 to <65 kg	75 mg	150 mg	225 mg	225 mg
65 to <100 kg	150 mg	225 mg	300 mg	375 mg
100 to <135 kg	150 mg	300 mg	375 mg	450 mg
≥135 kg	150 mg	300 mg	450 mg	525 mg

- The maximum recommended dosage is 5.8 mg/kg/day or 525 mg per day. (2.2)
- Interrupt VYKAT XR or reduce dosage for clinically significant elevations in fasting glucose or HbA1c; consider dosage reduction or interruption for clinically significant fluid overload. (2.3)
- See full prescribing information for VYKAT XR dosage modifications due to drug interactions (2.4)
- Following dosage interruption or a missed dose of 7 days or more, re-titrate according to Table 1 or Table 2. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------
Extended-release tablets: 25 mg, 75 mg, and 150 mg of diazoxide choline. (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to diazoxide, other components of VYKAT XR, or to thiazides. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *Hyperglycemia*: Hyperglycemia, including diabetic ketoacidosis, has been reported. During treatment, monitor fasting glucose and HbA1c. Monitor fasting glucose more frequently during first few weeks of treatment in patients with risk factors for hyperglycemia. (2.3, 5.1)
- *Risk of Fluid Overload*: Edema, including severe reactions associated with fluid overload, has been reported. Monitor for signs or symptoms of edema or fluid overload. (2.3, 5.2)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥10% and at least 2% greater than in placebo) are hypertrichosis, edema, hyperglycemia, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Soleno Therapeutics, Inc. at 1-833-765-3661 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Strong CYP1A2 Inhibitors*: Reduce VYKAT XR dosage. (2.4, 7)
- *CYP1A2 Substrates*: Concomitant use with VYKAT XR is not recommended. (7)
- See full prescribing information for additional clinically significant drug interactions. (7)

---------- USE IN SPECIFIC POPULATIONS ----------
- *Renal Impairment or Hepatic Impairment*: Use is not recommended. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Table 1. Diazoxide Choline Extended-Release Tablets[1,9]

Parameter	
Mechanism of Action	Exact mechanism in treatment of hyperphagia in PWS in unknown.
Oral Bioavailability	Peak concentrations occurs after 16 hours. Steady state is reached after 7 days.
Distribution and Protein Binding	Volume of distribution = 44.9 L Extensively protein bound: 91% to 93% (primarily albumin)
Elimination	Excreted primarily (85% to 92%) in urine as a free or conjugated compound
Half-Life	Healthy patients: 28.7 to 32.4 hours. Patients with PWS: 106 hours
Metabolism	Metabolized by CYP1A2 (major) and CYP3A4 (minor)

Abbreviations: L = liters; PWS = Prade-Willi Syndrome

Diazoxide Choline Extended-Release Tablets

Goals:

- Ensure appropriate utilization in people with hyperphagia due to Prader-Willi syndrome.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 months

Requires PA:

- Vykat XR (diazoxide choline extended-release tablets)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to Renewal Criteria	**No:** Go to #3
3. Is this an FDA-approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP. If eligible for EPSDT review: Go to #5.

Approval Criteria		
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity.
6. Is the medication prescribed by an endocrinologist or in consultation with a provider that specializes in caring for patients with Prader-Willi syndrome?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has extent of baseline hyperphagia behavior been documented using the caregiver Hyperphagia Questionnaire for Clinical Trials (HQ-CT) assessment or a comparable assessment tool?	**Yes:** Approve for 6 months Document baseline HQ-CT score: _____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has hyperphagia behavior decreased since beginning therapy as assessed by improvement in the HQ-CT score or a comparable assessment tool?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

P&T/DUR Review: 8/25; (DM)
Implementation: TBD