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, October 5, 2023 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)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)

A. CMS Annual Report
B. P&T Annual Report
C. Colony Stimulating Factor Class Update and New Drug Evaluation
D. Opioid Reversal Agents Class Update
E. Substance Use Disorder Literature Scan
F. Antipsychotics, Parenteral Literature Scan
G. Oncology Prior Authorization Updates
H. Orphan Drug Policy Updates
   1. Public Comment

III. PREFERRED DRUG LIST NEW BUSINESS

1:25 PM	A. RSV Prior Authorization Update	K. Sentena (OSU)
	1. Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
1:35 PM	B. Gene Therapies for Hemophilia A, Hemophilia B, & Beta-thalassemia DERP Summary & New Drug Evaluation	S. Fletcher (OSU)
	1. Hemophilia B and Beta-thalassemia DERP Summary	
	2. Roctavian™ (valoctocogene roxaparvovec-rvox) New Drug Evaluation	
	3. Prior Authorization Criteria	
	4. Public Comment	
	5. Discussion and Clinical Recommendations to OHA	

2:10 PM	C. SGLT-2 Inhibitors Class Update 1. Class Update/Prior Authorization Criteria 2. Brenzavvy™ (bexagliflozin) New Drug Evaluation 3. Inpefa™ (sotaglifozin) New Drug Evaluation 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:40 PM	D. Alzheimer's Drugs Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Leqembi® (lecanemab-irmb) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
3:00 PM	BREAK	
3:15 PM	E. VMAT-2 Inhibitors Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
	IV. DUR NEW BUSINESS	
3:25 PM	A. Asthma Rescue Inhalers Drug Use Evaluation 1. Drug Use Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
3:50 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribal Health	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, All Smiles Community Oral Health	Portland	December 2023
William Origer, MD, FAAFP	Physician	Physician Advisor, Hospital Utilization Review, Good Samaritan Hospital	Corvallis	December 2023
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2024
Russell Huffman, DNP, PMHNP	Public	Psychiatric Nurse Practitioner	Salem	December 2024
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia	Cornelius	December 2024
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	Pharmacy Director, Community Health Centers of Benton & Linn Counties	Corvallis	December 2025

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, August 3rd, 2023
1:05 PM - 4:45 PM
Via Zoom webinar

MEETING MINUTES

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

Members Present: Stacy Ramirez, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Tim Langford, PharmD; Cat Livingston, MD; Caryn Mickelson, PharmD; Eriko Onishi, MD; Bill Origer, MD; Eddie Saito, PharmD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Kathy Sentena, PharmD; Lan Starkweather, PharmD; Kendal Pucik, OSU COP P4; Brandon Wells; Trevor Douglass, DC, MPH; Amanda Parish, LCSW; Jennifer Bowen; Dee Weston, JD; John McIlveen, PhD, LMHC

Audience: Eleasa Sokolski, MD OHSU*; Eowyn Rieke, MD Fora Health*; Joey Razzano, NW Rett Syndrome Association; Benjamin Skoog, Acadia Pharm; Tiffany Dickey, Aimmune; Rochelle Yang, Teva*; Erin Nowak, AbbVie; Jennifer Davis, Gilead; Melissa Abbott, Eisai; Gary Parenteau, Dexcom; Matt Worthy, OHSU; Tiina Andrews, UHA; Brandie Feger, Advanced Health CCO; Mark Kantor, AllCare CCO; Saghi Maleki; Takeda Pharm; Lori McDermott, Viking HCS; Deron Grothe, Braeburn; Michael Foster, BMS; Rob Booth, AbbVie; Chris Johnson, Biomarin; Sean Staff, Acadia; Melissa Bailey, Hall; Georgette Dzwilewski, Indivior; Nirmal Ghuman, Janssen; Mike Donabedian, Sarepta; Michele Sabados, Alkermes; Jim Slater, CareOregon; Ann Nelson, Vertex; Manheet Malhi, UHA Student; Christine Donahue, CSL Behring; Renetta Mosley, Acadia; Mark Borkovec, ALK-Abello; Alison Bass, CSL Behring; Shauna Wick, Trillium; David Shirkey, ALK-Abello; Shannon Lee, Trillium; Pam Storey; Matt Metcalf, CSL Vifor; Norm Navarro, Providence; Jeff White, Sumitomo; Jennifer Davis, Gilead; Rick Kegler; Bryan Mauk, Vertex; Charlie Flynn; Seth Fritts; Lisa Pulver; Scott Brown; Mike Matoon , Acadia; Neil Bair, Acadia; June Sanson; Bill Robie, NHF; Jason Kniffin

(*) Provided verbal testimony

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I. CALL TO ORDER

A. Roll Call & Introductions
- 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 June 2023 Minutes presented by Roger Citron, RPh
ACTION: Motion to approve, 2nd, all in favor

D. Department Update provided by Andrew Gibler, PharmD

E. Legislative Update provided by Dee Weston, JD

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Report

B. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Epkinly™ (epcoritamab-bysp); and Columvi™ (glofitamab-gxbm) to Table 1 in the Oncology Agents prior authorization (PA) criteria

C. Calcitonin Gene-Related Peptide (CGRP) Inhibitors
Recommendation:
- Evaluate costs in executive session

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. **Psychotropic Use in Youth Enrolled in the Oregon Health Plan and Youth in Foster Care with an Emphasis on Antipsychotic Prescriptions**
2. **COVID-19 Therapeutics Update: Where Are We Now?**

IV. DUR NEW BUSINESS

A. Sublingual Buprenorphine Quantity Limit Policy Evaluation: Sarah Servid, PharmD
Recommendations:
- Increase dose limit to 32 mg daily for sublingual buprenorphine formulations
- Update current PA criteria to permit use of higher doses for OUD with medical justification

- Implement a days' supply limit for all sublingual buprenorphine formulations to support quantity limits

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

V. PREFERRED DRUG LIST (PDL) NEW BUSINESS

A. Daybue™ (trofinetide) New Drug Evaluation: Deanna Moretz, PharmD

Recommendations:

- Maintain trofinetide as non-preferred on the PDL
- Implement proposed PA criteria for trofinetide to ensure medically appropriate use

ACTION: The Committee amended the proposed PA criteria to remove assessment for type of Rett syndrome and to refer requests to the medical director when Rett syndrome has not been genetically confirmed

Motion to approve, 2nd, all in favor

B. Benign Prostatic Hyperplasia (BPH) Class Update: Kathy Sentena, PharmD

Recommendations:

- No PDL changes recommended based on review of recently published evidence
- Update PA criteria as proposed and remove the renewal criteria
- Evaluate costs in executive session

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

C. Vowst™ (oral fecal microbiota spores, live-brpk) NDE: Deanna Moretz, PharmD

Recommendations:

- Maintain oral fecal microbiota capsules as non-preferred on the PDL subject to PA
- Add oral fecal microbiota capsules to the "Prevention of C. difficile Recurrence" clinical PA criteria

ACTION: The Committee amended the proposed PA criteria to add step therapy that requires fecal microbiota transplant before use of bezlotoxumab

Motion to approve, 2nd, all in favor

D. Non-injectable Allergen Immunotherapy Class Review: Deanna Moretz, PharmD

Recommendations:

- Add Grastek®, Oralair ®, Ragwitek®, and Odactra® sublingual tablets to the "Immunotherapy Desensitization, Non-Injectable" PDL class as non-preferred
- Implement the proposed "Sublingual Immunotherapy Tablets" PA criteria to allow for coverage under the EPSDT program and for allergic rhinitis complicated by a comorbidity such as asthma
- Evaluate costs in executive session

ACTION: The Committee amended the proposed PA criteria to only permit the use of Odactra® (dust mite sublingual immunotherapy) in people with allergic rhinitis complicated by comorbid asthma
Motion to approve, 2nd, all in favor

E. Gene Therapies for Beta-thalassemia and Hemophilia B DERP Summary
Topic Deferred

F. Endocrine Therapies Class & Prior Authorization Updates
GnRH Agonists Class Update/PA Criteria: Deanna Moretz, PharmD
Estrogens & Testosterone PA Criteria: Sarah Servid, PharmD
Recommendations:
- No PDL changes recommended based on review of recently published evidence
- The Committee supported revising the GnRH agonists, estrogen, and testosterone PA criteria to comport with recently enacted state legislation, HB 2002, as well as to include an EPSDT assessment.
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Tim Langford, PharmD; Cat Livingston, MD; Caryn Mickelson, PharmD; Eriko Onishi, MD; Bill Origer, MD

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

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. CGRP Inhibitors
Make Ubrelvy™ (ubrogepant) preferred on the PDL contingent on acceptance of a supplemental rebate offer that is similar in population scope to current contract
ACTION: Motion to approve, 2nd, all in favor

B. Benign Prostatic Hyperplasia (BPH) Class
Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

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C. Clostridioides difficile Drug Class

Make no changes to the PDL

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

D. Allergen Immunotherapy

Make all sublingual tablets non-preferred

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

E. Endocrine Therapies Class

Make Lupron Depot-Ped kit formulations (1 month, 3 month, and 6 month) preferred

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

VII. ADJOURN

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Drug Class Update with New Drug Evaluation: Colony Stimulating Factors

Date of Review: October 2023

Date of Last Review: October 2022
Dates of Literature Search: 06/09/2022 – 07/11/2023
Brand Name (Manufacturer): Rolvedon™
Dossier Received: no

Generic Name: eflapegrastim

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

Purpose for Class Update:
Evaluate any new comparative evidence for the granulocyte colony stimulating factors (G-CSFs) and granulocyte-macrophage colony stimulating factors (GM-CSFs) since the last Pharmacy and Therapeutics (P & T) Committee review in 2022. Review safety and efficacy data for eflapegrastim, a new long-acting G-CSF.

Plain Language Summary:
- This review evaluates a new medicine, eflapegrastim, used to prevent neutropenia (a low white blood cell count), which can happen after receiving treatment for cancer with chemotherapy. Chemotherapy kills cancer cells as well as healthy white blood cells. A low number of white blood cells decreases the body's ability to fight infections. If someone with neutropenia also develops a fever, it is called febrile neutropenia, and it is life-threatening.
- Medicines known as granulocyte colony-stimulating factors help the body make white blood cells. These medicines are used to prevent complications from low white blood cell counts, such as infection or fever, when people receive some types of chemotherapy.
- The United States Food and Drug Administration has approved 3 granulocyte colony-stimulating factors: filgrastim, pegfilgrastim, and eflapegrastim. All 3 of these medicines are given by an injection that is administered by a doctor or nurse. Some people can be taught how to give these medicines to themselves at home.
- Eflapegrastim was approved in September 2022. In 2 clinical trials, eflapegrastim was compared to pegfilgrastim, a commonly used granulocyte colony-stimulating factor, in adults with early-stage breast cancer who received chemotherapy. There were no differences between eflapegrastim and pegfilgrastim in the number of days these patients had low white blood cell counts.
- Eflapegrastim can cause low blood platelet counts, which can lead to an increased chance of bleeding. If people who receive eflapegrastim notice unusual bruising or bleeding, they should contact their doctor right away. Eflapegrastim can also make people feel tired, have diarrhea, nausea, headache, bone pain, back pain or rash.
- Providers must explain to the Oregon Health Authority why someone needs eflapegrastim before Medicaid will pay for it. This process is called prior authorization.

Author: Deanna Moretz, PharmD, BCPS

Research Questions:

1. Is there any new comparative evidence for G-CSF treatments for important outcomes such as mortality, infection or hospitalizations?
2. Is there any new comparative evidence based on the harm outcomes (i.e., bone pain, nausea, therapy-related myeloid neoplasms) for G-CSF treatments?
3. Are there subpopulations based on race, ethnicity, age, gender, or socioeconomic status for which specific G-CSF therapies may be more effective or associated with less harm?
4. What is the evidence of efficacy and harms for the new G-CSF treatment, eflapegrastim, in preventing febrile neutropenia?

Conclusions:

- No new high-quality comparative evidence for the safety and efficacy of G-CSF treatments has been published since the last class review in October 2022.
- In September 2022, the FDA approved pegfilgrastim-fpgk (STIMUFEND®), a new biosimilar formulation of pegfilgrastim. This medication is indicated to reduce the incidence of febrile neutropenia in patients with cancer receiving myelosuppressive chemotherapy.[1]
- The pegfilgrastim biosimilar, pegfilgrastim-cbqv (UDENYCA®), received an expanded indication to increase survival in patients exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) in November 2022.[2]
- Pegfilgrastim-fpgk injection and pegfilgrastim-cbqv are not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantion.[1,2]
- No subpopulations based on race, ethnicity, age, gender, or socioeconomic status were identified for which specific G-CSF therapies may be more effective or associated with less harm.
- The FDA approved the long-acting G-CSF eflapegrastim-xnst (ROVLEDON™) for subcutaneous injection in September 2022.[3] Eflapegrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adults patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with clinically significant incidence of febrile neutropenia.[3]
- Efficacy of eflapegrastim was evaluated in 2 randomized, open-label, active-controlled, non-inferiority clinical trials ADVANCE[4] and RECOVER.[5] In each study, a fixed dose of eflapegrastim 13.2 mg or pegfilgrastim 6 mg was administered subcutaneously on day 2 of each chemotherapy cycle, 24 hours after the last dose of chemotherapy.[4,5] The primary non-inferiority efficacy endpoint was the duration of severe neutropenia in cycle 1, defined as the number of days of severe neutropenia (absolute neutrophil count [ANC] < 0.5×10^9 per L) from the day of first occurrence of an ANC below that threshold.[4,5]
- In the ADVANCE trial, the mean Cycle 1 duration of severe neutropenia was 0.20 ± 0.503 days for the eflapegrastim arm versus 0.35 ± 0.683 days for the pegfilgrastim arm.[4] The difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.148 days (95% CI -0.265 to -0.033 days; p<0.0001; low-quality evidence).[4] In the RECOVER trial, the difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.074 days (95% CI, -0.292 to 0.129; p<0.0001; low-quality evidence).[5] Non-inferiority to pegfilgrastim was demonstrated for eflapegrastim (upper bound of 95% CI <0.62 days) in both trials.[6]
- The most common adverse reactions (≥ 20%) for eflapegrastim treatment arms were fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia and back pain.[3]

Recommendations:

- No PDL recommendations based on clinical evidence.
- Review medication costs in the executive session.

Summary of Prior Reviews and Current Policy

- Evidence for the colony stimulating factors was last evaluated in October 2022. There are no class specific prior authorization criteria beyond preferred and non-preferred status. Preferred products include the G-CSFs; filgrastim and pegfilgrastim, and the GM-CSF, sargramostim. Non-preferred products billed through the pharmacy are required to meet nonspecific prior authorization criteria which requires validation of an FDA approved indication and funding level. The preferred drug list status for each colony stimulating factor is presented in **Appendix 1**.
- Previous evidence summaries concluded there were no compelling differences in efficacy or harms between G-CSF products.[7] G-CSF products are recommended for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[7] Evidence is generally of moderate quality for these indications.
- Guidelines from the National Comprehensive Cancer Network (NCCN) continue to recommend G-CSFs for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[8] The United States (U.S.) Food and Drug Administration (FDA) labeled indications vary by product and are summarized in **Appendix 5**.
- The number of patients with claims (pharmacy or medical) for G-CSF products is relatively small in the fee-for-service (FFS) population and most products are billed through medical claims where the preferred drug list (PDL) does not apply. Since 2021, utilization has shifted from use of originator products to almost exclusively biosimilar products.

Background:

Treatment with myelosuppressive chemotherapy puts patients at risk of developing neutropenia.[9] The risk of febrile neutropenia and life-threatening infections increases in patients with a low ANC. Neutropenia is usually defined as an ANC less than 1500 or 1000 cells/microL; severe neutropenia as an ANC less than 500 cells/microL or an ANC that is expected to decrease to less than 500 cells/microL over the next 48 hours; and profound neutropenia as an ANC less than 100 cells/microL.[10] Mortality rates in patients who are hospitalized for febrile neutropenia are around 10%, and increase to above 20% for patients with multiple and/or severe co-morbidities.[11] The duration and severity of neutropenia are major risk factors for the development of febrile neutropenia and for life-threatening infection in patients receiving chemotherapy.[9] In patients with febrile neutropenia, dose reductions or treatment delays can occur, which may compromise treatment outcomes.[9] Granulocyte colony-stimulating factors, which were first introduced for clinical use in the 1990s, reduce the incidence of neutropenia and improve patient outcomes.[9] The need for daily injections was reduced by development of the long-acting G-CSF pegfilgrastim.[9] However, G-CSF–induced bone pain, and continued vulnerability to infection in the first week after chemotherapy remain unmet medical needs.[9]

The 2023 NCCN clinical guidelines for prevention and management of chemotherapy-induced neutropenia recommend the use of supportive care with G-CSFs (i.e., filgrastim, Tbo-filgrastim, pegfilgrastim) in patients with solid tumors and non-myeloid malignancies with intermediate (10% to 20%) and high (>20%) risk factors which are based on the disease, chemotherapy regimen, patient risk factors, and treatment intent (curative versus palliative).[8] The role for G-CSF in myeloid malignancies is more limited due to concern for stimulation of the myeloid compartment by the G-CSF.[9] For this reason, G-CSF administration is not recommended during induction treatment for patients with acute myeloid leukemia but can be considered during consolidation therapy.[8] However, there are limited long-term outcomes data in these cases.[9]

Inclusion criteria for the phase 3 randomized controlled trials (RCTs) for eflapegrastim utilized the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale. This scale is used by researchers when planning cancer clinical trials to study new treatments.[12] This scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.).[12] It is also a way for physicians to track changes in a patient's level of functioning as a result of treatment during the trial.[12] A description of each ECOG grade is presented in **Table 1.**

Table 1. ECOG Performance Status Scale[13]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:
After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[14-16]

New Guidelines: No new guidelines were identified for this review.

New Formulations and Indications:
New Formulation
In September 2022, the FDA approved pegfilgrastim-fpgk (STIMUFEND®), a new biosimilar formulation of pegfilgrastim.[1] Pegfilgrastim-fpgk is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1] The approved dose is 6 mg administered subcutaneously once per chemotherapy cycle.[1] Pegfilgrastim-fpgk injection is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantion.[1]

New Indication

In November 2022, the FDA approved an expanded indication for pegfilgrastim-cbqv (UDENYCA®) to increase survival in patient exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).[2] Efficacy studies of pegfilgrastim-cbqv could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons.[2] Approval of this indication was based on efficacy studies conducted in animals and data supporting pegfilgrastim's effect on severe neutropenia in cancer patients receiving myelosuppressive chemotherapy.[2] The dosing for this indication is 6 mg administered subcutaneously one week apart for 2 doses.[2] The first dose should be administered as soon as possible after a suspected or confirmed exposure to myelosuppressive doses of radiation.[2] For pediatric patients weighing less than 45 kg, the manufacturer recommends weight based dosing according to a protocol provided in the prescribing information.[2] Prior to this approval, pegfilgrastim-cbqv was indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignances receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[2] Pegfilgrastim-cbqv is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantion.[2]

New Safety Alerts:

Table 1. Description of New FDA Safety Alerts[17]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Pegfilgrastim-jmdb and Pegfilgrastim-bmez	FULPHIA and ZIEXTENZO	3/2021	Warnings and Precautions	**Thrombocytopenia** Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts. **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer** MDS and AML have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.
Pegfilgrastim-apgf	NYVEPRIA	4/2021	Warnings and Precautions	**Thrombocytopenia** Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts. **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer** MDS and AML have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer.

				Monitor patients for signs and symptoms of MDS/AML in these settings.
Pegfilgrastim-cbqv	UDENYCA	6/2021	Warnings and Precautions	**Thrombocytopenia** Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts. **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer** MDS and AML have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.
Filgrastim-sndz	ZARXIO	7/2021	Warnings and Precautions	**Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)** Patients with Breast and Lung Cancer: MDS and AML have been associated with the use of filgrastim products in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.

Randomized Controlled Trials:
A total of 77 citations were manually reviewed from the initial literature search. After further review, 77 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Eflapegrastim-xnst (ROVLEDON™)
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

The FDA approved the long-acting G-CSF eflapegrastim-xnst (ROVLEDON™) for subcutaneous injection in September 2022.[3] Eflapegrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adults patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with clinically significant incidence of febrile neutropenia.[3] This medication consists of a recombinant human G-CSF analog conjugated to a human aglycosylated immunoglobulin (Ig) G4 Fc fragment with a short polyethylene glycol linker.[4] The addition of an Fc fragment and the large size of the molecule extends the drug half-life by decreasing clearance, and there is increased uptake in the bone marrow, possibly due to the interaction of the Fc fragment with receptors on surface of endothelial cells.[4] Similar to pegfilgrastim, eflapegrastim has not been evaluated in patients undergoing stem cell

mobilization.[6] Therefore, eflapegrastim is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[3] The recommended eflapegrastim dose is 13.2 mg administered subcutaneously by a healthcare professional once per chemotherapy cycle, 24 hours after completion of cytotoxic chemotherapy.[3]

Clinical Efficacy:
Efficacy of eflapegrastim was evaluated in 2 randomized, open-label, active-controlled, non-inferiority clinical trials of similar design called ADVANCE[4] and RECOVER.[5] The trials enrolled a total of 643 patients with early-stage breast cancer who received 4 cycles of docetaxel (**T**AXOTERE) with **c**yclophosphamide (TC) as the chemotherapy regimen.[4,5] Docetaxel and cyclophosphamide (TC) chemotherapy is considered a standard regimen for adjuvant therapy for node-negative or low-risk node-positive breast cancer.[6] However, according to the NCCN guidelines, the TC regimen is associated with high risk for febrile neutropenia (>20%) which necessitates the use of a G-CSF.[6] In each study, a fixed dose of eflapegrastim 13.2 mg or pegfilgrastim 6 mg was administered subcutaneously on day 2 of each chemotherapy cycle, 24 hours after the last dose of chemotherapy.[4,5] Dose modifications for eflapegrastim or pegfilgrastim were not permitted. The FDA approval of pegfilgrastim was based on 3 double-blind studies in patients with breast cancer, so it was an appropriate comparator for eflapegrastim in these 2 RCTs.[6] Both ADVANCE and RECOVER had identical endpoints, statistical hypotheses and methods.[6] The differences were the planned numbers of patient enrollment (ADVANCE: 400 patients, RECOVER: 218 patients) and statistical power.[6] The median age of patients enrolled in the 2 trials was 60 years (range 24 to 88 years), the majority of patients were female (> 99%), 77% were White and 12% were Black. Most of the patients (81%) were enrolled in clinical sites based in the United States.[6]

The Intent-to-Treat (ITT) Population included all patients who were randomized in each RCT.[6] Patients were analyzed in the treatment arm as randomized if the actual treatment assignments deviated from the randomization scheme.[6] The Per-Protocol (PP) Population included all patients in the ITT Population with no important protocol deviations that affected the analysis of the primary efficacy endpoint.[6] Patients were analyzed as treated if the actual treatment assignments deviated from the randomization scheme.[6] Primary efficacy analysis was based on the ITT Population.[6] Analysis based on the PP Population was performed as a sensitivity analysis.[6]

The primary non-inferiority efficacy endpoint was the duration of severe neutropenia in cycle 1, defined as the number of days of severe neutropenia (ANC < 0.5×10^9 per L) from the day of first occurrence of an ANC below that threshold.[6] The non-inferiority of eflapegrastim to pegfilgrastim would be declared if the upper bound of 95% CI of the difference in mean days of severe neutropenia between the treatment arms was less than 0.62 days.[6] The FDA recommended that a 0.62 day non-inferiority margin should be used in order to maintain the results of the randomized trials comparing the duration of neutropenia of pegfilgrastim to filgrastim which led to the approval of pegfilgrastim.[6] Blood samples for complete blood counts (CBCs) with differential were collected pretreatment and on day 1 and daily on days 4–15 of cycle 1 and on days 1, 4, 7, and 15 in subsequent cycles.[4] However, if an ANC equal to or less than 1.0×10^9/L was reported at any time in cycles 2 through 4, daily CBCs were performed until the ANC recovered to 1.5×10^9 per Liter or greater.[4] All blood analyses were performed by an independent central laboratory.[4]

In addition to duration of severe neutropenia in cycles 2 through 4, other secondary endpoints assessed in each cycle included time-to-ANC recovery (time-from-chemotherapy administration to ANC ≥1.5×10^9 per Liter after the expected nadir), depth of ANC nadir (lowest ANC value), incidence of febrile neutropenia (ANC <1.0×10^9 per L and either temperature >38.3°C or two consecutive readings ≥38.0°C over 2 hours); incidence of neutropenic complications (anti-infective use and/or hospitalizations); and safety (overall adverse event [AE] rates; AEs of special interest: musculoskeletal-related, splenic rupture, leukocytosis, and anaphylaxis).[4] Although a hierarchical closed testing procedure was planned for the key secondary efficacy endpoints, no clear statistical hypotheses were pre-

specified and stated in the statistical analysis plan.[6] According to the FDA reviewers, because the studies were not powered to test non-inferiority for any of the key secondary endpoints, failing on the superiority tests would not lead to any labeling claim.[6]

In the ADVANCE trial, the mean Cycle 1 duration of severe neutropenia was 0.20 ± 0.503 days for the eflapegrastim arm versus 0.35 ± 0.683 days for the pegfilgrastim arm.[4] The difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.148 days (95% CI -0.265 to -0.033 days; p<0.0001).[6] This met the study's primary endpoint of eflapegrastim non-inferiority to pegfilgrastim (upper bound of 95% CI < 0.62 days).[4] The incidence of severe neutropenia (Grade 4, $<0.5 \times 10^9$/L) in cycle 1 was 15.8% (n=31) for the eflapegrastim arm compared with 24.3% (n= 51) for the pegfilgrastim arm, resulting in an 8.5% absolute risk reduction (95% CI -16.1 to -0.2; p=0.034) for eflapegrastim versus pegfilgrastim.[4] In the RECOVER trial, the mean Cycle 1 duration of severe neutropenia was 0.31 ±0.69 days for the eflapegrastim arm versus 0.39 ±0.95 days for the pegfilgrastim arm.[5] The difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.074 days (95% CI, -0.292 to 0.129; p<0.0001).[5] Non-inferiority to pegfilgrastim was demonstrated for the eflapegrastim treatment arm (upper bound of 95% CI <0.62 days).[6]

Both studies individually met the non-inferiority criteria for the primary endpoint of duration of severe neutropenia in Cycle 1 in the ITT population.[6] The results in the Per Protocol population and additional sensitivity analyses were consistent with the results in the ITT population.[6] There were no outliers in the subgroup analyses of duration of severe neutropenia in Cycle 1 by age, gender, race, disease status, region, and body weight in both studies.[6] The analyses of all secondary efficacy endpoints including time to ANC recovery, depth of ANC nadir, and incidence of febrile neutropenia also showed that there were no significant differences between eflapegrastim and pegfilgrastim.[6] Additional study details are presented in the comparative evidence table (**Table 4**).

Study Limitations:
Both trials were open-label, non-inferiority assessments, which is lower quality evidence compared with blinded RCTs designed to demonstrate superiority of one agent over another. The enrollment in both trials lacked diversity, as the majority of enrolled patients were White. Safety and efficacy of eflapegrastim are not established in pediatric patients, although a trial is currently being conducted in this population.[6] In contrast, both pegfilgrastim and filgrastim are FDA-approved for use in pediatrics.[18] Given the marginal benefits of eflapegrastim compared with pegfilgrastim, selection of a preferred agent may be based on a cost comparison of both agents.

Clinical Safety:
The safety review of eflapegrastim was primarily based on a total of 640 patients (eflapegrastim: 314 patients, pegfilgrastim: 326 patients) who participated in the two phase 3 trials.[3] The most common adverse reactions (≥ 20%) for eflapegrastim treatment arms were fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia and back pain.[6] The overall incidence of serious adverse reactions (SAEs) was similar in the two arms (eflapegrastim: 2%, pegfilgrastim: 3%). The most frequently reported SAEs observed in more than 2 patients in the eflapegrastim arm were pyrexia, sepsis, febrile neutropenia, diarrhea and chest pain; and the incidences of these SAEs were similar to those observed in the pegfilgrastim arm.[6] Permanent discontinuation due to an AE occurred in 4% of patients who received eflapegrastim.[3] Rash was the adverse reaction requiring permanent discontinuation in 3 patients who received eflapegrastim.[3] A complete summary of common AEs occurring in more than 10% of study participants in the 2 RCTs is presented in **Table 2**.

Table 2. Common Adverse Reactions Observed In Clinical Trials With Eflapegrastim Compared To Pegfilgrastim.[3]

Adverse Effect	Eflapegrastim (n=314) N (%)	Pegfilgrastim (n=326) N (%)
Fatigue	181 (58%)	192 (59%)
Nausea	162 (52%)	166 (51%)
Diarrhea	125 (40%)	126 (39%)
Bone Pain	119 (38%)	121 (37%)
Headache	92 (29%)	90 (28%)
Pyrexia	87 (28%)	84(26%)
Anemia	77 (25%)	52 (16%)
Rash	77 (25%)	99 (30%)
Myalgia	69 (22%)	49 (15%)
Arthralgia	66 (21%)	48 (15%)
Back Pain	63 (20%)	55 (17%)
Decreased Appetite	61 (19%)	50 (15%)
Peripheral Edema	57 (18%)	53 (16%)
Abdominal Pain	53 (17%)	67 (21%)
Dizziness	50 (16%)	38 (12%)
Dyspnea	49 (16%)	44 (13%)
Cough	48 (15%)	51 (16%)
Thrombocytopenia	44 (14%)	17 (5%)
Pain	37 (12%)	42 (13%)
Pain in Extremity	36 (11%)	42 (13%)
Local Administration Reactions	34 (11%)	27 (8%)
Flushing	32 (10%)	27 (8%)

Look-alike / Sound-alike Error Risk Potential: No medications have been identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Incidence of infection
2) Incidence of febrile neutropenia
3) Duration of febrile neutropenia
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Duration of severe neutropenia (ANC < 0.5 x 10^9/L) in Cycle 1 of chemotherapy

Table 3. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Eflapegrastim-xnst is a recombinant human granulocyte growth factor that binds to G-CSF receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation, proliferation, migration and survival.
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd = 1.44 L; protein binding not reported.
Elimination	Not detected in urine.
Half-Life	36.4 hours
Metabolism	Eflapegrastim-xnst is expected to be metabolized by endogenous degradation following receptor-mediated internalization by cells bearing the G-CSF receptor.

Abbreviations: G-CSF = granulocyte colony-stimulating factor; L = Liters; N/A = not applicable; Vd = Volume of distribution

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Schwartzberg, L. et al.[4] ADVANCE OL, AC, MC, NI, Phase 3 RCT	1. Eflapegrastim 13.2 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy 2. Pegfilgrastim 6 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy	Demographics: 1.Female: >99% 2.Median Age: 61 yo 3. Age ≥ 65 yo: 40% 4.Race -White: 78% -Black: 14% -Asian: 4% -Other 4% 5. Ethnicity Hispanic/Latino: 18% 6. ECOG performance status of 0: 71% Key Inclusion Criteria: -Age ≥ 18 y -New diagnosis of histologically confirmed early-stage breast cancer (Stage I to Stage 3A). -Candidate for chemotherapy -Adequate hematological, renal and hepatic function -ECOG performance status ≤2 Key Exclusion Criteria: -Active concurrent malignancy	ITT: 1. 196 2 .210 PP: 1. 187 2. 196 Attrition: 1.28 (14%) 2.30 (14%)	Primary Endpoint: Mean number of days of severe neutropenia (ANC < 0.5 x 10^9/L in Cycle 1 of chemotherapy in ITT population 1 .0.20 ± 0.503 days 2. 0.35 ± 0.683 days Difference: -0.148 days 95% CI -0.265 to -0.033 P<0.0001 Secondary Endpoints: Time to ANC recovery in Cycle 1 1. 3.24 days 2. 3.49 days Difference: 0.25 days; P=0.685 Median depth of ANC nadir in Cycle 1 1. 1.6 x 10^9/L 2. 1.3 x 10^9/L Difference: 0.16; P=0.16	NA NS NS	Drug-Related AEs 1. 164 (83%) 2. 146 (70%) SAEs 1. 36 (18%) 2. 29 (14%) Discontinuation due to AEs 1. 3 (5%) 2. 2 (5%) Bone Pain 1. 63 (32%) 2. 67 (32%) Arthralgia 1. 38 (19%) 2. 26 (13%) 95% CI and p-values NR	NA for all	**Risk of Bias (Low/High/Unclear)**: Selection Bias: Low. Randomized 1:1 via IWRS. Baseline characteristics balanced between groups. Open-label study design permitted patients and investigators to be aware of treatment assignment. Performance Bias: High. No blinding due to open-label study design. Detection Bias: Unclear. All blood analyses were performed by an independent central laboratory. However, investigators were aware of treatment assignment. Attrition Bias: Low. Similar attrition rates in both arms. Attrition due to AEs and patient withdrawal of consent. Reporting Bias: Low. Study protocol available at clinicaltrials.gov website. All prespecified outcomes were reported. Other Bias: Unclear. Study funded by manufacturer. None of the clinical investigators were full or part-time employees of the Sponsor for the RCT. **Applicability**: Patient: Primarily white female population with limited diversity (78% of subjects were White). Intervention: Eflapegrastim dosing determined in Phase 2 weight-based, dose-ranging study in

		- Known sensitivity to *E.Coli* derived products -Concurrent adjuvant cancer therapy -Locally recurrent/ metastatic breast cancer -Active infection -Prior bone marrow or stem cell transplant		Incidence of febrile neutropenia in Cycle 1 1. 4 (2%) 2. 2 (1%) Difference: 1%; P=0.44 -Incidence of neutropenic complications 1. 8(4.1%) 2. 8 (3.8%) Difference: 0.3% P value NR: NS	NS NS			patients (n=148) with early breast cancer and candidates for chemotherapy. Comparator: Pegfilgrastim has demonstrated efficacy in reducing duration of neutropenia in early breast cancer patients and is an appropriate active comparator for this RCT. Outcomes: Duration of severe neutropenia in first cycle of chemotherapy was the primary efficacy outcome in pegfilgrastim RCTs. Appropriate to use a similar outcome in eflapegrastim trial. Setting: 82 sites in 3 countries. Percent of enrolled patients by country: United States (97%); Canada (2%); Korea (1%)
2. Cobb WC, et al.[5] RECOVER OL, AC, MC, NI, Phase 3 RCT	1. Eflapegrastim 13.2 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy 2. Pegfilgrastim 6 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy	Demographics: 1.Female: 100% 2.Median Age: 59 yo 3. Age ≥ 65 y: 35% 4. Race -White: 76% -Black: 5% -Asian: 15% -Other <1% 5. Ethnicity Hispanic/Latino: 14% 6. ECOG performance status of 0: 80% Key Inclusion Criteria: see above Key Exclusion Criteria: see above	ITT: 1. 118 2. 119 PP: 1. 100 2. 111 Attrition: 1. 14 (12%) 2. 16 (13%)	Primary Endpoint: Mean number of days of severe neutropenia (ANC < 0.5 x 10^9/L in Cycle 1 of chemotherapy 1 .0.31 ± 0.688 days 2. 0.39 ± 0.949days Difference: -0.073 days 95% CI -0.292 to 0.129 P<0.0001 Secondary Endpoints: Time to ANC recovery in Cycle 1 1. 3.49 days 2. 3.35 days Difference: 0.14 days; P=0.866 Median depth of ANC nadir in Cycle 1 1. 1.60 x 10^9/L 2. 1.57x 10^9/L Difference: 0.03 x 10^9/L P=0.36 Incidence of febrile neutropenia in Cycle 1 1. 1 (0.8%) 2. 4 (3.4%) Difference: 2.6%; P=0.37	NA NS NS NS	Drug-Related AEs 1. 74 (63%) 2. 72 (61%) SAEs 1. 12 (10%) 2. 15 (16%) Discontinuation due to AEs 1. 3 (3%) 2. 3 (3%) Bone Pain 1. 40 (34%) 2. 45 (38%) Arthralgia 1. 9 (8%) 2. 3 (3%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: see above Detection Bias: see above Attrition Bias: see above Reporting Bias: see above Other Bias: Unclear. Study funded by manufacturer. 3 authors are employees of the manufacturer. **Applicability**: Patient: All female, predominantly white population with limited diversity. Intervention: see above Comparator: see above Outcomes: see above Setting: 74 sites in 6 countries. Percent of enrolled patients by country: United States (55%); Canada (2%); Korea (9%); Hungary (20%); Poland (10%); India (3%)

				Incidence of neutropenic complications 1. 1 (0.8%) 2. 5 (4.2%) Difference: 3.4% P value NR: 0.21	NS			
Abbreviations : AC = active comparator; AEs = adverse effects; ANC = absolute neutrophil count; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ITT = intention to treat; IWRS = interactive web response system; L = liter; MC = multi-site; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open-label; PP = per protocol; RCT = randomized controlled trial; SAEs = serious adverse effects; SC = subcutaneous; Y = years.								

References:

1. Stimufend (pegfilgrastim-fpgk) for subcutaneous injection. Prescribing Information. Lake Zurich, IL; Fresenius Kabi, USA, LLC. September 2022.
2. Udenyca (pegfilgrastim-cbqv) for subcutaneous injection. Prescribing Information. Redwood City, CA; Coherus BioSciences, Inc. March 2023.
3. Rolvedon (eflapegrastim-xnst) Subcutaneous Injection. Prescribing Information. Irvine, CA; Spectrum Pharmaceuticals, Inc. September 2022.
4. Schwartzberg LS, Bhat G, Peguero J, et al. Eflapegrastim, a Long-Acting Granulocyte-Colony Stimulating Factor for the Management of Chemotherapy-Induced Neutropenia: Results of a Phase III Trial. *The Oncologist.* 2020;25(8):e1233-e1241.
5. Cobb PW, Moon YW, Mezei K, et al. A comparison of eflapegrastim to pegfilgrastim in the management of chemotherapy-induced neutropenia in patients with early-stage breast cancer undergoing cytotoxic chemotherapy (RECOVER): A Phase 3 study. *Cancer Medicine.* 2020;9(17):6234-6243.
6. Center for Drug Evaluation and Research. Clinical Review of Rolvedon (eflapegrastim-xnst). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761148Orig1s000MedR.pdf Accessed 7/12/23.
7. Fletcher, S. Drug Use Research and Management. Drug Class Literature Scan: Colony Stimulating Factors. April 2022. https://www.orpdl.org/durm/meetings/meetingdocs/2021_06_03/archives/2021_06_03_CSF_LitScan.pdf. Accessed September 5, 2022. .
8. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors Version 1.2023. https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1493. Accessed July 19, 2023.
9. Blayney DW, Schwartzberg L. Chemotherapy-induced neutropenia and emerging agents for prevention and treatment: A review. *Cancer Treat Rev.* 2022;109:102427.
10. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52(4):e56-e93.
11. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: An overview about well-established and recently emerging clinical data. *Critical Reviews in Oncology/Hematology.* 2017;120:163-179.
12. Datta SS, Ghosal N, Daruvala R, et al. How do clinicians rate patient's performance status using the ECOG performance scale? A mixed-methods exploration of variability in decision-making in oncology. *Ecancermedicalscience.* 2019;13:913.
13. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.
14. Zhu X, Zhang W, Zhang Y, et al. Pegfilgrastim on febrile neutropenia in pediatric and adolescent cancer patients: a systematic review and meta-analysis. *Hematol.* 2023;28(1):2172292.
15. Gebremariam GT, Fentie AM, Beyene K, Sander B, Gebretekle GB. Cost-effectiveness of pegfilgrastim versus filgrastim for prevention of chemotherapy-induced febrile neutropenia in patients with lymphoma: a systematic review. *BMC Health Serv Res.* 2022;22(1):1600.
16. Martin-Mateos R, González-Alonso R, Álvarez-Díaz N, et al. Granulocyte-colony stimulating factor in acute-on-chronic liver failure: Systematic review and meta-analysis of randomized controlled trials. *Gastroenterol Hepatol.* 2023;46(5):350-359.
17. Food and Drug Administration. Drug Safety Labeling Changes. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed July 25, 2023.

18. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed July 19, 2023.
19. Neupogen (filgrastim) Prescribing Information. Amgen, Inc. Thousand Oaks, Ca. Feb 2021.
20. Nivestym (filgrastim-aafi) Prescribing Information. Pfizer. Lake Forest, IL. Jul 2018.
21. Zarxio (filgrastim-sndz) Prescribing Information. Sandoz. Princeton, NJ. Aug 2019.
22. Granix (tbo-filgrastim) Prescribing Information. Teva Pharmaceuticals. North Wales, PA. Mar 2019.
23. Leukine (sargramostim) Prescribing Information. Sanofi. Bridgewater, NJ. Mar 2018.
24. Neulasta (pegfilgrastim) Prescribing Information. Amgen. Thousand Oaks, CA. Feb 2021.
25. Nyvepria (pegfilgrastim-apgf) Prescribing Information. Pfizer. New York, NY. Apr 2021.
26. Ziextenzo (pegfilgrastim-bmez) Prescribing Information. Sandoz. Princeton, NJ. Mar 2021.
27. Fulphila (pegfilgrastim-jmdb) Prescribing Information. Mylan Pharmaceuticals. Morgantown, WV. Mar 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
filgrastim	NEUPOGEN	INJECTION	VIAL	Y
filgrastim	NEUPOGEN	INJECTION	SYRINGE	Y
pegfilgrastim-apgf	NYVEPRIA	SUBCUT	SYRINGE	Y
sargramostim	LEUKINE	INJECTION	VIAL	Y
eflapegrastim-xnst	ROLVEDON	SUBCUT	SYRINGE	N
filgrastim-aafi	NIVESTYM	INJECTION	VIAL	N
filgrastim-aafi	NIVESTYM	SUBCUT	SYRINGE	N
filgrastim-ayow	RELEUKO	INJECTION	VIAL	N
filgrastim-ayow	RELEUKO	SUBCUT	SYRINGE	N
filgrastim-sndz	ZARXIO	INJECTION	SYRINGE	N
pegfilgrastim	NEULASTA	SUBCUT	SYRINGE	N
pegfilgrastim	NEULASTA ONPRO	SUBCUT	SYR W/ INJ	N
pegfilgrastim-bmez	ZIEXTENZO	SUBCUT	SYRINGE	N
pegfilgrastim-cbqv	UDENYCA	SUBCUT	SYRINGE	N
pegfilgrastim-cbqv	UDENYCA AUTOINJECTOR	SUBCUT	AUTO INJCT	N
pegfilgrastim-fpgk	STIMUFEND	SUBCUT	SYRINGE	N
pegfilgrastim-jmdb	FULPHILA	SUBCUT	SYRINGE	N
pegfilgrastim-pbbk	FYLNETRA	SUBCUT	SYRINGE	N
tbo-filgrastim	GRANIX	SUBCUT	VIAL	N
tbo-filgrastim	GRANIX	SUBCUT	SYRINGE	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to June Week 5 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to July 11, 2023

1	exp Febrile Neutropenia/ or Granulocyte Colony-Stimulating Factor/	3403194
2	exp Filgrastim/	2135
3	pegfilgrastim.mp.	946
4	sargramostim.mp.	207
5	eflapegrastim.mp.	10
6	tbo-filgrastim.mp.	25
7	2 or 3 or 4 or 5 or 6	2505
8	1 and 7	2139
9	limit 8 to (english language and humans and yr="2022 -Current")	77

Appendix 3: Prescribing Information Highlights

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

ROLVEDON™ (eflapegrastim-xnst) injection, for subcutaneous use
Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------
Rolvedon is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. (1)

Limitations of Use
Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended Dose: 13.2 mg administered subcutaneously once per chemotherapy cycle. (2.1)
- Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 13.2 mg/0.6 mL solution in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as eflapegrastim, pegfilgrastim or filgrastim products. (4)

----------WARNINGS AND PRECAUTIONS----------
- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Rolvedon in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Rolvedon in patients with serious allergic reactions. (5.3)
- Sickle Cell Crisis in Patients with Sickle Cell Disorders: Discontinue Rolvedon if sickle cell crisis occurs. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Rolvedon if causality is likely. (5.5)
- Leukocytosis: Monitor complete blood count (CBC) during Rolvedon therapy. (5.6)
- Thrombocytopenia: Monitor platelet counts. (5.7)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using Rolvedon in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.10)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥20%) are fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Spectrum Pharmaceuticals, Inc. at 1-888-713-0688 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

Revised: 09/2022

Appendix 4: Key Inclusion Criteria

Population	Patients receiving chemotherapy
Intervention	C-CSF and GM-CSF in **Appendix 1**
Comparator	See **Appendix 1**
Outcomes	Symptom improvement, morbidity, mortality/survival, serious adverse events
Timing	Any study duration
Setting	Inpatient/outpatient combination or outpatient

Appendix 5: Summary of FDA Labeled Indications of G-CSF and CM-CSF Products

FDA Labeled Indications	Filgrastim NEUPOGEN[19]	Filgrastim-aafi NIVESTYM[20]	Filgrastim-sndz ZARXIO[21]	tbo-Filgrastim GRANIX[22]	Sargramostim LEUKINE*[23]
Decrease the **incidence** of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.	x	x	x		
In adult and pediatric patients 1 month and older for reduction in the **duration** of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.				x	
Reduce the time to neutrophil recovery and the **duration** of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).	x	x	x		
To shorten time to neutrophil recovery and to reduce the **incidence** of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with AML.					x
Reduce the **duration** of neutropenia and neutropenia-related clinical sequelae, e.g., , febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).	x	x	x		
For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic BMT in adult and pediatric patients 2 years of age and older.					x
For the acceleration of myeloid reconstitution following allogeneic BMT in adult and pediatric patients 2 years of age and older.					x

For the acceleration of myeloid reconstitution following autologous BMT or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older.					x
Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.	x	x	x		
For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients.					x
Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia	x	x	x		
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)	x				x
	Pegfilgrastim NEULASTA†[24]	**Pegfilgrastim-apgf NYVEPRIA†[25]**	**Pegfilgrastim-bmez ZIEXTENZO†[26]**	**Pegfilgrastim-cbqv UDENYCA†[2]**	**Pegfilgrastim-jmdb FULPHILA†[27]**
Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically a significant incidence of febrile neutropenia.	x	x	x	x	x
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).	x			x	
	Pegfilgrastim-fpgk STIMUFEND†[1]	**Eflapegrastim ROLVEDON†[3]**			
Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving	x	x			

myelosuppressive anti-cancer drugs associated with a clinically a significant incidence of febrile neutropenia.					
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).					

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

[†]Limitation of Use: NOT indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

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Drug Class Update: Opioid Reversal Agents

Date of Review: October 2023

Date of Last Review: March 2016
Dates of Literature Search: 01/01/2016 - 08/04/2023

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

Purpose for Class Update:
The purpose of this update is to evaluate new evidence for the efficacy and safety of opioid reversal products and evaluate the place in therapy for recently approved medications.

Plain Language Summary:
- Two medicines, naloxone and nalmefene, are used to reverse the dangerous adverse effects of opioid overdose, including respiratory depression, sedation and low blood pressure. These medicines are sprayed into the nose or injected into the muscle or vein. People without medical training can give these medicines to someone who has overdosed.
- Evidence shows that injections of naloxone worked faster than the nasal spray. People receiving naloxone injections were also less likely to need a second dose of medicine to reverse the opioid overdose. Naloxone nasal spray may not fully reverse overdose symptoms if the person has taken a large amount of opioids or used a potent opioid such as fentanyl.
- Evidence shows that when naloxone is use in the community setting, not given by a medical professional, can decrease deaths due to opioid overdoses.
- The Veterans Administration (VA) recommends that veterans have access to naloxone nasal spray if they have a history of taking opioids on an ongoing basis or are at risk of overdosing on opioids. This guidance was published prior to the approval of the nalmefene nasal spray.
- The Oregon Health Plan (OHP) will pay for preferred naloxone injection or nasal spray for Fee-for-service (FFS) members. The Drug Use Research and Management Group recommends no changes to the current opioid reversal policy.

Research Questions:
1. What is the comparative effectiveness of opioid reversal agents when administered in the community by people without specific medical training (e.g., bystanders or first responders)?
2. What is the comparative effectiveness of opioid reversal agents based on route of administration when administered in the community by people without specific medical training?
3. What are the differences in harms of opioid reversal products for people who have an opioid overdose?
4. What is the evidence for efficacy in different subpopulations (e.g., type of opioid taken, route of opioid reversal agent)?

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Conclusions:

- There were 2 systematic reviews, 1 high quality guideline, 6 new formulations and one new safety warning published since the last review.
- A review published in June 2023 by the Drug Effectiveness Review Project (DERP) evaluated naloxone products (intramuscular [IM], intravenous [IV] and intranasal [IN]) for reversal of an opioid overdose. Most doses were given by a medical professional and only one study evaluated reversal with overdoses from fentanyl. There was moderate quality evidence that IM naloxone had a quicker time to response compared to IN formulations, and patients were less likely to require a second dose. There were no differences in hospitalizations. High dose naloxone was associated with a quicker response and less need for a second dose of naloxone (moderate quality evidence). One study comparing IM and IV naloxone found no difference in response time between formulations (very low quality evidence).
- A Canadian Agency for Drugs and Technology (CADTH) review on the use of naloxone in the community setting found low quality evidence that naloxone use by non-medical professionals reduced mortality due to fatal overdoses.
- Guidance from the Veterans Administration (VA) recommends the IN naloxone formulation be made available to all patients with opioid use disorder (OUD) or other risk factors for opioid overdose.
- Six new opioid reversal therapies, including 2 over-the-counter (OTC) products, were recently approved by the Food and Drug Administration (FDA).
- A warning for IN naloxone (NARCAN) was updated in the FDA labeling to include the risk of incomplete opioid reversal in the presence of potent or high dose opioid exposure.
- Limited data comparing different routes of opioid reversal therapies suggest similar adverse events (AEs) including headache, nausea and vomiting.
- There is limited evidence evaluating the use of opioid reversal agents given by non-medical professionals. Additional studies are needed to evaluate the most effective opioid reversal agents for high dose, synthetic opioid analogs, such as fentanyl.

Recommendations:

- No changes to the preferred drug list are recommended based on review of the current evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- The previous March 2016 review found no differences in effectiveness or harms between injectable and intranasal naloxone to reverse opioid overdose.
- Increased access to naloxone for opioid users at high risk for opioid overdose is recommended by local and national organizations due to low quality evidence that increased naloxone availability in the community reduces rates of opioid overdose deaths.

Background:

Drug overdoses have become a national epidemic in the US with unintentional opioid overdose deaths rising annually in Oregon since 2019.[1] In a 12-month period ending in October 2022, there were more than 101,750 reported fatal opioid overdoses in the US.[2] Deaths from opioids occur most often in those 18 to 65 years and in children 15-19 years of age.[3] In October 2017, the United States (US) federal government declared the opioid epidemic a public health emergency.[4] There has been a large increase the deaths of teens contributing to these statistics which is thought to be due in part to the availability of illegal synthetic opioids, such as fentanyl. Additional scenarios which may lead to opioid overdose include: initiating medication that may compete for the same metabolic pathway; addition of a medication that may also affect the central nervous system; concomitant alcohol use; and inadvertently taking a higher dose than prescribed to help better manage pain. All 50 states have policies called naloxone access law which are designed to expand access of naloxone for layperson use.[3] Despite efforts to increase distribution and use of opioid reversal agents, barriers still exist which prevent access.

Opioids can be lethal due to their ability to cause respiratory and central nervous system depression. Opioid reversal agents are antagonists at the opioid receptor which cause reversal of the effects of opioids (e.g., sedation, hypotension, and respiratory depression) and prevent hypoxia-associated injury and death.[3] The World Health Organization (WHO) and the American Society of Addiction Medicine (ASAM) recommend that people with OUD and those likely to witness an opioid overdose should have naloxone accessible.[5] Naloxone and nalmefene are the two opioid reversal agents approved by the FDA. Naloxone and nalmefene are available in several formulations: IM, IN, IV and SQ. Naloxone remains effective for 20-90 minutes after administration. Nalmefene has a longer half-life than naloxone and may be advantageous when overdoses occur in people who have taken opioids that have a longer half-life.[4] Prior to 2023, all opioid reversal products required a prescription. In 2023, the FDA approved 2 over-the-counter IN naloxone products, NARCAN and REVIVE (**Table 1**). Absorption differs across different tissue types, and therefore, doses differ depending on the route of administration. Evidence for naloxone suggests that the IM formulation has a quicker onset of action, approximately 2 minutes faster, compared to the IN route.[6] This difference is considered clinically meaningful according the DERP.[6] There is no evidence to evaluate what dose of naloxone is needed to counteract the effects of potent opioids, such as fentanyl, or high-dose opioids. The Centers for Disease Control and Prevention (CDC) has recommended that patients be counseled that multiple does of naloxone may be needed to treat a single overdose attack due to the potency and prolonged effects of potent fentanyl analogs.[7]

Table 1. FDA Approved Opioid Reversal Products

Drug	Route of Administration	Prescription Status	Community Use
Naloxone[8]	Injectable 0.02 mg, 0.4 mg or 1 mg per vial (IM, IV, SQ)	Prescription	No
Naloxone[8]	Nasal 2 mg and 4 mg	Prescription	Yes
Naloxone (Narcan®)[9]	Nasal 4 mg	OTC	Yes
Naloxone (ReVive™)[10]	Nasal 3 mg	OTC	Yes
Naloxone (Kloxxado®)[11]	Nasal 8 mg	Prescription	Yes
Naloxone (Zimhi®)[12]	Injectable 5 mg per syringe (IM or SQ)	Prescription	Yes
Naloxone (Rextovy™)[13]	Nasal 4 mg	Prescription	Yes
Nalmefene[14]	Injectable 2 mg (IM, IV, SQ)	Prescription	No
Nalmefene (Opvee®)[15]	Nasal 2.7 mg	Prescription	Yes
Abbreviations: IM = intramuscular; IV = intravenous; OTC = over the counter; SQ = subcutaneous			

Important outcomes for opioid reversal agents include response or reversal of overdose symptoms, time-to-response, number of people needing a second dose, hospital admission rates and adverse effects (AEs). It is recommended that those requiring an opioid reversal agent be evaluated by a medical professional but not all require hospitalization.

Methods:

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

quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The 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:

DERP – Effectiveness and Harms of Naloxone for Opioid Overdose

A recent publication by DERP evaluated the different FDA-approved naloxone products used for opioid overdose.[6] Twelve randomized and nonrandomized trials and cohort studies evaluating naloxone delivered by the IN and IM routes were included (**Table 1**). Five of the studies were randomized controlled trials (RCTs) (all compared IN naloxone to IM or IV naloxone) and 7 were nonrandomized cohort studies.[6] None of the RCTs were conducted in the United States (US). Intranasal naloxone was compared to IM naloxone in 4 studies, four studies compared IN naloxone with IV naloxone, one study compared IM naloxone with IV naloxone, and three studies compared low-dose naloxone with high-dose naloxone. Naloxone doses included in the studies ranged from 0.4 mg to 2 mg, which the maximum dose is lower than currently available high-dose naloxone products. Participants included in the studies were mostly adult males.[6] All studies looked at initial reversal of opioid overdose symptoms and without long-term follow-up. A majority of studies evaluated doses administered by a medical professional. The most common opioids involved in overdoses were opium and heroin, only one study included participants who had fentanyl exposure.[6] Response time was measured 8 to 10 minutes after administration.

Table 1. Naloxone Products Included in the DERP Report[6]

Drug	Route of Administration	FDA Approval Date
Naloxone	Injectable 0.02 mg, 0.4 mg or 1 mg per vial	1971
Naloxone (Narcan®)	Nasal 4 mg	11/18/2015
Naloxone	Nasal 2 mg and 4 mg	4/19/2019
Naloxone (Kloxxado®)	Nasal 8 mg	4/29/2021
Naloxone (Zimhi®)	Injectable 5 mg	10/15/2021

The results of the DERP review are presented in **Table 2**. All formulations effectively reversed opioid overdose; however some required additional doses. Intramuscular naloxone was found to have a quicker onset than the IN formulation. Withdrawal symptoms were more common with the IM dosage form.

Table 2. Key Findings from Naloxone Trials Included in the DERP Report[6]

Comparison	Results	Quality of Evidence
IN naloxone vs. IM naloxone (4 studies)	• Response was greater with IM naloxone compared to IN naloxone (OR 2.6; 95% CI, 1.2 to 1.5; p=0.02) • TTR was faster with IM naloxone vs. IN naloxone. Median time to respond was 8 minutes for 2 mg IN naloxone. Studies showed response time to be 2.3 minutes to 9 minutes longer with the IN formulation compared to IM. • A second dose was given more often when IN naloxone was used. Of people given IN naloxone, 18.1% to 29% needed a second dose vs. 4.5% to 9.3% given IM naloxone.	Moderate for all outcomes except hospitalizations and adverse events which was low

	• No difference in hospitalization rates between routes • IM naloxone may be associated with more AE compared to IN (e.g., agitation, nausea or vomiting, headaches)	
IN naloxone vs. IV naloxone (4 studies)	• No difference in response • TTR was faster with IV naloxone • A second dose was needed more often with IN naloxone. Of people receiving an IN dose, 42%-44% required a second dose vs. 11%-20% in the IV group. • No difference in hospital length of stay • Hospital length of stay was similar between groups • IV naloxone was associated with more AE	Very low
IM naloxone vs. IV naloxone (1 study)	• No difference in response (measured at 5 minutes) • No results on repeat doses were available	Very low
Low-dose vs. high-dose naloxone (3 studies)	• High-dose naloxone (2 mg to > 0.15 mg) had a greater response than low dose naloxone (≤ 0.15 mg to 0.4 mg) • TTR was quicker in those received high dose naloxone (multiple routes) compared to low dose (mostly given IV) • A second dose of naloxone was more commonly needed in those receiving low dose naloxone (mixed routes) compared to high dose (mostly IV) • No difference was found in hospital admissions • High dose naloxone was associated with more adverse events (e.g., agitation, nausea, and vomiting)	Very low

Abbreviations: AE – adverse effects; CI – Confidence Interval; IM – intramuscular; IN – intranasal; IV – intravenous; OR – Odds Ratio; TTR – time-to-response

Limitations to the review are that most of the studies included administration of naloxone by a medical professional. None of the high-dose naloxone formulations recently approved by the FDA were studied (e.g., Kloxxado® 8 mg IN or Zimhi® 5 mg IM).[6]

CADTH – Administration of Naloxone in the Home or Community Setting

An updated CADTH review in 2019 evaluated the clinical effectiveness of the administration of naloxone in the home or community setting by non-health care professionals.[16] Six publications met inclusion criteria for the review; one systematic review, 2 guidelines, 2 non-randomized studies and one economic evaluation.[16] The evidence was considered low quality.

Take-home naloxone was associated with decreased mortality due to reductions in fatal overdoses.[16] Slightly lower rates in opioid overdoses were demonstrated in communities with take-home naloxone. There was limited evidence of reductions in emergency department visits in those patients that received take-home naloxone when prescribed an opioid. Guidelines recommend the use of naloxone in people who are likely to witness an opioid overdose, such as patients and their family members or care givers.[16] World Health Organization strongly recommends the use of any route of naloxone (e.g., IM, IN, IV, SQ) based on similar effectiveness data.[16] Naloxone is not recommended for pregnant women except in life-threatening situations.

After review, one systematic review was 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).[17]

New Guidelines:

VA – Naloxone Rescue: Recommendations for Use

The VA published guidance on naloxone rescue in an effort to reduce the incidence of overdose amongst veterans.[18] The VA is required to offer opioid antagonists without requiring a copay. The IN naloxone formulations are preferred; however, the injection is available if contraindications to the IN formulation are present. The VA recommends the use of the Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) to assess risk of opioid overdose. The Stratification Tool for Opioid Risk Mitigation (STORM) is also used to identify patients at risk of drug overdose or suicide. The following naloxone rescue recommendations are to be utilized for VA patients[18]:

- Assess risk of opioid-related adverse events
- Discuss naloxone rescue as a mitigation option with patients and care givers
- Offer naloxone to veterans prescribed opioids that are at increased risk
- Educate on opioid overdose prevention, recognition and response

Guidelines for Clinical Context:

ASAM – National Practice Guideline for the Treatment of Opioid Use Disorder

In 2020 the American Society of Addiction Medicine (ASAM) updated recommendation for OUD including the use of naloxone for opioid reversal.[19] A risk of bias evaluation and grading of the recommendations was not provided and authors had conflicts of interest, therefore, guidelines are included for clinical context. Guideline recommendations for the use of naloxone include[19]:

- Naloxone should be administered in the event of suspected opioid overdose
- Naloxone can be administered to pregnant women in case of overdose to save the mother's life
- Patients who are treated for OUD, and family members, should be given and instructed on the use of naloxone kits or prescription naloxone (OTC naloxone not available at time of guideline publication)
- First responders should be trained and authorized to carry naloxone

There is a lack of comparative efficacy studies between different routes of administration of naloxone.[19] Additional evidence is needed to inform the most effective strategies for opioid reversal.

New Formulations or Indications:

Naloxone (Narcan®): In March 2023, IN naloxone 4 mg received FDA approval to be changed from a prescription product to an OTC non-prescription product.[3] The switch was prompted by FDA soliciting safety and effectiveness data for naloxone products from manufacturers to allow the switch from prescription to OTC status to increase availability and access to naloxone.

Intranasal naloxone is a single-use, fixed-dose product approved for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; for immediate administration as emergency therapy in settings where opioids may be present.[3] Naloxone rapidly reverses the effects of opioid overdose and this formulation may be used by those without medical training in community settings. The OTC naloxone formulation is indicated for neonates to adults.[3] The dose can be repeated every 2-3 minutes until emergency help arrives.

The FDA developed and validated a drug facts label (DFL) to ensure consumers could safely and effectively use the OTC naloxone. Pictures and corresponding wording allow for quick and clear directions for use.[20] No formulation changes were made to naloxone OTC compared to the prescription product and there was no new evidence presented to the FDA. Postmarketing safety results for the prescription IN naloxone were reviewed prior to OTC approval. Common adverse events include: increased blood pressure, constipation, toothache, and muscle spasms.

Nalmefene (Opvee®): A new IN formulation of nalmefene, previously available as an injectable, was approved in May of 2023.[15] The nalmefene nasal spray is an opioid antagonist indicated for the emergency treatment of known or suspected overdose caused by natural or synthetic opioids in adults and pediatrics 12 years and older.[15] Each nalmefene nasal spray delivers 2.7 mg into the nose. Nalmefene IN onset of action is 2.5 to 5 minutes.[15] Additional doses can be administered every 2-5 minutes if needed until emergency medical assistance arrives.

Nalmefene nasal spray approval was based on a study of healthy patients comparing the nalmefene nasal formulation to a single dose of nalmefene IM. There is pharmacokinetic and pharmacodynamic data that nalmefene has high affinity at μ-opioid receptors with a quick onset of action (0.250 hours to maximal concentration for IN nalmefene compared to 0.50 hours for IN naloxone) The half-life of nalmefene is 11.4 hours compared to a mean half-life for IN naloxone of 2.08 hours. There is no published direct comparative effectiveness data comparing IN nalmefene to IN naloxone.

The most common AEs are nasal discomfort, headache, nausea, dizziness, hot flush, vomiting, anxiety, fatigue, nasal congestion, throat irritation, rhinalgia, decreased appetite, dysgeusia, erythema, and hyperhidrosis.[15]

Naloxone (Zimhi®): A high-dose naloxone product, 5 mg IM or SQ in a single-dose prefilled syringe, was approved in October 2021 for use in pediatrics or adults or the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[12] Approval was based on pharmacokinetic data from 14 healthy volunteers. Adverse events associated with high-dose naloxone include: nausea, dizziness, lightheadedness, and elevated bilirubin.

Naloxone (Kloxxado™): A high-dose (8 mg), single use IN naloxone was approved in April 2021 for pediatric and adult use.[11] This high-dose IN naloxone product is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Emergency medical care should be sought after administration. Repeat does may be given every 2-3 minutes until arrival of emergency medical assistance.[11] The high-dose IN naloxone is designed for community or medical professional use. Approval was based off of the 505(b)(2) approval pathway under the Federal Food, Drug, and Cosmetic Act. This Act allows approval based on evidence from similar products. Pharmacokinetic data comparing IN naloxone to naloxone injection was used to demonstrate safety and efficacy.[21] Common adverse events associated with the use of high-dose IN naloxone are: abdominal pain, asthenia, dizziness, headache, nasal discomfort and presyncope.

Naloxone (Rextovy™): A 0.4 mg naloxone nasal formulation of naloxone was approved in March of 2023 for the use of for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients.[13] This formulation was approved under the 505 (b)(2) approval pathway. Pharmacokinetic comparisons to naloxone 4 mg IN, naloxone 0.4 mg IM, naloxone 2 mg IV and naloxone 10 mg IN was used to support the approval of Rextovy™. Naloxone IN demonstrated higher concentrations than naloxone injections but lower than the IV formulation. Clinical data suggests similar safety profile as other naloxone products.[22]

Naloxone (ReVive™): A second OTC IN naloxone product was approved in July 2023.[10] The 3 mg single dose spray is approved for the emergency treatment of opioid overdose. Approval was based on pharmacokinetic comparisons to other naloxone products.

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Naloxone[23]	Narcan®	January 2017	Warnings and precautions	Naloxone 2 mg dose may prevent precipitation of severe opioid withdrawal in those with opioid dependence but may not provide an adequate and timely reversal if potent or very high doses of opioid have been taken.

Randomized Controlled Trials:
A total of 12 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

References:

1. Oregon Health Authority. Opioid Overdose Public Health Surveillance Update April 20th, 2023. Available at: https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/quarterly_opioid_overdose_related_data_report.pdf. Accessed July 17, 2023.

2. Food and Drug Administration. FDA Approval of First Over-the-Counter Naloxone Nasal Spray. FDA News Release. March 29, 2023. Accessed July 20, 2023.

3. Food and Drug Administration. Executive Summary - Narcan (naloxone hydrochloride) nasal spray, 4 mg. Integrated Review Template. Available at: fda.gov. Accessed July 23, 2023.

4. Britch SC, Walsh SL. Treatment of opioid overdose: current approaches and recent advances. *Psychopharmacology*. 2022;239(7):2063-2081. doi:10.1007/s00213-022-06125-5.

5. Chao Y, Loshak H. Administration of Naloxone in a Home or Community Setting: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines. Ottawa:CADTH. December 2019.

6. Drug Effectiveness Review Project. Effectiveness and Harms of Naloxone for Opioid Overdose. June 2023.

7. Centers for Disease Control and Prevention. Increase in Fatal Drug Overdoses Across the United States Driven by Synthetic Opioids Before and During the COVID-19 Pandemic. CDC Health Alert Neetwork. December 17, 2020. Available at: https://emergency.cdc.gov/han/2020/han00438.asp. Accessed September 1, 2023.

8. Naloxone [prescribing information]. Richmond, VA; Kaleo, Inc. March 2023.

9. Narcan (naloxone) [prescribing information]. Plymouth Meeting, PA; Emergent Devices Inc. March 2023.

10. Rivive (naloxone) [prescribing information]. Bethesda, MD; Harm Reduction Therapeutics, Inc. June 30, 2023.

11. Kloxxado (naloxone) [prescribing information]. Columbus, OH: Hikma Specialty USA Inc. April 2021.

12. Zimhi (naloxone hydrochloride injection) [prescribing information]. San Diego, CA; Adamis Pharmaceuticals Corporation. October 2021.

13. Rextovy (naloxone) [prescribing information). So El Monte, CA; International Medication Systems, Limited. June 2023.

14. Nalmefene [Prescribing Information]. Stamford, CT: Purdue Pharma L.P. February 2022.

15. Opvee (nalmefene) [prescribing information]. Santa Monica, CA; Opiant Pharmaceuticals. May 2023.

16. Canadian Agency for Drugs and Technologies in Heatlh. Administration of Naloxone in a Home or Community Setting: A Review of the Clinical Effectiveness, Cost-Effectiveness and Guidelines. CADTH Rapid Repsonse Report: Summary with Critical Appraisal. December 18, 2019.

17. Dowling N, Merkouris S, Lubman D, et al. Pharmacological Interventions for the Treatment of Disordered and Problem Gambling. Cochrane Database of Systematic Reviews 2022; issue 9. Art. No. CD008936.

18. Veterans Affairs. Naloxone Rescue: Recommendations for Use. VA Pharmacy Benefits Managment Services, Medical Advisory Panel, and VISN Pharmacists Executives. February 2022.

19. ASAM Board of Directors. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder- 2020 Focused Update. American Society of Addiction Medicine. Available at: npg-jam-supplement.pdf. Accessed July 31, 2023.

20. Food and Drug Administration. Draft Labeling Review for Narcan (Naloxone Hydrochloride 4 mg) Nasal Spray. Labeling Review. 208411/S-006.

21. Food and Drug Administration. FDA Approves Higher Dosage of Naloxone Nasal Spray to Treat Opioid Overdose. April 30, 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-higher-dosage-naloxone-nasal-spray-treat-opioid-overdose. Accessed August 1, 2023.

22. Food and Drug Administration. Naloxone (Rextovy). Center for Drug Evaluation and Research - Summary Review. June 29, 2023.

23. Food and Drug Administration. Narcan safety labeling changes. January 24, 2017. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=809. Accessed July 20, 2023.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
naloxone HCl	NALOXONE HCL	AMPUL	INJECTION	Y
naloxone HCl	NARCAN	AMPUL	INJECTION	Y
naloxone HCl	NALOXONE HCL	SYRINGE	INJECTION	Y
naloxone HCl	NALOXONE HCL	VIAL	INJECTION	Y
naloxone HCl	KLOXXADO	SPRAY	NASAL	Y
naloxone HCl	NALOXONE HCL	SPRAY	NASAL	Y
naloxone HCl	NARCAN	SPRAY	NASAL	Y
nalmefene HCl	NALMEFENE HCL	VIAL	INJECTION	N
naloxone HCl	NALOXONE HCL	AUTO INJCT	INJECTION	N
naloxone HCl	NALOXONE HCL	CARTRIDGE	INJECTION	N
naloxone HCl	ZIMHI	SYRINGE	INJECTION	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 17, 2023

Search Strategy:

#	Searches	Results
1	Naloxone/ or naloxone.mp.	29387
2	nalmefene.mp.	504
3	1 and 2	107
4	limit 3 to (english language and humans and yr="2016 -Current")	12

Appendix 3: Key Inclusion Criteria

Population	All individuals suspected of opioid overdose
Intervention	Naloxone or nalmefene
Comparator	Placebo or active treatment
Outcomes	Mortality, reversal of overdose symptoms, time- to-response, number needing a second dose, hospitalization, and adverse effects
Setting	Outpatient

Drug Use Research & Management Program
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Drug Class Literature Scan: Substance Use Disorders, Opioid and Alcohol

Date of Review: October 2023

Date of Last Review: February 2023
Literature Search: 01/01/22 – 08/10/23

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

Plain Language Summary:

- The Food and Drug Administration (FDA) has approved these medicines to treat substance use disorders:
  - Lofexidine, methadone, buprenorphine, naloxone, and naltrexone for opioid use disorder.
  - Naltrexone, acamprosate, and disulfiram for alcohol use disorder.
- New evidence shows that methadone may be better than buprenorphine in helping people with opioid use disorder stay in treatment, but evidence is mixed. People with opioid use disorder have to go to their provider's office to take each dose of methadone, but this isn't required for buprenorphine tablets.
- Evidence shows that naltrexone may help people decrease gambling, but benefit is very uncertain.
- Naltrexone is probably more beneficial than baclofen for alcohol use disorder. Baclofen is a medicine that relaxes muscles, and we do not know if it will reduce alcohol use.
- The Oregon Health Plan covers nearly all medicines used to treat substance use disorder. Providers must explain to the Oregon Health Plan if they prescribe lofexidine or more than 32 mg per day of buprenorphine before the Oregon Health Plan will pay for the medicine. This process is called prior authorization. The goal of prior authorization is to make sure these medicines are used in a safe and effective way.
- We do not recommend any changes to this policy.

Conclusions:

- A systematic review evaluating buprenorphine compared to methadone for treatment of adults with opioid use disorder (OUD) found similar rates of retention at 1 month, but slightly higher treatment retention with methadone compared to buprenorphine for other time points up to 24 months (relative risk [RR] 0.65; 95% confidence interval [CI] 0.51 to 0.84). [1] At 12 months, treatment retention was on average 43% (95% CI 39 to 47) with sublingual buprenorphine and 47% (95% CI 38 to 56) for methadone.[1] There were no apparent differences in adherence to treatment or extra-medical opioid use between groups, and there was insufficient evidence for other outcomes of interest including use of other drugs, cravings, withdrawal symptoms, global functioning, treatment satisfaction, engagement with criminal justice system, non-fatal opioid overdose, and serious adverse events.[1]
- A systematic review evaluating therapies for problematic gambling found some evidence that opioid antagonists, naltrexone and nalmefene, given over 10 to 16 weeks may reducing gambling symptom severity but may not improve response to treatment.[2] The magnitude of benefit remains uncertain and is likely to change with additional research.[2]

Author: Sarah Servid, PharmD

- A systematic review found insufficient evidence to compare baclofen to naltrexone or acamprosate for treatment of alcohol use disorder. Baclofen may increase the risk of relapse compared to naltrexone (RR 2.50; 95% CI 1.12 to 5.56; n=60; 1 RCT; insufficient evidence), but evidence is very limited.[3]
- A systematic review evaluating efficacy of treatments for alcohol use disorder in low and middle-income countries found low quality evidence that combination use of pharmacologic and psychosocial interventions reduced harmful alcohol use and improved treatment remission compared to psychosocial interventions alone.[4] There was moderate quality evidence that combination treatment did not improve retention in treatment.[4] Limitations in the evidence precluded conclusions regarding pharmacologic treatment alone for outcomes of harmful alcohol use, remission, or relapse in low and middle-income countries.[4] Data from this review may be most applicable to Medicaid members who have immigrated to Oregon.
- The Food and Drug Administration (FDA) approved a new formulation of extended-release buprenorphine in 2023 based on results from a phase 3 randomized controlled trial (RCT) that demonstrated weekly or monthly subcutaneous injections were non-inferior to daily administration of sublingual buprenorphine.[5] The primary study outcomes were the proportion of opioid-negative urine drug screens from 1 to 24 weeks (35.1% vs. 28.4%; difference of 6.7%; 95% CI -0.1 to 13.6) and response to treatment based on opioid-negative urine drug screens at pre-specified times (17.4% vs. 14.4%; difference of 3.0%; 95% CI -4.0 to 9.9).[5]

Recommendations:

- No PDL changes are recommended based on new clinical evidence. Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Recent guidelines recommend either buprenorphine or methadone as first-line treatment options for opioid use disorder.[6] Methadone and injectable formulations of buprenorphine are administered in supervised settings and sublingual buprenorphine can be given in a non-supervised setting (e.g., dispensed by a pharmacy and taken by the member at home).
- For alcohol use disorder, recent guidelines from the Department of Veterans Affairs (VA) and Department of Defense (DoD) suggest naltrexone and topiramate for alcohol use disorder.[6] Acamprosate and disulfiram are suggested as first-line alternatives, and gabapentin is suggested as second-line therapy.[6]
- State law currently prohibits use of prior authorization (PA) within the first 30 days for drugs to treat substance use disorders. Multiple drugs for opioid or alcohol use disorder are currently preferred without PA in the fee-for-service (FFS) program including acamprosate tablets, buprenorphine/naloxone films and tablets (SUBOXONE, ZUBSOLV and generics), naltrexone tablets and injection (DEPADE, REVIA, VIVITROL and generics), and buprenorphine (SUBLOCADE) monthly injection. Prior authorization is required for sublingual buprenorphine formulations prescribed for more than 32 mg daily and for lofexidine which is non-preferred.

Methods:

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

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

New Systematic Reviews:

A 2023 systematic review evaluated efficacy of methadone compared to buprenorphine for treatment of adults with opioid use disorder.[1] The review excluded people who were pregnant and studies evaluating buprenorphine for detoxification. Primary outcomes for the systematic review included retention in treatment, adherence to treatment, and extra-medical opioid use. The review identified 32 RCTs (n=5,808) and 69 observational studies (n=323,340) comparing buprenorphine and methadone. Fifty-one RCTs (n=11,644) and 124 observational trials (n=700,035) evaluating treatment retention with buprenorphine were also included. The mean age of participants was 27 years and 66% of people identified as male. More than half of trials were conducted in North America (49 RCTs and 113 observational trials). Fifteen trials evaluated buprenorphine use during hospitalization, and 7 trials evaluated buprenorphine during incarceration or post-release from incarceration. Sublingual formulations of buprenorphine were studied in all except one trial. All observational trials had some risk of bias concerns, primarily due to confounding. About 25% of observational trials had serious concerns. There were some risk of bias concerns, primarily due to the randomization process, for more than half of RCTs. There was high risk of bias for about 25% of RCTs based on missing outcome data. Authors noted potential for publication bias, bias derived from *post-hoc* analyses, and selective outcome reporting. Sensitivity analyses were conducted based on trial quality and outcomes did not appear to differ based on study quality. Primary results are outlined below.

- Retention in treatment: There was no difference between methadone and buprenorphine at 1 month for observational studies or RCTs. In both RCTs and observational studies, methadone had better treatment retention at subsequent time points up to 24 months (RR 0.65; 95% CI 0.51 to 0.84) compared to buprenorphine. At 12 months treatment retention was on average 43% (95% CI 39 to 47%) with sublingual buprenorphine and 47% (95% CI 38 to 56) for methadone. Data was limited by high heterogeneity (I^2 of 57% to 99%). Sensitivity analyses indicated that buprenorphine retention at 1 month varied based on publication date which may be an indicator of changing clinical practice over time. Publication date was not a significant factor for other outcomes. Retention also varied by location (with lower retention with buprenorphine in studies done in Australasia and higher retention rates in eastern European studies). Individuals recruited from clinic sites also had higher retention rates with buprenorphine compared to individuals identified via databases which generally included a broader population.
- Adherence to treatment: Only 3 RCTs and 2 observational studies evaluated adherence to treatment. Adherence was evaluated using pill count in 3 studies, visits attended in 2 studies and biological methods in one study. Buprenorphine and methadone had similar adherence rates.
- Extra-medical opioid use: In 3 RCTs, extra-medical opioid use evaluated via urinalysis was lower for people treated with buprenorphine, but there were no apparent differences in observational studies or when evaluating extra-medical opioid use by self-report.
- Secondary outcomes were rarely evaluated in more than a few trials. Outcomes included use of other drugs, cravings, withdrawal symptoms, global functioning, treatment satisfaction, engagement with criminal justice system, non-fatal opioid overdose, and serious adverse events. Overall, there was insufficient evidence of differences between buprenorphine and methadone for these outcomes.

Authors noted other areas where there was insufficient published evidence including: outcomes for people dependent on fentanyl, extended-release buprenorphine compared to methadone, effects of dose on treatment retention, needs of different populations and how these might impact outcomes, supervised versus unsupervised dosing, and data on clinically relevant outcomes like non-fatal overdose, criminal justice system engagement, and global functioning.

A 2023 Cochrane review evaluated efficacy and safety of interventions to treat alcohol use disorder in low and middle-income countries.[4] Generally, harms related to alcohol use are disproportionally higher in low and middle-income countries compared to high-income countries. Studies note similar trends related to harmful alcohol use for people with lower socioeconomic status who live in high-income countries. While prevalence of any drinking tends to be lower among

low socioeconomic groups, people who report drinking tend to have a more harmful pattern of drinking. Both pharmacologic and psychosocial interventions were included in this review. Of the 66 RCTs included, 6 studies evaluated pharmacological treatment alone and 8 evaluated combined pharmacologic and psychosocial treatment. Drugs included disulfiram, naltrexone, acamprosate, ondansetron, topiramate, gabapentin, baclofen, mirtazapine, and amitriptyline. The primary outcome was harmful alcohol use; secondary outcomes included retention in treatment and adverse effects. Trials were most commonly conducted in India (n=14), Brazil (n=12), Thailand (n=9), South Africa (n=5), and Kenya (n=4). They predominantly included male patients (median enrollment of 89% for trials that recruited both men and women). Data was limited by substantial heterogeneity in study design. Risk of bias was high for all interventions primarily from lack of blinding, high attrition rates, and selective outcome reporting. Duration of trials was relatively short (6 months for most trials) and many outcomes were evaluated using measures that have not been validated. Data may be most applicable to Medicaid members who have immigrated to Oregon. Results from the analysis are outlined here:

- There is low quality evidence that combination use of pharmacologic and psychosocial interventions are more effective at reducing harmful alcohol use compared to psychosocial interventions alone (standardized mean difference [SMD] = -0.43, 95% CI -0.61 to -0.24; I^2= 0%; n=475, 4 RCTs). Drugs evaluated in this analysis included naltrexone, disulfiram, ondansetron, and topiramate. Remission was slightly improved with combination pharmacological and psychosocial treatment compared to psychosocial interventions alone (RR=1.19, 95% CI 1.01 to 1.40; I2=18%; n = 462, 4 RCTs).
- There is insufficient evidence to determine if pharmacologic treatment alone reduces harmful alcohol use. No RCTs evaluating pharmacologic treatments assessed this outcome compared to placebo or another active treatments.
- Two trials compared acamprosate to another active therapy (baclofen, naltrexone, or disulfram). These studies found higher rates of relapse and lower rates of remission for members receiving acamprosate compared to another pharmacologic treatment (RR = 0.58, 95% CI 0.42 to 0.79; I^2=15%, 2 RCTs, n=171, insufficient evidence).
- Retention in treatment did not differ with acamprosate or gabapentin compared to placebo (RR 1.13; 95% CI 0.89 to 1.44; I^2=46%; n=247; 3 RCTs, low quality evidence) or with the combination of pharmacologic therapy and psychosocial interventions compared to psychosocial interventions alone (RR = 1.15, 95% CI 0.95 to 1.40, n=363, 3 RCTs, moderate quality evidence).

A 2023 Cochrane review evaluated efficacy of baclofen for alcohol use disorder.[3] Of the 17 RCTs included in the review, baclofen was compared to acamprosate or naltrexone in only 2 studies each.[3] Overall authors found insufficient evidence that baclofen may increase the risk of relapse (RR 2.50; 95% CI 1.12 to 5.56; n=60; 1 RCT) and decrease the number of people with an adverse event (RR 0.35; 95% CI 0.15 to 0.80; n=80; 2RCTs) compared to naltrexone.[3] There was no difference in any efficacy or safety outcomes when comparing baclofen to acamprosate based on one small RCT (n=60).[3] Baclofen tablets are available as a preferred muscle relaxant in FFS. Guidelines updated in 2021 from the VA/DOD recommend against use of baclofen for alcohol use disorder based on evidence from 2 RCTs which provided low quality evidence for efficacy but had inconsistent results for alcohol consumption outcomes.[6]

A 2022 Cochrane review evaluated treatments for management of disordered and problem gambling.[2] Treatments evaluated in this review included mood stabilizers, antidepressants, antipsychotics, and opioid antagonists. Studies were excluded if they evaluated efficacy of combination pharmacotherapy and psychosocial therapy. The primary outcome was reduction in severity of gambling symptoms. This summary focuses on data for opioid antagonists, which are included in this PDL class. Oral naltrexone was evaluated in 4 studies and 2 studies evaluated nalmefene. Most studies had risk of bias concerns, and there was a large amount of statistical heterogeneity across studies.[2] Duration of trials was on average 10 to 16 weeks and symptom severity was evaluated using a variety of clinician or self-reported measures.[2] Compared to placebo, opioid antagonists reduced mean gambling severity symptoms (SMD 0.46; 95% CI 0.74 to 0.19; n=259; 3 RCTs; low quality evidence). A standardized mean difference of 0.46 generally represents a medium effect size.[2] However, there was no difference in responder status (assessed by gambling abstinence or improvement on other various measures) with opioid antagonists compared to placebo (RR 1.65; 95% CI 0.86 to 3.14; n=562; 4 RCTs; very low quality evidence).[2] Low quality evidence from a single RCT (n=77) also showed opioid antagonists improved depressive

symptoms (SMD 0.76; 95% CI 1.29 to 0.23), anxiety symptoms (SMD 1.36; 95% CI 1.96 to 0.83), and functional impairment (SMD 0.53; 95% CI 1.06 to 0.01) at 18 weeks compared to placebo.[2] There was no studies assessing gambling expenditure, gambling frequency, or time spent gambling. There was insufficient information to compare nalmefene and naltrexone, to explore effects of different doses, or examine long-term outcomes. Authors of the review concluded that there is preliminary support for opioid antagonists for reducing gambling symptom severity, but not response to treatment in the short-term.[2] The magnitude of benefit remains uncertain and is likely to change with additional research.[2]

After review, 7 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
No new high quality guidelines were identified.

New Formulations:
In May 2023, the FDA approved Brixadi™, an extended-release subcutaneous buprenorphine injection that can be administered monthly or weekly. RCTs evaluating efficacy and safety of this formulation are detailed in **Table 1**. The primary phase 3 trial used for FDA approval evaluated subcutaneous buprenorphine compared to sublingual buprenorphine/naloxone tablets for outcomes of opioid-negative urine drug screens, self-reported opioid use, and retention in treatment.[5] Outcomes were assessed at a variety of time points that were defined *a priori* in conjunction with regulatory authorities.[5] Subcutaneous buprenorphine was non-inferior to sublingual buprenorphine/naloxone for all primary and key secondary endpoints including response rate, mean percent of opioid-negative urine drug screens from weeks 1 to 24, and treatment retention.[5] Of the participants randomized, 69% of people given subcutaneous buprenorphine and 72.6% of people given sublingual buprenorphine/naloxone completed the 24 week randomized period. For efficacy outcomes, missing data was imputed as a positive urine drug screen.

Safety outcomes included severe adverse events, overdose, hospitalization, and discontinuation due to adverse events. People randomized to sublingual buprenorphine had a numerically higher rate of severe adverse events (7% vs. 2.8%), nonfatal serious events (6% vs. 2.3%), hospitalizations (5.6% vs. 1.4%), and drug overdoses (2.3% vs. 0%) when compared to people receiving subcutaneous buprenorphine.[5] People randomized to subcutaneous buprenorphine had numerically more treatment discontinuations due to adverse events (3.3% vs. 1.4%) compared to sublingual buprenorphine.[5] The most common adverse events included injection-site reactions (pain, pruritus, erythema), headache, constipation, and nausea.

A long-term observational study also evaluated safety and tolerability of extended-release buprenorphine over 12 months.[7] Of the 227 people enrolled, 84% (n=190) switched from sublingual buprenorphine treatment.[7] Patients with OUD were excluded if they had comorbid substance use disorder for a different substance other than opioids or had comorbid chronic pain requiring opioid therapy. About 56% of people enrolled were in the United States, and about 26% were previously arrested.[7] Heroin was the primary opioid of use for 59% of patients.[7] Serious adverse events occurred in 5% (n=12) of participants and 2% (n=5) of patients discontinued treatment due to an adverse event.[7] The most common adverse events were injection site reactions.

An open-label RCT conducted in Australia evaluated patient-reported outcomes associated with extended-release subcutaneous buprenorphine compared to daily sublingual therapy (**Table 1**).[8] The trial primarily enrolled participants with OUD, primarily people who were already on therapy with sublingual buprenorphine and were willing to continue with treatment for the duration of the trial. The primary outcome was treatment satisfaction at 24 weeks using the Treatment Satisfaction Questionnaire for Medication (TSQM) Global Satisfaction Score (range 0-100 with higher scores indicating more satisfaction).[8] The TSQM

score evaluates 3 categories including effectiveness, side effects and convenience. The minimum clinically important difference for this score was not reported. Average satisfaction scores were 71 and 74 points at baseline for subcutaneous and sublingual groups, respectively.[8] After 24 weeks, scores had increased to 82 points for extended-release subcutaneous buprenorphine compared to 73 points with sublingual buprenorphine (MD 8.2 points; 95% CI 1.7-14.6; p=0.01).[8] This difference was driven primarily by the subcategory evaluating convenience. Secondary outcomes included treatment satisfaction using a variety of other scales, treatment retention and illicit opioid use evaluated by UDS. However, the study was not powered to determine differences in these secondary outcomes.

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

References:

1. Degenhardt L, Clark B, Macpherson G, et al. Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomised and observational studies. *The lancet Psychiatry.* 2023;10(6):386-402.
2. Dowling N, Merkouris S, Lubman D, Thomas S, Bowden-Jones H, Cowlishaw S. Pharmacological interventions for the treatment of disordered and problem gambling. *The Cochrane database of systematic reviews.* 2022;9:CD008936.
3. Agabio R, Saulle R, Rosner S, Minozzi S. Baclofen for alcohol use disorder. *The Cochrane database of systematic reviews.* 2023;1:CD012557.
4. Greene MC, Kane J, Alto M, et al. Psychosocial and pharmacologic interventions to reduce harmful alcohol use in low- and middle-income countries. *The Cochrane database of systematic reviews.* 2023;5:CD013350.
5. Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. *JAMA Intern Med.* 2018;178(6):764-773.
6. The Department of Veterans Affairs and the Department of Defense. VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF SUBSTANCE USE DISORDERS. 2021.
7. Frost M, Bailey GL, Lintzeris N, et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. *Addiction (Abingdon, England).* 2019;114(8):1416-1426.
8. Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine: A Randomized Clinical Trial. *JAMA network open.* 2021;4(5):e219041.
9. Jutras-Aswad D, Le Foll B, Ahamad K, et al. Flexible Buprenorphine/Naloxone Model of Care for Reducing Opioid Use in Individuals With Prescription-Type Opioid Use Disorder: An Open-Label, Pragmatic, Noninferiority Randomized Controlled Trial. *The American journal of psychiatry.* 2022;179(10):726-739.
10. Brixadi (buprenorphine) extended-release injection for subcutaneous use. [package labeling]. Plymouth Meeting, PA: Braeburn Inc; May 2023.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
acamprosate calcium	ACAMPROSATE CALCIUM	TABLET DR	ORAL	Y
buprenorphine	SUBLOCADE	SOLER SYR	SUBCUTANEOUS	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	FILM	SUBLINGUAL	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	FILM	SUBLINGUAL	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	TAB SUBL	SUBLINGUAL	Y
buprenorphine HCl/naloxone HCl	ZUBSOLV	TAB SUBL	SUBLINGUAL	Y
naltrexone HCl	DEPADE	TABLET	ORAL	Y
naltrexone HCl	NALTREXONE HCL	TABLET	ORAL	Y
naltrexone HCl	REVIA	TABLET	ORAL	Y
naltrexone microspheres	VIVITROL	SUS ER REC	INTRAMUSCULAR	Y
buprenorphine	BRIXADI	SOLER SYR	SUBCUTANEOUS	V
buprenorphine HCl	BUPRENORPHINE HCL	TAB SUBL	SUBLINGUAL	V
disulfiram	DISULFIRAM	TABLET	ORAL	V
lofexidine HCl	LUCEMYRA	TABLET	ORAL	N

Appendix 2: New Comparative Clinical Trials

A total of 165 citations were manually reviewed from the initial literature search. After further review, all except 3 randomized controlled trials were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). These remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome(s)	Results	Notes/Limitations
Jutras-Aswad, et al, 2022.[9] NCT03033732 Phase 4, OL, MC, NI, RCT N=272 24 weeks	1. Buprenorphine/ naloxone, flexible dosing from 4 to 24 mg/day (n=138) 2. Methadone, flexible dosing from 30 mg to 120 mg/day (n=134) Take home doses were allowed after 2-3 months of supervised ingestion for methadone and after 2	Adults with prescription OUD People with pain requiring opioids or people who primarily used heroin were excluded. Canada Enrollment from October 2017 to March	Proportion of opioid-free urine drug screens over 24 weeks (NI margin of 15%)	Proportion of opioid-free UDS 1. 24% (SD 34.4) 2. 18.5% (SD 30.5) MD 5.6%; 95% CI -0.3 to ∞ P=0.040 NI established Various sensitivity analyses with different populations had similar results.	<u>Internal Validity</u> An accidental protocol deviation affected allocation at 4 sites (14.7% of enrolled participants). High and differential attrition between groups (41% methadone and & 49% buprenorphine/naloxone groups). Missing data from UDS prior to March 2020 were considered positive. After the pandemic, visits were conducted by telephone and no UDS were performed. Values were considered missing at random.

<table>
<tr><td></td><td>weeks for buprenorphine/ naloxone</td><td>2020. Follow-up ended July 2020.</td><td></td><td></td><td><u>Applicability:</u> Follow-up visits occurred every 2 weeks and participants were compensated $40 per visit. Protocols for take home medications may differ between Canada and the United States.</td></tr>
<tr><td>Lofwall, et al.[5]

NCT02651584

DB, double-dummy, NI, phase 3 RCT

N=428

24 weeks</td><td>1. buprenorphine SC weekly for 12 weeks then monthly
2. buprenorphine/naloxone SL tablets daily

Patients who tolerated one 4mg SL buprenorphine dose were randomized</td><td>Adults with moderate to severe OUD
- 61% male
- Mean age: 34 years
- Primarily heroin use: 70-71%
- COWS score: 12
- SOWS score: 31-32
- Fentanyl positive UDS:
o SC: 29%
o SL: 23%

35 sites in the US from December 2015 to October 2016

Exclusion criteria:
- MOUD in prior 60 days
- Chronic pain requiring opioids
- AIDS
- Suicidal ideation or behavior
- Prolonged QTc or risk of torsades de pointes
- ALT/AST >3x ULN
- Bilirubin or serum creatinine >1.5x ULN</td><td><u>Primary (NI margin)</u>
- Response rate* (10%)
- Mean percent of opioid-negative UDS at 1-24 weeks (11%)
<u>Secondary</u>
- Mean percent of opioid-negative samples examined by CDF** at 4-24 weeks (5%)
- Study retention (15%)</td><td><u>Response rate</u>
1. 37 (17.4%)
2. 31 (14.4%)
Difference: 3.0% (95% CI -4.0 to 9.9); p<0.001 for NI

<u>Mean % Negative UDS at 1-24 weeks</u>
1. 35.1% (SD 2.5)
2. 28.4% (SD 2.5)
Difference: 6.7% (95% CI -0.1 to 13.6); p<0.001 for NI

<u>Retention</u>
1. 147 (69%)
2. 156 (72.6%)
Difference -3.5% (95% CI -12.2 to 5.1); p=0.006 for NI

<u>Mean % negative (CDF) at 4-24 weeks</u>
1. 35.1% (SE 2.5)
2. 26.7% (SE 2.5)
P=0.009 for NI</td><td>Non-inferiority established for primary endpoints.

<u>Internal Validity</u>
Randomization via a central system, but baseline characteristics differed for:
<table><tr><td></td><td>SL</td><td>SC</td></tr><tr><td>male</td><td>66%</td><td>57%</td></tr><tr><td>employment</td><td>33%</td><td>35%</td></tr><tr><td>history of arrest</td><td>67%</td><td>61%</td></tr><tr><td>non-opioid drug use</td><td>69%</td><td>73%</td></tr><tr><td>Fentanyl use</td><td>23%</td><td>29%</td></tr></table>Staff administering SC injections were unblinded as appearance of the injection was not identical to placebo.
Attrition: ITT analysis used. 26% of UDS were missing and imputed as positive for illicit opioids.

<u>Applicability</u>
Frequent provider visits (e.g., weekly) and attendance stipends provided to patients may increase adherence and treatment retention and may not be reflective of current clinical practice. Adherence to sublingual tablets was not assessed. Only one treatment site was primary-care based.</td></tr>
</table>

<table>
<tr>
<td>Lintzeris, et al. 2021.[8]

OL, MC, RCT

N=119

Duration: 24 weeks</td>
<td>1. Buprenorphine SC up to 32 mg weekly or 160 mg monthly (n=60)
2. Buprenorphine SL (most commonly with naloxone) up to 32 mg daily (n=59)</td>
<td>Adults with opioid dependence who were established on SL buprenorphine treatment
- Baseline TSQM score: 71-74
- Illicit opioid use: 38-32%
- Age: 44-45 yrs
- Duration of OUD: 19-20 yrs

Australia
October 2018 to September 2019</td>
<td><u>Primary</u>
Treatment satisfaction score at 24 weeks (TSQM Global Satisfaction Score; range 0-100 with higher scores indicating more satisfaction)

<u>Select secondary</u>
Treatment retention

Illicit opioid use by UDS</td>
<td>Treatment satisfaction at week 24 (baseline score 71-73)
1. 82.5 (SD 2.3)
2. 74.3 (SD 2.3)
MD 8.2 (95% CI 1.7-14.6) p=0.01

Treatment retention
1. 53 (88.3%)
2. 56 (93.3%)

Illicit opioid use by UDS
1. 69.9% (95% CI 60.6%-79.3%)
2. 73.5% (95%CI 64.1%-82.9%)
Not significant</td>
<td>Higher global treatment satisfaction with SC forms of buprenorphine compared to SL forms. The minimum clinically important difference for TSQM score was not reported.

<u>Internal Validity</u>
OL study design may increase risk of performance bias. Differences in study groups at baseline may increase risk of selection bias.
<table>
<tr><td></td><td>SL</td><td>SC</td></tr>
<tr><td>Heroin use</td><td>54%</td><td>73%</td></tr>
<tr><td>Hepatitis C</td><td>36%</td><td>57%</td></tr>
<tr><td>Amphetamine use</td><td>20%</td><td>40%</td></tr>
<tr><td>Depression</td><td>61%</td><td>48%</td></tr>
</table>
<u>Applicability</u>
Provider visits monthly and psychosocial interventions were provided in accordance with local guidelines. Possible differences in study setting between Australia & the United States.</td>
</tr>
</table>

*Responder defined as no illicit opioid use by UDS and self-report at pre-specified time points which included at least 2 of 3 assessments from 9 to 11 weeks, at week 12, and at least 5 of 6 assessments from 12 to 24 weeks including weeks 21 to 24.

**The cumulative distribution function of the percent of negative opioid assessments included data from urine drug screens and self-reports for negative illicit opioid use.[10] This type of analysis is often used when there is a lack of consensus on a responder threshold. It is intended to evaluate and show a graphical representation of a variety of responder thresholds. Treatment groups generally differentiated themselves at lower responder thresholds. If treatment response was defined as ≥80% negative opioid assessments, there was no difference between groups.[10]

Abbreviations: AIDS = acquired immunodeficiency syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDF = cumulative distribution function; CI = confidence interval; COWS = clinical opiate withdrawal scale; DB = double-blind; ITT = intention to treat; MC = multicenter; MD = mean difference; MOUD = medication for opioid use disorder; OL = open label; OUD = opioid use disorder; NI = non-inferiority; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; SE = standard error; SL = sublingual; SOWS = subjective opiate withdrawal scale; TSQM = Treatment Satisfaction Questionnaire for Medication; UDS = urine drug screen; ULN = upper limit of normal; yrs = years

Appendix 3: Abstracts of Comparative Clinical Trials

Jutras-Aswad D, Le Foll B, Ahamad K, et al. Flexible Buprenorphine/Naloxone Model of Care for Reducing Opioid Use in Individuals With Prescription-Type Opioid Use Disorder: An Open-Label, Pragmatic, Noninferiority Randomized Controlled Trial. *The American journal of psychiatry.* 2022;179(10):726-739.

OBJECTIVE: Extensive exposure to prescription-type opioids has resulted in major harm worldwide, calling for better-adapted approaches to opioid agonist therapy. The authors aimed to determine whether flexible take-home buprenorphine/naloxone is as effective as supervised methadone in reducing opioid use in prescription-type opioid consumers with opioid use disorder.

METHODS: This seven-site, pan-Canadian, 24-week, pragmatic, open-label, noninferiority, two-arm parallel randomized controlled trial involved treatment-seeking adults with prescription-type opioid use disorder. Participants were randomized in a 1:1 ratio to treatment with sublingual buprenorphine/naloxone (target dosage, 8 mg/2 mg to 24 mg/6 mg per day; flexible take-home dosing) or oral methadone (=60-120 mg/day; closely supervised). The primary outcome was the proportion of opioid-free urine drug screens over 24 weeks (noninferiority margin, 15%). All randomized participants were analyzed, excluding one who died shortly after randomization, for the primary analysis (modified intention-to-treat analysis).

RESULTS: Of 272 participants recruited (mean age, 39 years [SD=11]; 34.2% female), 138 were randomized to buprenorphine/naloxone and 134 to methadone. The mean proportion of opioid-free urine drug screens was 24.0% (SD=34.4) in the buprenorphine/naloxone group and 18.5% (SD=30.5) in the methadone group, with a 5.6% adjusted mean difference (95% CI=-0.3, +). Participants in the buprenorphine/naloxone group had 0.47 times the odds (95% CI=0.24, 0.90) of being retained in the assigned treatment compared with those in the methadone group. Overall, 24 drug-related adverse events were reported (12 in the buprenorphine/naloxone group [N=8/138; 5.7%] and 12 in the methadone group [N=12/134; 9.0%]) and mostly included withdrawal, hypogonadism, and overdose.

CONCLUSIONS: The buprenorphine/naloxone flexible model of care was safe and noninferior to methadone in reducing opioid use among people with prescription-type opioid use disorder. This flexibility could help expand access to opioid agonist therapy and reduce harms in the context of the opioid overdose crisis.

Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. *JAMA Intern Med.* 2018;178(6):764-773.

Importance: Buprenorphine treatment for opioid use disorder may be improved by sustained-release formulations.

Objective: To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is noninferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder.

Design, Setting, and Participants: This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder.

Interventions: Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group).

Main Outcomes and Measures: Primary end points tested for noninferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21-24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4-24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated noninferiority.

Results: A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (n = 215) or the SC-BPN group (n = 213). The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0% difference (95% CI, -4.0% to 9.9%; P < .001). The proportion of opioid-negative urine samples was 1099 of 3870 (28.4%) for the SL-BPN/NX

group and 1347 of 3834 (35.1%) for the SC-BPN group, a 6.7% difference (95% CI, -0.1% to 13.6%; P < .001). The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group (0; P = .004). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.

Conclusions and Relevance: Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use. These data suggest that depot buprenorphine is efficacious and may have advantages.

Trial Registration: ClinicalTrials.gov Identifier: NCT02651584.

Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine: A Randomized Clinical Trial. *JAMA network open.* 2021;4(5):e219041.

Importance: Patient-reported outcomes in the treatment of opioid dependence may differ between subcutaneously administered depot buprenorphine and daily sublingual buprenorphine.

Objective: To compare patient satisfaction between depot buprenorphine and sublingual buprenorphine in adult outpatients with opioid dependence.

Design, Setting, and Participants: This open-label, randomized clinical trial was conducted among adult patients with opioid dependence at 6 outpatient clinical sites in Australia from October 2018 to September 2019. Data analysis was conducted from October 2019 to May 2020.

Interventions: Participants were randomized to receive treatment with weekly or monthly depot buprenorphine or daily sublingual buprenorphine over 24 weeks.

Main Outcomes and Measures: The primary end point was the difference in global treatment satisfaction, assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4 (range, 0-100; higher score indicates greater satisfaction) at week 24. Secondary end points included other patient-reported outcomes, including quality of life, treatment burden, and health-related outcomes, as well as measures of opioid use, retention in treatment, and safety.

Results: A total of 119 participants (70 [58.8%] men; mean [SD] age, 44.4 [10.5] years) were enrolled, randomized to, and received either depot buprenorphine (60 participants [50.4%]) or sublingual buprenorphine (59 participants [49.6%]). From the initial sample of 120, a participant (0.8%) in the sublingual buprenorphine group withdrew consent and did not receive study treatment. All participants were receiving sublingual buprenorphine when enrolled. The mean TSQM global satisfaction score was significantly higher for the depot group compared with the sublingual group at week 24 (mean [SE] score, 82.5 [2.3] vs 74.3 [2.3]; difference, 8.2; 95% CI, 1.7 to 14.6; P = .01). Improved outcomes were also observed for several secondary end points after treatment with depot buprenorphine (eg, mean [SE] treatment burden assessed by the Treatment Burden Questionnaire global score, on which lower scores indicate lower burden: 13.2 [2.6] vs 28.6 [2.5]; difference, -15.4; 95% CI, -22.6 to -8.2; P < .001). Thirty-nine participants (65.0%) in the depot buprenorphine group experienced 117 adverse drug reactions, mainly injection site reactions of mild intensity following subcutaneous administration, and 12 participants (20.3%) in the sublingual buprenorphine group experienced 21 adverse drug reactions. No participants withdrew from the trial medication or the trial due to adverse events.

Conclusions and Relevance: In this study, participants receiving depot buprenorphine reported improved treatment satisfaction compared with those receiving sublingual buprenorphine. The results highlight the application of patient-reported outcomes as alternative end points to traditional markers of substance use in addiction treatment outcome studies.

Trial Registration: anzctr.org.au Identifier: ANZCTR12618001759280.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to August 10, 2023

1	acamprosate.mp. or exp Acamprosate/	988
2	lofexidine.mp.	225
3	exp buprenorphine/ or exp buprenorphine, naloxone drug combination/	7391
4	exp Naltrexone/	8676
5	exp Disulfiram/	3735
6	exp substance-related disorders/ or alcoholism/	311045
7	exp Alcohol Deterrents/	13140
8	exp Prescription Drug Misuse/	17229
9	1 or 2 or 3 or 4 or 5	19973
10	6 or 7 or 8	320659
11	9 and 10	17117
12	limit 11 to yr="2022 -Current"	1197
13	limit 12 to (english language and humans)	1085
14	limit 13 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	165

Appendix 5: Key Inclusion Criteria

Population	People with substance use disorder
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1
Outcomes	Quality of life, function, maintenance in treatment, abstinence, hospitalizations, mortality, non-fatal overdose
Setting	Outpatient

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 diagnosis funded by the OHP?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. 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 #4	**No:** Go to #8
4. Is there documentation of inadequate symptom improvement with 32 mg daily?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there recent documentation (within past month) from a urine drug screen indicating that buprenorphine is being taken?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Has the prescriber evaluated the PDMP in the past 3 months?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. 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
8. 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 #9
9. 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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Drug Class Literature Scan: Antipsychotics, Parenteral

Date of Review: October 2023

Date of Last Review: February 2022
Literature Search: 01/01/2022 – 07/21/2023

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

Plain Language Summary:

- The purpose of this review is to scan recently published evidence for injectable antipsychotic medicines.
- Oral antipsychotics are used to relieve symptoms such as delusions or hallucinations that can occur in people with schizophrenia or bipolar disorder. If a person has a hard time remembering to take the oral forms of these medicines, they can be started on a long-acting injection that can be given anywhere from every 2 weeks to every 6 months (depending on the prescribed medication) by a health care provider.
- Six different antipsychotics (fluphenazine, haloperidol, aripiprazole, olanzapine, paliperidone, and risperidone) are available to be administered as an injection. These medicines can help prevent a relapse or admission to the hospital.
- Side effects reported with antipsychotics include tremors, restlessness, muscle stiffness, dizziness, weight gain, diabetes, or sleepiness. Using the lowest dose that helps symptoms in order to limit the side effects.
- The Oregon Health Plan provides open access to injectable antipsychotic medicines for members with a valid prescription.

Conclusions:

- Since the last Pharmacy and Therapeutics (P & T) Committee review two systematic reviews[1],[2] and one guideline[3] were published. New formulations of long-acting risperidone and aripiprazole injections received Food and Drug Administration (FDA) approval.
- A 2021 systematic review and meta-analysis evaluated comparative evidence for LAI antipsychotics and oral antipsychotics.[2] Long acting injectable antispychotics (LAIs) were associated with a lower risk of hospitalization or relapse than oral antipsychotics in each of 3 study designs (randomized controlled studies [RCTs]: 29 studies, 7,833 patients, relative risk [RR] 0.88, 95% confidence interval [CI] 0.79 to 0.99, p=0.033; cohort studies: 44 studies, 106,136 patients, RR 0.92, 95% CI 0.88 to 0.98, p=0.0044; pre–post studies: 28 studies, 17,876 patients, RR 0.44, 95% CI 0.39 to 0.51, p<0.0001).[2]
- A 2022 CADTH systematic review evaluated evidence for safety and efficacy of second-generation LAI antipsychotic medications versus first-generation LAI antipsychotics or second-generation oral antipsychotics in patients with schizophrenia and/or bipolar disorders.[1] The evidence in this report is low quality because limited statistical information was adequately reported in the included studies.[1] No difference in treatment success or adverse events were identified between paliperidone palmitate and haloperidol decanoate LAI formulations (low quality of evidence).[1] No differences in discontinuation of treatment or hospitalization rates were noted between: risperidone LAI versus haloperidol LAI administered concurrently with fluphenazine LAI; risperidone LAI and any oral second-generation antipsychotics; olanzapine LAI and oral olanzapine; and aripiprazole LAI and oral aripiprazole (low quality of evidence).[1] No differences in adverse events were observed between aripiprazole LAI and oral aripiprazole (low quality of evidence).[1] Hospitalization rates appear

higher for patients who received haloperidol LAI compared with those who received risperidone LAI or aripiprazole LAI (low quality of evidence; no statistical comparison was reported).[1] Patients on olanzapine LAI had a shorter number of hospital days than those on oral olanzapine (low quality of evidence; no statistical comparison was reported).[1]

- In 2023, the Department of Veterans Affairs and the Department of Defense (VA/DoD) updated their guidance for management of schizophrenia.[3] The VA/DoD now recommends LAI antipsychotics to improve medication adherence in individuals with schizophrenia (weak recommendation; very low quality of evidence).[3] Limitations to the adherence evidence for LAIs include small study sample sizes, imprecision across studies, and risk of bias from lack of blinding.[3] The benefits of LAIs, including greater adherence and lower rates of hospitalization observed over oral medications, may outweigh potential risk of adverse events and the resource training needed with LAIs.[3]
- In January 2023, the FDA approved a new extended release intramuscular (IM) formulation of risperidone (RYKINDO) injection.[4] RYKINDO is indicated for treatment of schizophrenia and as monotherapy or as an adjunctive therapy to lithium or valproate for the maintenance of bipolar I disorder in adults.[4] The recommended dose is 25 mg IM every 2 weeks administered in the gluteal muscle by a healthcare provider.[4]
- The FDA approved a new extended-release IM formulation of aripiprazole (ABILIFY ASIMTUFII) injection in April 2023.[5] This product is indicated for treatment of schizophrenia and as maintenance monotherapy treatment of bipolar I disorder in adults.[5] The recommended dose is 960 mg IM once every 2 months in the gluteal muscle by a healthcare professional.[5]
- In April 2023 the FDA approved a new extended-release subcutaneous (SC) formulation of risperidone (UZEDY) injection.[6] This medication is indicated for treatment of schizophrenia in adults.[6] Dosing ranges from 50 mg to 125 mg SC once a month or 100 mg to 250 mg SC every 2 months administered in the abdomen or upper arm by a healthcare professional.[6]

Recommendations:

- No changes to the PDL are recommended based on the clinical evidence.
- Evaluate medication costs in executive session.

Summary of Prior Reviews and Current Policy

- The Oregon P&T committee last reviewed evidence for the comparative effectiveness of parenteral antipsychotic products in February 2022.
- In the Oregon Health Plan, antipsychotic medications are exempt from traditional PDL and prior authorization (PA) requirements. However, clinical PA criteria, which address safety concerns or medically inappropriate use, may be implemented. The parenteral antipsychotics included on the Oregon PDL are presented in **Appendix 1.** Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and trifluoperazine are preferred on the PDL. A summary of LAI antipsychotic medications is presented in **Table 1**.
- During the second quarter of 2023, paliperidone, aripiprazole, risperidone, fluphenazine decanoate, and haloperidol decanoate were 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 major depressive disorder (MDD). There is insufficient evidence to determine if new formulations of LAI aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents.

Table 1. Long-Acting Injectable Antipsychotic Medications

Generic Name	Brand Name	Route	Frequency	Need for Initial Oral Supplementation
First-generation Agents				
Fluphenazine decanoate	PROLIXIN	IM	2-4 weeks	Decrease oral dose by half after first injection, then discontinue with second injection
Haloperidol decanoate	HALDOL	IM	4 weeks	Taper and discontinue after 2 to 3 injections
Second-generation Agents				
Aripiprazole monohydrate	ABILIFY MAINTENA	IM	4 weeks	Continue oral dose for 14 days after initial injection
Aripiprazole lauroxil	ARISTADA INITIO	IM	Single initiation dose: not for repeated dosing	Must be administered in conjunction with aripiprazole 30mg oral dose
Aripiprazole lauroxil	ARISTADA	IM	4, 6, or 8 weeks (dose dependent)	Give 21 days of stabilized oral aripiprazole in conjunction with Aristada injection. (Conversion of oral aripiprazole to IM aripiprazole is based on current oral aripiprazole dose.)
Aripiprazole monohydrate	ABILIFY ASTIMTUFII	IM	8 weeks	Establish tolerability with oral aripiprazole prior to initiating extended-release injection. Give with oral aripiprazole 10 to 20 mg per day for 14 consecutive days after initial injection.
Olanzapine pamoate	ZYPREXA RELPREVV	IM	2 or 4 weeks (dose dependent)	Not required
Paliperidone palmitate	INVEGA SUSTENNA	IM	4 weeks	Not required
Paliperidone palmitate	INVEGA TRINZA	IM	12 weeks	Not applicable: change to Trinza after at least 4 maintenance doses of Sustenna
Paliperidone palmitate	INVEGA HAFYERA	IM	24 weeks	Not applicable: establish dose with 4- and 12-week IM preparations prior to conversion to 6-month regimen
Risperidone microspheres	RISPERDAL CONSTA	IM	2 weeks	Continue oral risperidone for 3 weeks after initial injection.
Risperidone	PERSERIS	SC	4 weeks	Establish tolerability with oral risperidone prior to initiating long-acting injection.
Risperidone	UZEDY	SC	4-8 weeks	Establish tolerability with oral risperidone prior to initiating long-acting injection.
Risperidone	RYKINDO	IM	2 weeks	Establish tolerability with oral risperidone prior to initiating long-acting injection. Continue oral risperidone for 7 days after initial injection.
Abbreviations: IM = intramuscular; mg = milligram; SC = subcutaneous				

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

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

New Systematic Reviews:
Long-Acting Injectable Versus Oral Antipsychotics for Maintenance Treatment of Schizophrenia
A 2021 systematic review and meta-analysis evaluated comparative evidence for LAI antipsychotics and oral antipsychotics.[2] Three study designs were included in the analysis: RCTs, cohort trials, and pre-post studies.[2] The authors identified 137 studies (n=397,319) which met the inclusion criteria (32 RCTs, 65 cohort studies, and 40 pre–post studies).[2] The quality of studies in terms of risk of bias varied across study designs and within each study design from low to high.[2] Long acting injectable antispychotics were associated with a lower risk of hospitalization or relapse than oral antipsychotics in each of the three study designs (RCTs: 29 studies, 7,833 patients, RR 0.88, 95% CI 0.79 to 0.99; p=0.033; cohort studies: 44 studies, 106,136 patients, RR 0.92, 95% CI 0.88 to 0.98, p=0.0044; pre–post studies: 28 studies, 17,876 patients, RR 0.44, 95% CI 0.39 to 0.51, p<0.0001).[2] In all other outcomes related to effectiveness, efficacy, safety, quality of life, and cognitive function, LAIs were more beneficial than oral antipsychotics in 60 (18.3%) of 328 comparisons, not different in 252 (76.8%) comparisons, and less beneficial in 16 (4.9%) comparisons when analyzed by study design.[2] Significant heterogeneity was observed across all 3 study designs.[2] Publication biases were apparent in cohort and pre-post studies.[2]

Canadian Agency for Drugs and Technologies in Health: Clinical Effectiveness of Second-Generation Injectable Antipsychotics
A 2022 CADTH systematic review evaluated evidence for safety and efficacy of second-generation LAI antipsychotic medications versus first-generation LAI antipsychotics or second-generation oral antipsychotics in patients with schizophrenia and/or bipolar disorders.[1] Eight publications met inclusion criteria and were comprised of 7 international systematic reviews (Italy, Mexico, Canada, Australia, Germany, South Korea, United States) and 1 RCT conducted in China.[1] The primary outcomes of interest were clinical effectiveness (e.g., adherence to therapy, quality of life, reduction in symptoms, hospital readmission), time to relapse, and safety (e.g. tolerability, adverse effects, relapse).[1] All of the evidence evaluated in the systematic reviews were conducted in adults; 5 focused on populations with schizophrenia and 2 focused on populations with either schizophrenia or bipolar disorder.[1] Long-acting injectable antipsychotics included in the systematic reviews were aripiprazole, olanzapine, paliperidone, risperidone, haloperidol, and fluphenazine. Oral antipsychotics included in the reviews were olanzapine, quetiapine, risperidone, ziprasidone, and paliperidone. Study durations ranged from 2.5 months to 2.5 years.[1] Limitations to the body of evidence identified by the CADTH authors included: very few comparisons of second-generation LAI antipsychotics with first-generation LAI antipsychotics; a lack of statistical findings to form conclusions; unclear comparability across studies due to use of different outcome measures to determine safety and efficacy; and unclear quality of evidence.[1] The conclusions from the CADTH review are as follows:

- When comparing second-generation paliperidone palmitate LAIs and first-generation haloperidol decanoate LAIs, there was no difference in treatment success or adverse events (low quality of evidence).[1]
- When comparing risperidone LAI versus haloperidol decanoate and fluphenazine decanoate injections given together, there was no difference in whether patients discontinue treatment early (low quality of evidence).[1]
- Hospitalization appeared higher for patients who receive haloperidol decanoate LAI compared to those who received risperidone or aripiprazole LAI (low quality of evidence; no statistical comparison was reported).[1]
- There was no difference in hospitalization rates when comparing risperidone LAI versus haloperidol decanoate and fluphenazine decanoate given together (low quality of evidence; no statistical comparison was reported).[1]
- There was no difference between patients who discontinued treatment early when comparing risperidone LAI to any oral second-generation antipsychotics, olanzapine LAI compared to oral olanzapine, or aripiprazole LAI compared to oral aripiprazole (low quality of evidence). There was no difference in adverse events between patients given aripiprazole LAI compared to those given oral aripiprazole(low quality of evidence).[1]
- Patients had a shorter number of hospital days when given olanzapine LAI compared to those who received oral olanzapine (low quality of evidence).[1]

After review, 8 systematic reviews were excluded due to poor quality,[7-9] wrong study design of included trials (e.g., observational),[10-13] comparator (e.g., no control or placebo-controlled),[14] or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Department of Veterans Affairs and the Department of Defense: Management of First-Episode Psychosis and Schizophrenia

In 2023, the VA/DoD updated their guideline for management of schizophrenia.[3] The clinical practice guideline was developed after a systematic review of recent evidence.[3] One systematic review from 2021 (32 RCTs, n=8,577) was identified since the publication of their 2021 guideline.[2] Findings from this systematic review suggest that patients receiving LAI antipsychotics demonstrate higher levels of adherence rates than patients receiving oral antipsychotics, as indicated by statistically significant differences in the mean Medication Adherence Rating Scale and the proportion of patients with at least 75% days of adherence during the treatment period.[2] Of note, only two RCTs with fewer than 100 patients each contributed data to adherence outcomes.[3] Among important outcomes, LAI antipsychotics were associated with fewer hospitalizations than oral antipsychotics; however, no difference occurred in outcomes, such as symptom reduction, quality of life, functional status, and treatment discontinuation.[3]

A recently added recommendation in the guideline is a weak recommendation to offer long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia (quality of evidence = very low.[3] The body of evidence for adherencehad some limitations, including a small sample size, imprecision, and risk of bias because of the lack of blinding of personnel and participants.[3] The benefits of LAIs, including greater adherence and lower rates of hospitalization, slightly outweighed the potential harm of any adverse events, or training needed to administer LAIs.[3]

After review, one guideline was excluded due to poor quality.[15]

New Formulations:

- In January 2023, the FDA approved a new extended-release IM formulation of risperidone (RYKINDO) injection.[4] Extended-release risperidone injection is indicated for treatment of schizophrenia and as monotherapy, or as an adjunctive therapy, to lithium or valproate for the maintenance of bipolar I disorder

in adults.[4] Tolerance to oral risperidone should be established prior to initiating extended-release injections of risperidone.[4] Oral risperidone should be continued for 7 days when initiating RYKINDO.[4] The recommended dose is 25 mg IM every 2 weeks administered in the gluteal muscle by a healthcare provider.[4] Patients not responding to 25 mg may benefit from 37.5 mg or 50 mg.[4] The maximum recommended dose is 50 mg every 2 weeks.[4] In patients with renal or hepatic impairment, a starting dose of 12.5 mg may be appropriate.[4] As with all second generation antipsychotics, the medication has a black boxed warning regarding the risk of increased mortality in elderly patients with dementia-related psychosis.[4] Safety and efficacy of extended-release risperidone were based on clinical trials of risperidone long-acting IM injection (RISPERIDAL CONSTA) and oral risperidone.[4] Safety and effectiveness of RYKINDO have not been established in pediatric patients.[4] RYKINDO as supplied as a refrigerated vial, which contains powder that must be reconstituted with the supplied diluent prior to administration.

- The FDA approved a new extended-release IM formulation of aripiprazole monohydrate (ABILIFY ASIMTUFII) in April 2023.[5] This product is indicated for treatment of schizophrenia and as maintenance monotherapy treatment of bipolar I disorder in adults.[5] For patients naïve to aripiprazole, tolerance should be established with oral aripiprazole for 14 consecutive days prior to initiating treatment with the extended-release injection.[5] The recommended dose is 960 mg IM once every 2 months in the gluteal muscle by a healthcare professional.[5] The dose can be reduced to 720 mg IM in patients with adverse reactions, or poor CYP2D6 metabolizers.[5] As with all second generation antipsychotics, the medication has an FDA black boxed warning regarding the risk of increased mortality in elderly patients with dementia-related psychosis.[5] The safety and efficacy of ABILIFY ASIMTUFII are based on studies of ABILIFY MAINTENA (once monthly IM dosing).[5] Safety and effectiveness of ABILIFY ASIMTUFII have not been established in pediatric patients.[5] ABILIFY ASIMTUFII is supplied as single-dose, prefilled syringe.

- In April 2023, the FDA approved a new extended-release SC formulation of risperidone (UZEDY) injection.[6] This medication is indicated for treatment of schizophrenia in adults.[6] Tolerance to oral risperidone should be established prior to initiating extended-release injections of risperidone.[6] Dosing ranges from 50 mg to 125 mg SC once a month or 100 mg to 250 mg SC every 2 months administered in the abdomen or upper arm by a healthcare professional.[6] Subcutaneous dosing is determined by the established dose of the oral risperidone regimen. In patients with renal or hepatic impairment, the maximum recommended dose is 50 mg SC once monthly.[6] As with all second generation antipsychotics, the medication has a black boxed warning regarding the risk of increased mortality in elderly patients with dementia-related psychosis.[6] The safety and efficacy of UZEDY in adults was based on clinical trials of oral risperidone.[6] Safety and effectiveness of UZEDY have not been established in pediatric patients.[6] UZEDY is supplied as a refrigerated, single-dose, prefilled syringe.

New FDA Safety Alerts: No new FDA safety alerts were issued since the last class review of these medications.

References:

1. Canadian Agency for Drugs and Technologies in Health (CADTH) Clinical Effectiveness Review. Second Generation Injectable Antipsychotics. May 2022. https://www.cadth.ca/clinical-effectiveness-second-generation-injectable-antipsychotics Accessed August 9, 2023.
2. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *The lancet Psychiatry*. 2021;8(5):387-404.

3. VA/DoD Clinical Practice Guideline. (2023). Management of First-Episode Psychosis and Schizophrenia Work Group. Washington, DC: U.S. Government Printing Office. https://www.healthquality.va.gov/guidelines/MH/scz/VADoDCPGSchizophreniaCPG_Final_508.pdf. Accessed August 9, 2023.
4. RYKINDO (risperidone) extended-release subcutaneous injection. Yantai, Shandong Province, China; Shandong Luye Pharmaceutical Co., Ltd. January 2023.
5. ABILIFY ASIMTUFII (aripiprazole) extended-release intramuscular injection. Rockville, MD; Otsuka America Pharmaceutical, Inc. April 2023.
6. UZEDY (risperidone) extended-release subcutaneous injection. Parsippany, NJ; Teva Neuroscience, Inc. April 2023.
7. Okoli CTC, Kappi A, Wang T, Makowski A, Cooley AT. The effect of long-acting injectable antipsychotic medications compared with oral antipsychotic medications among people with schizophrenia: A systematic review and meta-analysis. *Int J Ment Health Nurs.* 2022;31(3):469-535.
8. Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet (London, England).* 2022;399(10327):824-836.
9. Huang MW, Gibson RC, Jayaram MB, Caroff SN. Antipsychotics for schizophrenia spectrum disorders with catatonic symptoms. *Cochrane Database Syst Rev.* 2022;7:CD013100.
10. Baeza I, Fortea A, Ilzarbe D, Sugranyes G. What Role for Long-Acting Injectable Antipsychotics in Managing Schizophrenia Spectrum Disorders in Children and Adolescents? A Systematic Review. *Paediatric drugs.* 2023;25(2):135-149.
11. Lian L, Kim DD, Procyshyn RM, et al. Efficacy of long-acting injectable versus oral antipsychotic drugs in early psychosis: A systematic review and meta-analysis. *Early intervention in psychiatry.* 2022;16(6):589-599.
12. Cristarella T, Castillon G, Nepveu JF, Moride Y. Impact of schizophrenia relapse definition on the comparative effectiveness of oral versus injectable antipsychotics: A systematic review and meta-analysis of observational studies. *Pharmacol Res Perspect.* 2022;10(1):e00915.
13. Benarous X, Cottin G, Lahaye H, et al. Efficacy, Tolerability, and Acceptance of Long-Lasting Antipsychotics in Children and Adolescents: A Systematic Review. *Journal of Child & Adolescent Psychopharmacology.* 2022;32(6):312-327.
14. Wang D, Schneider-Thoma J, Siafis S, et al. Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. *Schizophr Bull.* 2023.
15. Janas-Kozik M, Dudek D, Heitzman J, et al. Polish Psychiatric Association diagnostic and therapeutic management guidelines for patients with early-onset schizophrenia. *Psychiatria Polska.* 2022;56(4):675-695.
16. Xiao L, Zhao Q, Li AN, et al. Efficacy and safety of aripiprazole once-monthly versus oral aripiprazole in Chinese patients with acute schizophrenia: a multicenter, randomized, double-blind, non-inferiority study. *Psychopharmacology.* 2022;239(1):243-251.
17. Najarian D, Sanga P, Wang S, et al. A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia. *Int J Neuropsychopharmcol.* 2021;25(3):238-251.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
aripiprazole	ABILIFY ASIMTUFII	SUSER SYR	IM	Y
aripiprazole	ABILIFY MAINTENA	SUSER SYR	IM	Y
aripiprazole	ABILIFY MAINTENA	SUSER VIAL	IM	Y
aripiprazole lauroxil	ARISTADA	SUSER SYR	IM	Y
aripiprazole lauroxil, submicr.	ARISTADA INITIO	SUSER SYR	IM	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	AMPUL	IJ	Y
chlorpromazine HCl	THORAZINE	AMPUL	IJ	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	VIAL	IJ	Y
fluphenazine HCl	FLUPHENAZINE HCL	VIAL	IJ	Y
haloperidol decanoate	HALDOL DECANOATE 100	AMPUL	IM	Y
haloperidol decanoate	HALDOL DECANOATE 50	AMPUL	IM	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	AMPUL	IM	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	AMPUL	IM	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	VIAL	IM	Y
haloperidol lactate	HALOPERIDOL LACTATE	SYRINGE	IM	Y
haloperidol lactate	HALOPERIDOL LACTATE	VIAL	IJ	Y
paliperidone palmitate	INVEGA HAFYERA	SYRINGE	IM	Y
paliperidone palmitate	INVEGA SUSTENNA	SYRINGE	IM	Y
paliperidone palmitate	INVEGA TRINZA	SYRINGE	IM	Y
risperidone	PERSERIS	SUSER SYR	SQ	Y
risperidone microspheres	RISPERDAL CONSTA	VIAL	IM	Y
olanzapine	OLANZAPINE	VIAL	IM	V
olanzapine	ZYPREXA	VIAL	IM	V
olanzapine pamoate	ZYPREXA RELPREVV	VIAL	IM	V
risperidone	UZEDY	SUSER SYR	SQ	V
ziprasidone mesylate	GEODON	VIAL	IM	V
ziprasidone mesylate	ZIPRASIDONE MESYLATE	VIAL	IM	V

Appendix 2: New Comparative Clinical Trials

A total of 86 citations were manually reviewed from the initial literature search. After further review, 84 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Endpoint	Results	Notes/Limitations
Xiao L, et al.[16] DB, MC, NI RCT 12 weeks	1. Aripriprazole 400 mg IM once monthly Vs. 2. Aripiprazole 10-20 mg oral tablet once daily	-Adults aged 18 to 65 yo with an acute psychotic episode from 15 clinical sites across China -PANSS score ≥ 70 points N=436 (218 in each arm)	Change in PANSS and CGI-S scores from baseline to week 10. Prespecified NI margin: lower bound of 95% CI < -7.5	Change in PANSS from baseline to week 10: 1. -33.6 2. -34.8 LSM Difference = -1.2 (95% CI -4.1 to 1.7; NS) NI met due to lower CI of -4.1 Changes in CGI-S score from baseline to week 10 1. -2.2 2. -2.3 LSM Difference = -0.1 (95% CI -0.3 to 0.1; P=0.357)	-Limited to patients of Chinese descent, cannot generalize results to other races/ethnicities -Noninferiority trial design is not as robust as superiority trial design -Short trial duration This study confirmed the non-inferiority of once monthly aripiprazole to oral aripiprazole based on PANSS score in patients experiencing an acute schizophrenia episode
Najarian D, et al.[17] DB, NI, MC RCT 12 months	1. Paliperidone 350 mg or 525 mg IM every 3 months Vs. 2. Paliperidone 700 mg or 1000 mg IM every 6 months	-Patients aged 18 to 70 yo -Diagnosis of schizophrenia ≥ 6 months prior to study enrollment -Stabilized on maintenance IM paliperidone 1 or 3 months -PANSS score < 70 points N=702, randomized 2:1	-Percent of patients who did not relapse (hospitalized for psychiatric reason, change in PANSS* score > 25%, patient demonstrated self-harm) over 12 months Prespecified NI margin: lower bound of 95% CI < 10%	Percent of patients who did not relapse over 12 months: 1. 94.8% 2. 91.9% Difference -2.9% (95% CI -6.8% to 1.1%; NS) NI met due to lower CI of -6.8%	-Noninferiority trial design is not as robust as superiority trial design This study demonstrated the noninferiority of 6-month paliperidone injection at 700 and 1000 mg equivalent doses in patients with schizophrenia, suggesting comparable efficacy with its 3-monthly equivalent formulation for patients who remained relapse free at the end of the 12-month DB phase.

		1. n=224 2. n=478			

Abbreviations: CGI-S = Clinical Global Impressions – Severity; CI = confidence interval; DB = double blind; IM = intramuscular; LSM = least squares mean; MC = multi-center; NI = noninferiority; NS = not statistically significant; OL = open-label; PANSS = Positive and Negative Syndrome Scale*; RCT = randomized clinical trial; YO = years old

*The neuropsychiatric symptoms of schizophrenia were assessed using the 30-item PANSS scale, which provides a total score (sum of the scores for all 30 items) and scores for 3 subscales: the 7-item positive-symptom (P) subscale, the 7-item negative-symptom (N) subscale, and the 16-item general-psychopathology symptom (G) subscale. Each item is rated on a scale from 1 (absent) to 7 (extreme). The PANSS total score ranges from 30 (absent disease)-210 (more severe neuropsychiatric symptoms of schizophrenia).[17]

Appendix 3: Abstracts of Comparative Clinical Trials

Efficacy And Safety Of Aripiprazole Once-Monthly Versus Oral Aripiprazole In Chinese Patients With Acute Schizophrenia: A Multicenter Randomized, Double Blind, Non-Inferiority Study.[16]

OBJECTIVE: The present study aimed to evaluate the efficacy and safety of aripiprazole once-monthly (AOM) compared to oral aripiprazole in treating acute schizophrenia.

METHODS: This randomized, double blind, non-inferiority study recruited patients from 15 trial sites across China from May 2017 to April 2019. Patients with an acute psychotic episode received AOM at 400 mg or oral aripiprazole at 10-20 mg for 12 weeks. The primary and secondary efficacy endpoints were the difference in scores from baseline to week 10, as assessed on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) scores, respectively.

RESULTS: A total of 436 patients were randomized. Among them, 159/218 (72.9%) and 165/218 (75.7%) in the AOM and oral aripiprazole groups completed 10 weeks of treatment, respectively. The least squares (LS) mean changes from baseline to endpoint (week 10) in PANSS were - 33.6 for the AOM group and - 34.8 in the oral aripiprazole group, respectively, with a difference of - 1.2 (95% CI: - 4.1, 1.7). The non-inferiority margin of AOM to oral aripiprazole was - 4.1, which was above the lower limit of the pre-defined margin. The altered CGI-S score was - 2.2 and - 2.3 in the AOM and oral aripiprazole groups, respectively. The incidence of treatment-emergent adverse events (TEAEs) was similar in both groups. The rate of discontinuation due to TEAEs was 2.3% and 3.2% in the AOM and oral aripiprazole groups, respectively.

CONCLUSIONS: This study confirmed the efficacy and safety of AOM for the treatment of Chinese patients with acute schizophrenia. The non-inferiority of AOM to oral aripiprazole was established, with comparable efficacy and tolerability. These findings suggested that AOM could be used as a treatment option for patients experiencing an acute episode of schizophrenia.

TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT03172871.

A Randomized, Double-Blind, Multicenter, Noninferiority Study Comparing Paliperidone Palmitate 6-Month Versus the 3-Month Long-Acting Injectable in Patients With Schizophrenia[17]

This double blind (DB), randomized, parallel-group study was designed to evaluate efficacy and safety of paliperidone palmitate 6-month (PP6M) formulation relative to paliperidone palmitate 3-month (PP3M) formulation in patients with schizophrenia. Following screening, patients entered an open-label (OL) maintenance phase and received 1 injection cycle of paliperidone palmitate 1-month (PP1M; 100 or 150 mg eq.) or PP3M (350 or 525 mg eq.). Clinically stable patients were randomized (2:1) to receive PP6M (700 or 1000 mg eq., gluteal injections) or PP3M (350 or 525 mg eq.) in a 12-month DB phase; 2 doses of PP6M (corresponding to doses of PP1M and PP3M) were chosen. Overall, 1036 patients were screened, 838 entered the OL phase, and 702 (mean age: 40.8 years) were randomized (PP6M: 478; PP3M: 224); 618 (88.0%) patients completed the DB phase (PP6M: 416 [87.0%]; PP3M: 202 [90.2%]). Relapse rates were PP6M, 7.5% (n = 36) and PP3M, 4.9% (n = 11). The Kaplan-Meier estimate of the difference (95% CI) between treatment groups (PP6M − PP3M) in the percentages of patients who remained relapse free was −2.9% (−6.8%, 1.1%), thus meeting noninferiority criteria (95% CI lower bound is larger than the pre-specified noninferiority margin of −10%). Secondary efficacy endpoints corroborated the primary analysis. Incidences of treatment-emergent adverse events were similar between PP6M (62.1%) and PP3M (58.5%). No new safety concerns emerged. The efficacy of a twice-yearly dosing regimen of PP6M was noninferior to that of PP3M in preventing relapse in patients with schizophrenia adequately treated with PP1M or PP3M.Clinical Trials.gov identifier: NCT03345342

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to July Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to July 31, 2023

1	exp CHLORPROMAZINE/	1912
2	exp HALOPERIDOL/	6489
3	exp FLUPHENAZINE/	344
4	exp ARIPIPRAZOLE/	2895
5	exp Paliperidone Palmitate/	1038
6	exp RISPERIDONE/	6529
7	ziprasidone.mp.	1883
8	Olanzapine/	6224
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	22186
10	exp Schizophrenia/	75019
11	exp Bipolar Disorder/	32276
12	10 or 11	101649
13	9 and 12	8405
14	limit 13 to (english language and humans and yr="2022 -Current")	240
15	limit 14 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	86

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: *10/23 (DM); 2/22 (DM); 9/18 (DM); 9/17; 9/16; 5/05*
Implementation: *TBD; 10/13/16; 11/18/04*

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**
elranatamab-bcmm	ELREXFIO
niraparib and abiraterone acetate	AKEEGA
quizartinib	VANFLYTA
talquetamab-tgvs	TALVEY

Recommendation:

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

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: 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.

Approval Criteria		
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**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**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:** Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #8
8. 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 #9
9. 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 #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria
10. 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 08/31/2023)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

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

Generic Name	Brand Name
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elacestrant	ORSERDU
elotuzumab	EMPLICITI
elranatamab-bcmm	ELREXFIO
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
epcoritamab-bysp	EPKINLY
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
futibatinib	LYTGOBI
gilteritinib	XOSPATA
glasdegib	DAURISMO
glofitamab-gxbm	COLUMVI
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA

Generic Name	Brand Name
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mobecertinib	EXKIVITY
mosunetuzumab-axgb	LUNSUMIO
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib and abiraterone acetate	AKEEGA
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
nivolumab; relatlimab-rmbw	OPDUALAG
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
omidubicel-onlv	OMISIRGE
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN

Generic Name	Brand Name
pralsetinib	GAVRETO
quizartinib	VANFLYTA
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
retifanlimab-dlwr	ZYNYZ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
talquetamab-tgvs	TALVEY
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF

Generic Name	Brand Name
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. New orphan drugs

Generic Name	Brand Name
palovarotene	SOHONOS
pozelimab-bbfg	VEOPOZ

Recommendation:

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

Orphan Drugs

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

Length of Authorization:
- Up to 6 months

Requires PA:
- See Table 1 (pharmacy and physician administered claims)

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

Table 1. Indications for orphan drugs based on FDA labeling

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

	FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	≥ 2 yrs	• <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 mg for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max dose 2 mg/kg or 180mg every 2 wks)	• Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only: • Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels • Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Belumosudil (REZUROCK)	Treatment of chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy	≥ 12 yrs	200 mg orally once daily with food 200 mg twice daily when coadministered with strong CYP3A inducers or proton pump inhibitors	Baseline & Ongoing Monitoring • Total bilirubin, AST, ALT at least monthly • Pregnancy test (if childbearing potential)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 yrs	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
Elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2 mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 wks)	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.

	cofactor deficiency (MoCD) Type A		Initial: 0.4mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 wks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥1 yr: 0.9 mg/kg	
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 yrs	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests • Blood homocysteine levels-If homocysteine elevated, assess folate, vitamin B12, and vitamin B6
Leniolisib (JOENJA)	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)	≥ 12 years AND ≥ 45kg	70 mg administered orally twice daily approximately 12 hours apart	Baseline and ongoing monitoring • Pregnancy test (if childbearing potential)
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 mo AND ≥0.39 m^2 BSA	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary and plasma oxalate levels	N/A	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months	N/A

			≥ 20 kg Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 yr	Initial: 1 mg/kg SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 3 mo	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 380 mcg/kg once daily after 1 week on initial dose, as tolerated	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Mitapivat (PYRUKYND)	Hemolytic anemia in adults with pyruvate kinase (PK) deficiency.	≥ 18 yr	Initial: 5 mg twice daily Titration: If Hb less than normal range or patient required transfusion in previous 8 weeks, then after 4 weeks increase to 20 mg twice daily, and after another 4 weeks increase to 50 mg twice daily. Max dose: 50 mg twice daily Discontinuation should include down-titration.	Baseline/Ongoing Monitoring • Hgb, transfusion requirement

Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)	≥ 3 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments Max dose: 120 mcg/kg once daily; not to exceed 6 mg	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Olipudase alfa-rpcp (XENPOZYME)	Non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD)	N/A	Initial: Age based dose escalation table per Package insert Maintenance: 3 mg/kg via IV infusion every 2 weeks Weight: • If BMI ≤ 30, use actual body weight • If BMI > 30, use adjusted body weight Adjusted body weight (kg) = (actual height in M)^2 x 30	Baseline Monitoring • Liver function tests (ALT, AST) within 1 month • Pregnancy test (if childbearing potential) Ongoing Monitoring • Liver function tests (ALT, AST) within 72 hours of infusions during dose escalation, then during routine clinical management once at maintenance dose
Palovarotene, (SOHONOS)	Fibrodysplasia ossificans progressive (FOP)	≥ 8 yr females ≥ 10 yr males	≥ 14 years: Daily: 5 mg Flare wk 1-4: 20 mg once daily Flare wk 5-12: 10 mg once daily <14 years weight based: Daily 10-19.9 kg: 2.5 mg 20-39.9 kg: 3 mg 40-59.9 kg: 4 mg ≥ 60 kg: 5 mg Flare week 1-4 (daily dose) 10-19.9 kg: 10 mg 20-39.9 kg: 12.5 mg 40-59.9 kg: 15 mg ≥ 60 kg: 20 mg Flare week 5-12 (daily dose) 10-19.9 kg: 5 mg 20-39.9 kg: 6 mg	Baseline Monitoring • Pregnancy test (if childbearing potential) • Assessment of skeletal maturity in growing pediatric patients: hand/wrist & knee x-ray, standard growth curves, pubertal staging. • Psychiatric symptoms or signs of depression Ongoing Monitoring • Pregnancy test (if childbearing potential) • Assessment of skeletal maturity in growing pediatric patients every 6-12 months until skeletal maturity or final adult height. • Spine assessment for bone density • New or worsening psychiatric symptoms or signs of depression

			40-59.9 kg: 7.5 mg ≥ 60 kg: 10 mg Week 5-12 flare dosing may be extended in 4-week intervals and continued until symptoms resolve. If marked worsening of original symptoms or another flare occurs during flare-up treatment, may restart 12 week flare-up dosing. (all ages)	
Plasminogen, human-tvmh (RYPLAZIM)	Treatment of patients with plasminogen deficiency type 1 (hypoplasmino-genemia)	N/A	6.6 mg/kg body weight given IV every 2 to 4 days	Baseline Monitoring • Plasminogen activity level (allow 7 day washout if receiving with fresh frozen plasma) • CBC (bleeding) Ongoing Monitoring • Trough Plasminogen activity level 72 hours after initial dose and every 12 wks with ongoing therapy • CBC (bleeding)
pozelimab-bbfg (VEOPOZ)	CD55-deficient protein-losing enteropathy (PLE or CHAPLE disease)	≥ 1 yr	Day 1 loading dose: 30 mg/kg single IV infusion Day 8 and after maintenance dose): 10 mg/kg SC weekly May increase to 12 mg/kg if inadequate response after at least 3 weekly doses Max maintenance dose: 800 mg once weekly	Baseline Monitoring • Meningococcal vaccination at least 2 wk prior to first drug dose unless risks of delayed therapy outweigh risk of meningococcal infection. Ongoing Monitoring • Signs of meningococcal infection
Sodium thiosulfate (PEDMARK)	Decrease ototoxicity associated with cisplatin infusions lasting ≤ 6 hours. Not approved for use with longer infusions.	≥ 1 mo to ≤18 yr	< 5 kg: 10 g/m^2 5-10 kg: 15 g/m^2 >10 kg: 20 g/m^2	Baseline Monitoring • Serum potassium and sodium
Sutimlimab-jome (ENJAYMO)	Decrease need for RBC transfusion due to hemolysis in cold agglutinin disease (CAD)	≥ 18 yr	Dosed IV infusion weekly for two weeks, then every two weeks thereafter. **39 to <75 kg:** 6500 mg **≥75 kg:** 7500 mg	Baseline Monitoring • Vaccination against encapsulated bacteria (*Neisseria meningititides* (any serogroup), *Streptococcus pneumonia,* and *Haemophilus influenza*) at least prior to treatment or as soon as possible if urgent therapy needed

Trientine tetrahydrochloride (CUVRIOR)	Stable Wilson's disease who are de-coppered and tolerant to penicillamine	≥ 18 yr	Total daily dose in transition from penicillamine per table in package insert.	<u>Baseline/Ongoing Monitoring</u> • Serum NCC levels at baseline, 3 months, then roughly every 6 months serum levels or 6 to 12 months with urinary copper excretion
Velmanase alfa-tycv (LAMZEDE)	Treatment of non-central nervous system manifestations of alpha-mannosidosis	N/A	1 mg/kg (actual body weight) once weekly by IV infusion	<u>Baseline and ongoing monitoring</u> • Pregnancy test (if childbearing potential)
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase, AST = aspartate aminotransferase; BG = blood glucose; BSA = body surface area; CBC = complete blood count; CrCL = creatinine clearance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycalated hemoglobin; Hgb = hemoglobin; INR = international normalized ratio; IV = intravenous; mo = months; NCC = non-ceruloplasmin copper; RBC = red blood cells; SC = subcutaneously; wks = weeks; yrs = years				

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3
3. 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 **Table 1**?	**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
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
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
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

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Prior Authorization Criteria Update: Respiratory Syncytial Virus (RSV) Prophylaxis

Plain Language Summary:

- This update highlight new treatments that can be used to prevent respiratory syncytial virus (RSV) in newborns, infants and children who are at high risk.
- In most parts of the U.S., RSV circulation is seasonal, typically starting during the fall and peaking in the winter; it is transmitted from person to person through close contact with someone who is infected.
- The medicine SYNAGIS (palivizumab) requires multiple monthly injections and has been the only treatment available for several years, but two other treatment options are also now available: a medicine called BEYFORTUS (nirsevimab) that requires a single dose, and a vaccine called ABRYSVO that is administered to the pregnant woman before the baby is born.
- SYNAGIS should not be given to infants who have already received a dose of BEYFORTUS in the same RSV season. If a mother received the ABRYSVO vaccine, the baby does not need SYNAGIS or BEYFORTUS to protect them from RSV.
- More than 5 doses of SYNAGIS may be considered for infants and vulnerable children if there are high levels of RSV infections, even if it is outside the normal RSV season.
- The Oregon Health Plan fee-for-service program will ensure that SYNAGIS and BEYFORTUS are not used together, and infants born to mothers who received ABRYSVO do not also get SYNAGIS.

Purpose of Update: To briefly summarize new therapies recently approved by the Food and Drug Administration (FDA) for prevention of lower respiratory tract disease from respiratory syncytial virus (RSV) and highlight current clinical practice guidelines for these therapies. BEYFORTUS is part of the Vaccines for Children (VFC) program and thus federally funded with open access to Oregon Health Plan (OHP) members, and therefore will not be extensively reviewed. An evidence review for AVRYSO was not performed because it is a vaccine and does not fall under the purview of the P and T committee.

Recommendation:

- Update the clinical prior authorization (PA) criteria for palivizumab to align with the Advisory Committee on Immunization Practices (ACIP) recommendations for combination use of prophylactic therapy. Prevention with more than one agent each RSV season is not currently recommended.

New Evidence:

<u>BEYFORTUS™ (nirsevimab):</u>

Nirsevimab was approved in July of 2023 and is a RSV F protein-directed fusion inhibitor that was approved by the FDA for the prevention of RSV lower respiratory tract disease (LRTD) in all neonates and infants born during or entering their first RSV season, or in children up to 24 months of age who remain

vulnerable to severe RSV disease through their second RSV season. Efficacy was based on 3 clinical trials in term and preterm infants; 2 phase 2 trials and one phase 3 trial.[1] Two studies were done in infants entering their first RSV season and the third trial was done in infants born at less than 35 weeks gestation with chronic lung disease (CLD) or chronic heart disease (CHD) entering their first RSV season and in those infants with CLD or CHD only entering their second RSV season. In the phase 3 trial, term and late preterm infants with a gestational age greater than or equal to 35 weeks entering their first RSV season were enrolled. The primary endpoint was the incidence of Medically Attended Respiratory Syncytial Virus Lower Respiratory Tract Infection (MA RSV LRTI) caused by a reverse transcription-polymerase chain reaction (RT-PCR)-confirmed RSV, characterized predominantly as bronchiolitis or pneumonia through 150 days after dosing. The number of medically attended RSV LRTD was 1.2% in the nirsevimab group compared to 5.0% in the placebo group (efficacy 74.9%; 95% CI, 50.6 to 87.3; p <0.001).[1] The most common adverse reaction was rash at the injection site.[1]

Palivizumab should not be given to infants who have already received nirsevimab in the same season because of lack of evidence. Nirsevimab may be given in the second RSV season to those infants who are up to 24 months of age who received palivizumab in the first RSV season.[1] Labeling provides instructions for co-administration of other immunoglobulin products.[1] There is no evidence to support the use of BEYFORTUS in a baby born to an individual immunized against RSV during their pregnancy.

ABRYSVO™ (RSV Vaccine):

In August 2023, the RSV vaccine ABRYSVO received an additional indication for active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV) in infants from birth through 6 months of age.[2] One phase 3, double-blind, randomized controlled trial provided evidence for efficacy.[3] RSV-associated LRTD in infants was defined as a medically attended visit with a RT-PCR confirmed RSV illness with one or more of the following respiratory symptoms: tachypnea (respiratory rate ≥60 breaths/minute [<2 months of age], ≥50 breaths/minute [≥2 to 12 months of age], or ≥40 breaths/minute [≥12-24 months of age]); SpO2 measured in room air <95%; chest wall indrawing. RSV-associated severe LRTD was a subset defined as meeting the LRTD RSV criteria plus at least one of the following: tachypnea (respiratory rate ≥70 breaths per minute [<2 months of age], ≥60 breaths per minute [≥2 to 12 months of age], or ≥50 bpm [≥12 to 24 months of age]); SpO2 measured in room air <93%; high-flow nasal cannula or mechanical ventilation (invasive or noninvasive), ICU admission for >4 hours and/or failure to respond/unconscious.[3] Six infants born to individuals who received ABRYSVO experienced severe LRTD caused by RSV within 90 days of birth compared to 33 infants who received placebo (vaccine efficacy 81.8%; 99.5% CI, 40.6 to 96.3%).[3] At 180 days from birth, 19 infants born to individuals who received ABRYSVO experienced severe LRTD caused by RSV compared to 62 infants who received placebo (vaccine efficacy 69.4%; 97.58% CI, 44.3 to 84.1%).[3] There is no evidence to support use of palivizumab in infants born to individuals who received ABRYSVO.

American Academy of Pediatrics Recommendations

In November 2022, the American Academy of Pediatrics (AAP) updated recommendations for use of palivizumab for RSV prophylaxis.[4] These recommendations take into account the changes in RSV season onset and offset and inter-seasonal variability observed in the 2021-2022 RSV seasons due to precautions taken due to COVID-19 and interactions with SARS-CoV-2 virus and other viruses. The AAP now recommends that more than 5 consecutive doses of palivizumab be

considered for eligible infants or children if RSV activity persists at high levels within a given region.[4] Evidence of increased risk of adverse events with additional doses of palivizumab is currently insufficient.

The AAP updated their guidance in August 2023 after the approval of nirsevimab to recommend that a single dose of nirsevimab be used in all neonates and infants born during or entering their first RSV season, or in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The AAP also recommends that palivizumab be used in those neonates, infants or children who are not able to access nirsevimab.[5]

Centers for Disease Control Recommendation

The Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended nirsevimab for all infants under 8 months and those older than 8 months with risk factors for severe respiratory illness due to RSV.[6]

Conclusion:
Palivizumab and nirsevimab are both monoclonal antibodies indicated for the prevention of RSV LRTD. There is currently insufficient evidence to use nirsevimab and palivizumab concomitantly in the same RSV season. Additionally, infants born to individuals who receive ABRYSVO receive passive immunity to RSV and there is no evidence to suggest palivizumab would offer additional protection in this population.

Database(s): **Ovid MEDLINEI ALL** 1946 to August 10, 2023
Search Strategy:

#	Searches	Results
1	Palivizumab/	874
2	limit 1 to 3nglish language and humans and ”r=”2022 -Current”)	51
3	limit 2 to (clinical trial, phase iii or meta analysis or practice guideline “r “systematic review”)	8

References:

1. Beyfortus (nirsevimab) [prescribing information]. Swiftwater, PA; Sanofi Pasteur, Inc. July 2023.
2. ABRYSVO™ (respiratory Syncytial Virus Vaccine)[prescribing information). New York NY; Pfizer, Inc. August 2023.
3. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med*. 2023;388(16):1451-1464. doi:10.1056/NEJMoa2216480.

4. American Academy of Pediatrics. Updated Guidance: Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the 2022-2023 RSV Season. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/. Accessed August 11, 2023.

5. ACIP and AAP Recommendations for Nirsevimab. Published online August 15, 2023. Available at: https://publications.aap.org/redbook/resources/25379/ACIP-and-AAP-Recommendations-for-Nirsevimab. Accessed August 22, 2023.

6. Centers for Disease Control and Prevention Newsroom. CDC Recommends a Powerful New Tool to Protect Infants from the Leading Cause of Hospitalization. August 3, 2023. Available at: https://www.cdc.gov/media/releases/2023/p-0803-new-tool-prevent-infant-hospitalization-.html. Accessed August 22, 2023.

Palivizumab (Synagis®)

Goal(s):

- Promote safe and effective use of palivizumab in high-risk infants and children. Prophylaxis against RSV should cover up to 5 months during high viral activity season, usually spanning from November through March in Oregon.

Length of Authorization:

- Based on individual factors; may extend up to 5 months (5 total doses)

Requires PA:

- Synagis (palivizumab) pharmacy and physician-administered claims

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Has the patient been receiving monthly palivizumab prophylaxis and been hospitalized for a breakthrough RSV infection?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Go to #3
3. Is the request consistent with the current Advisory Committee on Immunization Practices (ACIP) recommendations for combination prophylactic agents (outlined here)? 2023 ACIP update: if the patient, or birth mother of the patient, has received other therapies for the prevention of RSV during or prior to the RSV season, palivizumab is not indicated ~~? Follow Advisory Committee on Immunization Practices (ACIP) guidance on combination prophylaxis recommendations which currently does not support combination therapy.~~	**Yes:** Go to #4 ~~Pass to RPh; deny for medical appropriateness.~~	**No:** Pass to RPh; deny for medical appropriateness. ~~Go to #4~~

Approval Criteria		
4. Is the request for RSV prophylaxis to be administered during the typical high viral activity season from November through March?	**Yes:** Go to #6	**No:** Go to #5
5. Is the request for prophylaxis starting in October due to interseasonal increase in RSV activity with season onset designated by the OHA*? * Data provided by the Oregon's Weekly Respiratory Syncytial Virus Surveillance Report from the Oregon Public Health Division based on regions. Weekly updates are found at: https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40)	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated only during high viral activity.
6. Is the current age of the patient < 24 months at start of RSV season?	**Yes:** Go to #7~~6~~	**No:** Pass to RPh. Deny; medical appropriateness. Not recommended for patients ≥24 months old.
7. GROUP A Does the patient have the CLD (chronic lung disease) of prematurity ICD10 Q331through Q339 **and** in the past 6 months has required medical treatment with at least one of the following: a. diuretics b. chronic corticosteroid therapy c. supplemental oxygen therapy	**Yes:** Go to #19~~8~~	**No:** Go to #~~8~~7
8. GROUP B Has the patient received a cardiac transplant during the RSV season?	**Yes:** Go to #191~~8~~	**No:** Go to #9~~8~~
9. GROUP C Is the child profoundly immunocompromised during the RSV season (i.e. solid organ transplant or hematopoietic stem cell transplantation)?	**Yes:** Go to #19~~8~~	**No:** Go to #10~~9~~

Approval Criteria		
10. GROUP D Does the infant have cystic fibrosis and manifestations of severe lung disease or weight or length less than the 10th percentile?	**Yes:** Go to #19	**No:** Go to #112
11. GROUP E Is the request for a second season of palivizumab prophylaxis for a child born <32 weeks, 0 days gestation who required at least 28 days of oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of start of second RSV season?	**Yes:** Go to #1918	**No:** Go to #12
12. Will the patient be <12 months at start of RSV season?	**Yes:** Go to #132	**No:** Pass to RPh. Deny; medical appropriateness.
13. GROUP F Was the infant born before 29 weeks, 0 days gestation?	**Yes:** Go to #198	**No:** Go to #143
14. GROUP G Does the infant have pulmonary abnormalities of the airway or neuromuscular disease compromising handling of secretions?	**Yes:** Go to #198	**No:** Go to #154

Approval Criteria		
15. GROUP H Does the patient have hemodynamically significant congenital heart disease (CHD) ICD10: P293, Q209, Q220-Q223, Q225, Q229-Q234, Q238, Q240-Q246, Q248-Q249, Q250-Q256, Q278-Q279,Q282-Q283,Q288-Q289, Q2560-Q2565,Q2568-Q2569, Q2570-Q2572, Q2579,Q2731-Q2732 and at least one of the following: a. Acyanotic heart disease who are receiving treatment to control congestive heart failure and will require cardiac surgical procedures; OR b. Have moderate to severe pulmonary hypertension; OR c. History of lesions adequately corrected by surgery AND still requiring medication for congestive heart failure?	**Yes:** Go to #198	**No:** Go to #165
16. GROUP I Does the patient have chronic lung disease (CLD) of prematurity defined as gestational age <32 weeks, 0 days and requirement for >21% oxygen for at least the first 28 days after birth?	**Yes:** Go to #198	**No:** Go to #176
17. GROUP J Does the patient have cyanotic heart defects and immunoprophylaxis is recommended?	**Yes:** Go to #198	**No:** Go to #187
18. GROUP K Does the patient have cystic fibrosis with clinical evidence of CLD and/or nutritional compromise?	**Yes:** Go to #198	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
19. Is the request for more than 5 doses within the same RSV season or for dosing <28 days apart?	**Yes:** Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated for 5 months maximum and doses should be administered ≥28 days apart. May approve for the following on a case-by-case basis: a. >5 doses; b. Prophylaxis for a second / subsequent RSV season	**No:** Go to #2019
20. Has the patient had a weight taken within the last 30 days?	**Yes:** Document weight and date and go to #21 Weight:_____ Date:_____	**No:** Pass to RPh. Obtain recent weight so accurate dose can be calculated.
21. Approve palivizumab for a dose of 15 mg/kg. Document number of doses received in hospital and total number approved according to month of birth (refer to Table 1): Total number of doses approved for RSV season:_____ Number of doses received in the hospital:_____ Prior to each refill, the patient's parent/caregiver and prescriber must comply with all case management services, including obtaining current weight for accurate dosing purposes throughout the approved treatment period as required by the Oregon Health Authority.		

Table 1. Maximum Number of Doses for Palivizumab for RSV Prophylaxis

MONTH	ALL GROUPS
April	5
May	5
June	5
July	5
August	5

September	5
October	5
November	5
December	4
January	3
February	2
March	1

* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

Notes:

- Dose: 15 mg/kg via intramuscular injection once monthly throughout RSV season.
- The start date for Synagis® is November 1 each year (or sooner when the Oregon Public Health Division has determined that RSV season onset has occurred) for a total of up to 5 doses.
- Approval for more than 5 doses or additional doses after March 31 will be considered on a case-by-case basis. Results from clinical trials indicate that Synagis® trough concentrations greater than 30 days after the 5th dose are well above the protective concentration. Therefore, 5 doses will provide more than 20 weeks of protection.

P&T/DUR Review: *8/23 (KS); 2/22 (KS); 11/16 (DE); 9/14; 5/11; 5/12*
Implementation: *TBD; 12/1/22; 4/1/22; 1/1/17; 3/30/12*

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OHSU Drug Effectiveness Review Project Summary Report – Gene Therapies for Hemophilia A and B (Feb 2023) Gene Therapies for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia (Nov 2022)

Date of Review: October 2023

Date of Last Review: n/a
DERP Literature Search: Hemophilia A and B, database inception to 09/22/22
Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia, database inception to 07/26/22

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

Plain Language Summary:

- This is a summary of 2 different research reports from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). The reports studied gene therapies which are Food and Drug Administration (FDA) approved for beta-thalassemia and hemophilia B. Gene therapies are currently being studied for 2 other conditions, sickle cell anemia and hemophilia A, but are not included in this report summary.
- Beta thalassemia is an inherited blood disorder where there is not enough hemoglobin made in the body, resulting in decreased production of healthy red blood cells (RBCs.) Hemophilia B is another inherited disorder that results in uncontrolled bleeding and mostly affects males assigned at birth.
- Gene therapies are a newer type of medication that usually involve getting just one dose. Most conditions being studied for gene therapy are uncommon. Studies for these treatments are often small and do not have a "placebo" group (a group that does not get the active therapy) to compare how safe and how well the drug works. This can make it difficult to understand how well these treatments work and what side effects they may have. We do not know how long the effect of gene therapies last.
- Betibeglogene autotemcel (ZYNTEGLO) is approved for adult and pediatric patients with beta-thalassemia who must have frequent red blood cell transfusions. Transfusions are when a person is given blood that came from a blood donor. Most patients who have received this gene therapy do not require as many red blood cell transfusions, and many no longer need red blood cell transfusions. We do not know if this improvement will last more than 2.5 years, but studies are happening now to answer this question. Many patients experienced adverse events when getting this treatment. Nearly every patient had mucositis (inflammation of mucosa such as the mouth), and it was significant in more than half of the patients. At least one in five patients had each of these: febrile neutropenia (fever in a person who has a low number of the blood cells that fight infections), vomiting, fever, hair loss, nose bleed, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder (changing of the

color of skin), and itching. The most common severe adverse reactions were low counts of the different kinds of blood cells. This gene therapy requires treatment to destroy the bone marrow (inner part of the bone that includes stem cells and makes different kinds of blood cells) before it can be given. Patients must stay in the hospital for many weeks because they are at very high risk of bleeding and infections after getting this type of treatment.

- Etranacogene dezaparvovec (HEMGENIX) is approved for adult patients with severe forms of hemophilia B. Data show that patients who receive this therapy have fewer bleeding episodes each year than they did before receiving this therapy. Some patients no longer need to take other therapies to prevent bleeding such as the blood product known as Factor IX ("Factor 9"). We do not know if this improvement will last more than 18 months, but studies are happening now to answer this question. Some patients who received this medication had side effects, including reactions when the drug was being infused, and signs of damage to their liver. Some patients needed to take certain medications, called steroids, for many months while they had signs of inflammation in the liver after getting this medicine.
- Drug Use Research and Management (DURM) recommends that doctors who prescribe one of these medicines to a person enrolled in the Oregon Health Plan must show that certain criteria have been met to ensure the medicine is used safely and correctly before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the effectiveness of gene therapies for beta-thalassemia and hemophilia B?
2. What are the harms of gene therapies for beta-thalassemia and hemophilia B?
3. Are there any important subgroups of patients where these gene therapies have not been studied?

Conclusions:

Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia[1]

- Three non-controlled, open-label studies with 5 total publications for participants with transfusion dependent beta thalassemia (TDT) receiving betibeglogene were identified by DERP. The primary publications reported results for 45 total participants. Additional presentation abstracts provided quality of life (QoL) and long-term follow-up outcomes for participants enrolled in the primary studies. The studies were rated as having a *high* Risk of Bias (RoB) due to lack of a control group. All outcomes are rated very low certainty of evidence due to risk of bias, imprecision, and indirectness in 3 non-randomized studies. The primary efficacy endpoint of NORTHSTAR-2 was transfusion independence defined as a hemoglobin(Hb) of $\geq$ 9 g/dL starting 60 days after the last transfusion in patients who had not received RBC transfusions in 12 months or longer.
- Transfusion frequency was reduced and many patients achieved transfusion independence up to 29.5 months. NORTHSTAR-2 found transfusion independence was achieved in 91% (20 of 22) of patients with an average Hb level of 11.7 g/dL (range 9.5 to 12.8 g/dL), the two patients who did not achieve transfusion independence had a 67.4% and 22.7% reduction in transfusion volume.[1]
- Transfusion independence was achieved in 79.5% (35 of 44) of all evaluated patients in the combined study populations, and 3 of 9 (33%) of patients with the β^0/β^0 genotype. The β^0/β^0 genotype was excluded from NORTHSTAR-2.
- A high incidence of adverse events (AEs) occurred with betibeglogene, most often around the time of infusion. More than 20% of patients experienced each of the following at any severity: mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus.[2] Severe adverse events were common, including febrile neutropenia (51%) and mucositis (63%).[2] No deaths were reported.

Etranacogene dezaparvovec for Hemophilia B[3,4]

- Two non-controlled, open-label studies with 4 total publications in participants with hemophilia B were identified by DERP. The largest study was the phase 3, HOPE-B study which enrolled 54 participants with interim results reported via abstract. The full study was published after the DERP report was completed and was reviewed and graded by DURM. The second study, a phase 2b trial, enrolled 3 participants. Both are rated as having a *high* RoB and all conclusions are very low certainty of evidence due to high risk of bias and indirectness.
- Etranacogene reduced the annualized bleeding rate (ABR) in the phase 3 study from 4.19 (95% confidence interval [CI] 3.22 to 5.45) at baseline to 1.51 (95% CI 0.81 to 2.82) during months 7 to 18 post treatment vs. the 6 month baseline period ($P < 0.01$).
- Factor IX (FIX) replacement use decreased significantly by -248,825.0 IU (95% CI -291,149.9 to -206,500.1) during months 7 to 18 post treatment compared to the 6 month baseline period in the HOPE-B study ($P < 0.01$). Baseline unadjusted mean annualized exogenous factor IX consumption was 257,339±149,013 IU/year.
- Etranacogene administration resulted in improved FIX activity at 6 months (least-squares mean [LSM] 36.2%; 95% CI 31.4% to 41.0%) and 18 months (LSM 34.3%; 95% CI 29.5 to 39.1) after treatment.
- Elevations in liver enzymes was a common AE. Alanine aminotransferase (ALT) was elevated for 20% of patients and 17% of patients were given glucocorticoid treatment for weeks to months.

Recommendations:

- Designate betibeglogene autotemcel and etranacogene dezaparvovec as non-preferred on the preferred drug list (PDL)
- Apply prior authorization (PA) to ensure clinically appropriate utilization.

Summary of Prior Reviews and Current Policy

- Gene therapies are a relatively new type of medication. Many currently available agents fall under the Oncology Policy, and several others have drug-specific prior authorization criteria. These 2 therapies are being reviewed by the Pharmacy and Therapeutics (P & T) committee for the first time and are the first gene therapy agents available for beta-thalassemia and hemoglobin B.
- Gene therapies are extremely costly and some have been introduced with prices of several million dollars for a one-time treatment, in addition to costs for necessary supportive care.
- Gene therapies often target relatively rare or uncommon conditions which have a clear genetic cause. Consequently, many of the conditions disproportionately affect those of a specific race or sex. For example, hemophilia B is more common in males assigned at birth with XY chromosomes because it is X-linked. Beta-thalassemia most prevalent in Asia and in the Mediterranean basin.

Methods:
The November 2022 drug class report on Gene Therapies for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia and the February 2023 drug class report on Gene Therapies for Hemophilia A and B by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon P & T Committee members upon request.

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

Summary Findings:
Gene therapy is a developing field of therapeutics. The Food and Drug Administration (FDA) has approved a number of gene therapies for oncology and non-oncology uses.[5] Data from recent Drug Effectiveness Review Project (DERP) reports will be summarized for the recent approvals of betibeglogene autotemcel (ZYNTEGLO) for use in certain beta-thalassemia patients and etranacogene dezaparvovec-drlb (HEMGENIX) for specific hemophilia B patients.[1,3]

<u>Beta Thalassemia</u>
Beta thalassemia is an inherited, genetic blood disorder where there is insufficient production of β-hemoglobin (β+) or an absence of β-globin (β°), resulting in decreased production of healthy RBCs. This may result in anemia and based on the severity of phenotype, beta thalassemia can be labeled as transfusion dependent beta thalassemia (TDT) or transfusion nondependent. There are different genotypic forms of this disease. Individuals with severe forms of the disease can require regular transfusions of packed RBCs, which can result in iron overload and the need for concomitant iron chelation therapy.[1]

A complete blood count is generally required to diagnose beta thalassemia. It is most prevalent in Asia and the Mediterranean basin, but is estimated to have increased 7.5% over the last 50 years in the United States. Migration was considered as an important factor for this higher trend in beta thalassemia prevalence.[1] Global incidence of symptomatic disease is approximately 1 in 100,000 and can vary greatly geographically.[6]

Treatment options for TDT include splenectomy, hematopoietic stem cell transplant (HSCT), and FDA-approved drug therapies such as luspatercept. Donor matching, reduced survival rate for adults, and risk of graft versus host disease (GVHD) are concerns when HSCT is used to treat people with beta thalassemia.[1] While HSCT is potentially curative, it is generally most successful in younger children with an HLA-identical sibling donor.[7] The FDA approved the first gene therapy for beta thalassemia in the form of betibeglogene autotemcel in August 2022.[2] Other gene therapies are currently under investigation. Outcomes used when caring for patients with TDT or researching interventions include hemoglobin levels, frequency of transfusions, fatigue, and QoL.[1] There are no clear minimum clinically important differences (MCID) for these outcomes. An evaluation by the National Institute for Health and Excellence (NICE) discussing the methodological challenges in evaluating gene therapy products was published in 2021 and reviewed the initial NORTHSTAR results.[7] The NICE recommendation was that "betibeglogene autotemcel is not recommended, within its marketing authorisation, for treating TDT in patients aged ≥12 years who do not have a $beta^0/beta^0$ genotype, when HSCT is appropriate, but an HLA- matched related hematopoietic stem cell donor is not available".[8] The conditional EU and UK marketing authorization was for those with TDT who do not have the $beta^0/beta^0$ genotype and when HSCT would be appropriate but there is not suitable donor.[9] The manufacturer withdrew its marketing application from the Medicines and Healthcare products Regulatory Agency in 2021 and the European Medicines Agency in 2022.[10,11]

Efficacy

Betibeglogene Autotemcel (ZYNTEGLO) is an autologous hematopoietic stem cell-based gene therapy indicated for treatment of adult and pediatric patients with beta-thalassemia who require regular RBC transfusions.[2] Efficacy and safety were evaluated in 3 non-randomized, single arm studies. The β^0/β^0 genotype or the IVS1-110 mutation was found in 9 of 22 patients of patients in the NORTHSTAR trial (which is a pooled summary of 2 phase 1-2 studies), while the NORTHSTAR-2 trial excluded patients with the β^0/β^0 genotype.[1] The ongoing NORTHSTAR-3 Study does allow the β^0/β^0 genotype in its inclusion parameters.[1] Published studies (N=45 patients) are at high risk of bias due to lack of control group, and GRADE ratings for confidence of evidence in relevant outcomes is very low.[1] The phase 1/2 NORTHSTAR study focused on engraftment, while the phase 3 NORTHSTAR-2 study primary efficacy endpoint was transfusion independence defined as a Hb of $\geq$ 9 g/dL starting 60 days after the last transfusion in patients who had not received RBC transfusions in 12 months or longer.[1] The median age across trials was 13 years and most patients were Asian.[2] While one study allowed inclusion up to 50 years of age, the combined age ranges for those enrolled in the studies are 4 to 34 years. Those under 5 years had to meet a minimum weight threshold of 6 kg to reasonably provide the minimum number of cells for the product manufacturing process.[1] Patients in all studies required a history of transfusion of at least 100 mL/kg/year of packed RBCs in the 2 years before enrollment, or at least 8 transfusions of packed RBCs/year in the past 2 years for those 12 years in older.[1,7] NORTHSTAR-2 found transfusion independence was achieved in 91% (20 of 22) patients with an average Hb level of 11.7 g/dL (range 9.5 to 12.8 g/dL), the two patients who did not achieve transfusion independence had a 67.4% and 22.7% reduction in transfusion volume.[1] NORTHSTAR found transfusion independence in 68% (15 of 22) of patients with a median Hb level of 11.2 g/dL.[1] Of those with the β^0/β^0 genotype or the IVS1-110 mutation, 3 of 9 (33%) achieved transfusion independence.[1,7]

Harms

Overall survival during study follow-up was 100% in published studies. The most common adverse events experienced in at least 20% of patients were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. Grade 3 or higher febrile neutropenia (51%) or mucositis (63%) were common.[2] Serious adverse events were experienced by 37% of patients. The most common serious adverse events were pyrexia, thrombocytopenia, liver veno-occlusive disease, febrile neutropenia, neutropenia, and stomatitis.[2] The median duration of hospitalization from conditioning though discharge (N=30) was 44 days (range 29 to 92 days).[1] No deaths were reported.[1] Study characteristics can be found in **Table 1** and complete demographics and results can be found in the full report.[1] The package insert states there is a potential risk for insertion oncogenesis after treatment and that patients should be monitored lifelong for hematologic malignancies with a complete blood count at months 6, 12, and then annually for at least 15 years, in addition to an integration site analysis at months 6, 12 and then as warrented.[2]

Table 1. Study Characteristics of Betibeglogene for Transfusion-Dependent Beta Thalassemia[1]

Author, Year Trial Number Trial Name	Participants	Treatment Protocol	Study Design	Follow-up	Risk of Bias
Thompson et al., 2018 HGB-204 NCT01745120 HGB-205 NCT02151526 NORTHSTAR	N = 22 n = 18, HGB-204 n = 4, HGB-205	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 1/2 study	26 months	High
Locatelli et al., 2022 HGB-207 NCT02906202 NORTHSTAR-2	N = 23	Single infusion of autologous CD34+ hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector Target Dose: at least 5.0 million CD34+ cells per kilogram of body weight	Single-arm, open label, phase 3 study	29.5 months	High
Kwiatkowski et al., 2021 Kulozik et al., 2021 HGB-207 NCT02906202 NORTHSTAR-2 HGB-212 NCT03207009 NORTHSTAR-3	N = 30	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 3 studies	24 months	Not performed (conference abstract)
Yannaki et al., 2021 LTF-303 NCT02633943	N = 44	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, long-term follow-up study	45.6 months	Not performed (conference abstract)

Hemophilia B

Hemophilia B is a recessive, X chromosome-linked bleeding disorder mainly affecting males assigned at birth. Hemophilia B represents a deficiency in factor IX (FIX) and affects 1 in 25,000 live male births. Females assigned at birth are more likely to experience mild or moderate hemophilia than severe hemophilia B. Bleeding most often occurs in large joints, leading to hemophilic arthropathy, which results in significant pain and physical disability. Physical activity can greatly increase the risk for weight-bearing joint bleeds, and many affected people with hemophilia avoid sports, exercise, and physical activities. Risk of bleeding associated with physical activity and frequent infusions of on-demand and prophylactic clotting factor concentrates (CFCs) contribute to the reduced QoL in individuals with hemophilia B. The severity of hemophilia B, defined by percent of normal clotting factor level, is detailed in **Table 2**. Factor IX activity of over 5% of normal is associated with a lower risk of spontaneous bleeding than those with moderate or severe hemophilia and is generally the target level for routine prophylactic therapy to prevent or reduce the incidence of spontaneous bleeds.[3]

Table 2. Hemophilia B Disease Severity by Factor IX Levels[3]

Percent of Normal Factor IX activity	Disease Severity
<1%	Severe
1-5%	Moderate
5-40%	Mild

The current standard of care for hemophilia B is regular administration of prophylactic CFCs or other hemostasis products to prevent bleeding. This prophylaxis is recommended prior to the age of 3 years to prevent both acute bleeds and the long-term development of hemarthroses and joint disease.[3] Many CFCs have a short half-life, leading to breakthrough bleeding as factor levels fall close to baseline between intravenous administration of FIX.[3] Newer formulations of CFCs with an increased half-life and the use of monoclonal antibodies allow for extended intervals between administrations.[3] Outcomes used when caring for patients and researching interventions for hemophilia B tend to include annualized bleeding rate (ABR), response to treatment (e.g., number of CFC infusions or dose required to resolve a bleed or time from last infusion to bleeding episode), need for other therapies, and quality of life. There are no clear MCIDs for these. The Haem-A-Qol is a common questionnaire used for assessment of health-related quality of life.[12] It has been validated in adult patients ≥ 17 years old with hemophilia.[12] Questions use a 5-point Likert-type frequency scale (1= never, 2=rarely, 3=sometime, 4=often, 5=all the time).[12] Higher total scores indicate more impairment and the maximum score is 100.[12] There are 10 different domains (e.g., physical health, sports & leisure, work & school) with varying numbers of items in each domain.[12]

Efficacy

Etranacogene dezaparvovec-drlb (HEMGENIX) is an adeno-associated virus vector-based gene therapy.[13] It is indicated for adults with hemophilia B who currently use FIX prophylaxis therapy; or have current or historical life threatening bleeding; or have repeated, serious spontaneous bleeding episodes.[13] It was evaluated in 2 non-randomized, single arm studies. HOPE-B study was a phase 3, open-label study, using intra-subject comparison as the control (n=54).[3,4] Patients had 18 months of post-treatment follow-up.[4] Patients were observed for FIX prophylaxis during the ≥ 6 month lead-in period (baseline) and had a 64% reduction in ABR (all bleeds, primary endpoint) from 4.19 (95% CI 3.22 to 5.45) at baseline to ABR 1.51 (95% CI 0.81 to 2.82; $P < 0.01$) during months 7 to 18 after etranacogene was administered.[4] The adjusted ABR ratio was 0.36 (95% CI 0.20 to 0.64), meeting predetermined criteria for non-inferiority (primary endpoint) and superiority (secondary endpoint) compared to lead-in period.[4] The mean FIX activity increase was 39.0 ± 18.7% (range 8.2 to 97.1%) at 6 months, most patients had <1% FIX activity at diagnosis. These were sustained at 12 and 18 months.[4] Baseline unadjusted mean annualized exogenous factor IX consumption was 257,339±149,013 IU/year. Factor IX annualized consumption decreased by 248,825.0 IU/year (95% CI -291,149.9 to -206,500.1).[4] Fifty-two of 54 participants

(96.3%) stopped prophylactic FIX infusions.[4] One non-responder received a subtherapeutic dose equivalent to approximately 10% of the intended dose, and the other non-responder was noted to have an adeno-associated virus serotype 5 (AAV5) neutralizing antibody titer of 3,212.[4] Clinical thresholds for this titer are unknown and being assessed with further research.[13] The Haem-A-QoL showed a total mean score of 25.56 compared with 20.06 in the lead-in and post-treatment periods, respectively, resulting in a 21.5% score improvement ($P < 0.01$).[3,4] The FDA noted that with the single-arm open label trial design that reliable assessments of patient-reported outcomes cannot be made and the information would not be in the label.[14] Study characteristics can be found in **Table 3** and complete demographics and results can be found in the published article.[3,4]

Von Drygalski and colleagues reported efficacy outcomes for etranacogene in 3 participants in the phase 2b study. All participants had a baseline FIX activity of less than 1%. Mean FIX activity increased to 31% at 6 weeks, 38% at 12 weeks, and 47% at 26 weeks. No bleeds or FIX administration was reported during the study period (26 weeks).

Table 3. Study Characteristics of Etranacogene for Hemophilia B[3,4]

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment Protocol	Study Design	Follow-up	Risk of Bias
Miesbach et al., 2022 Pipe et al., 2022 Pipe et al., 2023 NCT03569891 HOPE-B	Men ≥ 18 years with FIX coagulant activity ≤ 2% who had received continuous prophylaxis for ≥ 2 months N = 54	2 x 10 vg/kg	Open-label, multicenter, non-randomized, phase 3 study	18 months	High
Von Drygalski et al., 2019 NCT03489291	Men ≥ 18 years with moderate to severe hemophilia B (FIX coagulant activity ≤ 2%) receiving either prophylactic FIX or on-demand FIX with ≥ 4 bleeds/year or chronic hemophilic arthropathy N = 3	2 x 10 vg/kg	Open-label, multicenter, non-randomized study	Interim assessment at 26 weeks published; planned 52 weeks; additional long-term follow-up assessments over 4 years	High
Abbreviations: FIX: factor IX; vg/kg: vector genomes per kilogram.					

Harms

The HOPE-B study includes safety information for etranacogene in 54 participants in the phase 3 study. There were 92 treatment-related adverse events (TRAEs) affecting 69% of participants.[3,4] Of these TRAEs, 74 (80.4%) were mild, 16 (17.4%) were moderate, and 2 (2%) were severe.[3,4] An increase in alanine aminotransferase (ALT) was noted in 9 participants (16.7%), all of whom received corticosteroid treatment (mean duration = 79 days ± 26.6, range 51 to 130 days) and maintained FIX expression.[3,4] Additional TRAEs include headache (n = 8; 14.8%), influenza-like illness (n = 7; 13%), infusion-related reaction (n = 7; 13%), AST increase (n = 5; 9.3%), increase in blood creatine phosphokinase (n = 4; 7.4%), fatigue (n =4; 7.4%), nausea (n = 4; 7.4%), and arthralgia (n = 3; 5.6%).[3,4] Two SAEs were reported, these included 1 death related to cardiogenic shock and 1 case of hepatocellular carcinoma, neither of which were determined to be related to etranacogene.[4] The follow-up time was 18 months. No patients developed FIX inhibitors.[4]

Von Drygalski and colleagues reported harm outcomes for etranacogene in 3 participants in the phase 2b study.[3] Two adverse events possibly related to etranacogene were reported in 1 participant, including a self-limited headache on day 1 and a mild increase in C-reactive protein on day 14, neither of which required intervention.[3] Changes in liver transaminase concentrations were not determined to be clinically significant. One participant required prednisone at 50 mg daily for 5 days at day 94 for bronchitis.[3] No serious adverse events (SAEs) were reported.[3] **Table 4** summarizes adverse events reported in the 2 trials.

Table 4. Adverse events from Etranacogene for Hemophilia B Studies[3,4]

Author, Year **Study Name** **Study Name**	**Adverse Events**	**Serious Adverse Events**
Miesbach et al., 2022 Pipe et al., 2022 Pipe et al., 2023 NCT 03569891 HOPE-B	• Alanine aminotransferase increase: n=9 (16.7%) • Headache: n=8 (14.8%) • Influenza-like illness: n=7 (13%) • Infusion-related reaction: n=7 (13%) • Aspartate aminotransferase increase: n=5 (9.3%) • Blood creatinine kinase increase: n=4 (7.4%) • Fatigue: n=4 (7.4%) • Nausea: n= 4 (7.4%) • Arthralgia: n=3 (5.6%)	• Death: n=1; cardiogenic shock unrelated to study treatment • Hepatocellular carcinoma: n=1; unrelated to study treatment
Von Drygalski et al., 2019 NCT03489291 Not applicable	• Headache: n=1 • Elevation in C-reactive protein: n=1	

References:

1. Lindsey WT, Steuber TD, Grabowsky AB. Gene therapies for sickle cell disease and transfusion-dependent beta thalassemia. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2022.
2. Zynteglo (betibeglogene autotemcel) package insert. bluebird bio, Inc. Somerville, MA: https://www.fda.gov/media/160991/download. August 2022.
3. Lindsey W, Alexander C, Yang H, Grabowsky A. Gene therapies for hemophilia A and B. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2023.
4. Pipe SW, Leebeek FWG, Recht M, et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. New England Journal of Medicine. 2023;388(8):706-718.
5. Food and Drug Administration. Approved Cellular and Gene Therapy Product. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Update: June 30, 2023. Accessed June 30, 2023.
6. DynaMed. Beta-Thalassemia Major and Intermedia. EBSCO Information Services. Accessed July 3, 2023. https://www.dynamed.com/condition/beta-thalassemia-major-and-intermedia#GUID-CA33D0DD-80A1-49D3-B041-C7396B30A546.
7. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. New England Journal of Medicine. 2018;378(16):1479-1493.
8. Pinho-Gomes AC, Cairns J. Evaluation of Advanced Therapy Medicinal Products by the National Institute for Health and Care Excellence (NICE): An Updated Review. Pharmacoecon Open. 2022;6(2):147-167.
9. National Institute for Health and Care Excellance. Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia. Updated March 4, 2021. Available at: https://www.nice.org.uk/consultations/1225/1/recommendations. Accessed July 3, 2023.
10. National Institute for Health and Care Excellance. Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID968]. Updated December 16, 2022. Available at: https://www.nice.org.uk/guidance/discontinued/gid-ta10334. Accessed July 3, 2023.
11. European Medicines Agency. Zynteglo Withdrawal of the marketing authorization in the European Union. Updated March 30, 2022. Available at: https://www.ema.europa.eu/en/documents/public-statement/public-statement-zynteglo-withdrawal-marketing-authorisation-european-union_en.pdf. Accessed July 3, 2023.
12. Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Haemophilia. 2015;21(5):578-584.
13. Hemgenix (etranacogene dezaparvovec-drlb) package insert.uniQure, Inc Lexington, MA: https://www.fda.gov/media/163467/download. November 2022.
14. Food and Drug Administration. Etranacogene dezaparvovec BLA 125772/0 Clinical Review Memorandum. https://www.fda.gov/media/164332/download. Completion date: Nov 22, 2022. Accessed: June 30, 2023.

Appendix 1: Current Preferred Drug List

PDL unassigned

Generic	Brand	Route	Form	PDL
etranacogene dezaparvovec-drlb	HEMGENIX	IV	VIAL	
etranacogene dezaparvovec-drlb	HEMGENIX	IV	KIT	
betibeglogene autotemcel	ZYNTEGLO	IV	PLAST. BAG	

Betibeglogene Autotemcel

Goal(s):
- Approve Betibeglogene Autotemcel (ZYNTEGLO) for conditions supported by evidence of benefit

Length of Authorization:
- Once in a lifetime dose.

Requires PA:
- Betibeglogene Autotemcel (billed as pharmacy or physician 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 for any diagnosis?	**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 genotype documented?	**Yes:** Go to #6 Genotype_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. 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 (patients 12 years and older)	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient between 5 years and 35 years old?	**Yes**: Go to #9	**No:** Go to #8
8. Is the patient younger than 5 years old and weighs at least 6 kg?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have cirrhosis or advanced liver disease?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is there documentation that the patient does not have active or chronic infections of HIV, hepatitis B, or hepatitis C?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. 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	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient (and/or guardian, if applicable) been educated on the risk of insertional oncogenesis and need for lifelong monitoring (bloodwork) at least annually?	**Yes**: Go to #13.	**No**: Pass to RPh. Deny; medical appropriateness
13. Is the patient of childbearing potential OR capable of fathering a child?	**Yes:** Go to #14	**No:** Approve one lifetime dose.
14. Is the patient pregnant, actively trying to conceive, or trying to father a child?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #15

Approval Criteria		
15. 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:** Approve for one lifetime dose	

P&T/DUR Review: 10/23 (SF)
Implementation: TBD

Etranacogene dezaparvovec

Goal(s):
- Approve Etranacogene dezaparvovec (HEMGENIX) for conditions supported by evidence of benefit

Length of Authorization:
- Once in a lifetime dose.

Requires PA:
- Etranacogene dezaparvovec (billed as pharmacy or physician 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 it the FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is there documentation that the patient has never received another gene therapy for any diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient require continuous routine factor IX prophylaxis?	**Yes**: Go to #7	**No:** Go to #5
5. Does the patient have a history of repeated, serious spontaneous bleeding OR current or historical life threatening hemorrhage?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Did these events occur during adherence to physician recommended and maximally adjusted factor IX therapy (including routine factor IX prophylaxis, if indicated) AND adherence to appropriate lifestyle precautions?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Send to Medical Director for review.
7. Does patient have congenital hemophilia B with: • Severe Factor IX deficiency (<1% plasma factor IX activity) OR • Moderately-Severe Factor IX deficiency (1 to 2% plasma factor IX activity) with a severe bleeding phenotype?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Send to Medical Director for review.
8. Is the patient 18 years or older?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there documentation that the patient does not have factor IX inhibitors by a test within the past 3 months? Note: If positive initial test, may retest, ideally within approximately 2 weeks of original test.	**Yes**: Go to #10 Test Date_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Has this patient had a liver health assessment including all of the following: AST, ALT, ALP, total bilirubin, hepatic ultrasound, elastography, and recent (previous 3 months) screening for hepatitis B and C?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Were all hepatic enzymes and hepatic radiological tests normal AND were hepatitis B and C screenings negative? Note: Enzyme elevations which are transient and mild (less than twice the upper limit of normal) may answer "Yes" to this question.	**Yes**: Go to #13	**No:** Go to #12
12. Has the patient been evaluated and cleared for gene therapy treatment by a gastroenterologist or hepatologist?	**Yes**: Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is there documentation that the patient is either: • HIV negative OR • HIV positive and controlled (CD4 count ≤ 200/μL)?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Has the provider discussed enrollment in a study to measure pre-existing anti-AAV5 neutralizing antibodies with patient? Note: study details and contact information in gene therapy package insert.[1]	**Yes:** Approve one lifetime dose.	**No:** Pass to RPh. Deny; medical appropriateness

1. Hemgenix (etranacogene dezaparvovec-drlb) package insert.uniQure, Inc Lexington, MA: https://www.fda.gov/media/163467/download. November 2022.

P&T/DUR Review: 10/23 (SF)
Implementation: TBD

Drug Use Research & Management Program
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New Drug Evaluation: Valoctocogene suspension for intravenous infusion

Date of Review: October 2023
End Date of Literature Search: 07/14/2023
Generic Name: valoctocogene roxaparvovec-rvox
Brand Name (Manufacturer): Roctavian (Biomarin Pharmaceutical Inc.)

Dossier Received: yes

Plain Language Summary:

- Hemophilia A is an inherited disorder in which blood does not clot properly due to a lack of clotting factor VIII. This results in uncontrolled bleeding from cuts or injuries, unexplained nosebleeds, and many large bruises. Some patients bleed unexpectedly into joints without having an injury. This condition mostly affects males assigned at birth. Patients are usually given replacement clotting factor to prevent or treat bleeding.
- Valoctocogene roxaparvovec-rvox is a new gene therapy used to increase factor VIII (a part of the blood that helps a person stop bleeding) and to reduce bleeding in adults with severe hemophilia A. The new gene to make factor VIII must go through steps in the liver to work.
- One small study shows that valoctocogene roxaparvovec-rvox increases the factor VIII activity in many patients enough to reduce or eliminate need for replacement factor VIII products and reduce the number of bleeds that have to be treated with factor VIII products. This treatment remains effective for up to two years. We do not known how long this treatment remains effective beyond two years.
- Most patients had signs of liver damage after receiving this treatment. This may also put the patient at risk of having less benefit from the gene therapy effect of factor VIII. Patients who experienced this had to take corticosteroids for 2 months or longer until lab tests were back to normal and so that the treatment could continue to work.
- Gene therapies are a newer type of treatment. People who receive this therapy must be monitored for new cancers over time, especially liver cancer, because of possible risks.
- Some people with Hemophilia A have immune systems that have created certain types of inhibitors or antibodies, and they should not get this gene therapy because they will not receive benefit.
- Providers must explain to the Oregon Health Authority why someone needs valoctocogene roxaparvovec-rvox before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the effectiveness of valoctocogene roxaparvovec-rvox for hemophilia A?
2. What are the harms of valoctocogene roxaparvovec-rvox for hemophilia A?
3. Are there any important subgroups of patients where valoctocogene roxaparvovec-rvox has not been studied or may have different effects?

Author: Sara Fletcher, PharmD, MPH, BCPS

Conclusions:

- There is low quality evidence based on one poor quality, open-label, single-arm, phase 3 trial with 2 year extension in patients with severe hemophilia A that valoctocogene roxaparvovec-rvox treatment increased factor VIII activity levels at week 49-52 after treatment compared to baseline levels (mean change: 41.9 IU/dL [95% confidence interval [CI] 34.1 to 49.7; P<0.001]). Annualized treated bleeding rates were also improved after 4 to 52 weeks (Change -4.1 bleeds/yr [95% CI, -5.3 to -2.8; P<0.001]) and 104 weeks post treatment (Change -4.1 bleeds/yr [95% CI, -5.3 to -2.98; P<0.001]) compared to baseline.[1,2] Evidence quality for outcome and trial were downgraded due to risk of bias.
- All patients enrolled in the trial experienced adverse reactions and 16.4% experienced serious adverse reactions. Alanine aminotransferase (ALT) increase was the most common adverse reaction and 79.1% of patients received glucocorticoids (median 230 days) in accordance with the study protocol. Therapeutic prednisone 60 mg daily, tapered over a minimum of 8 weeks, was used to protect gene transduced hepatocytes and maintain factor VIII expression.[2]
- Data are limited for use in people with risk factors for, or preexisting hepatic dysfunction.[2]

Recommendations:

- Implement prior authorization to ensure safe and appropriate use.
- Maintain valoctocogene roxaparvovec-rvox as non-preferred on the Oregon Health Plan (OHP) preferred drug list (PDL).

Background:

Hemophilia A is a recessive, bleeding disorder that is linked to the X chromosome and primarily affects males assigned at birth.[3] Hemophilia A represents a deficiency in clotting factor VIII and affects 1 in 5,000 live male births.[4] Females assigned at birth are more likely to experience mild or moderate hemophilia A.[3] Bleeding most often occurs in large joints, leading to hemophilic arthropathy, which results in significant pain and physical disability.[3,4] Physical activity can greatly increase the risk for weight-bearing joint bleeds, and as a result, many people with hemophilia avoid sports, exercise, and physical activities.[3] Risk of bleeding associated with physical activity and frequent infusions of on-demand and prophylactic clotting factor concentrates (CFCs) contribute to the reduced quality of life (QoL) in individuals with hemophilia A.[3] The severity of hemophilia A is defined by percent of normal clotting factor level. Factor VIII activity of less than 1% or less than 0.01 unit/mL is considered severe and places individuals at risk of spontaneous bleeding.[4] Factor VIII activity of 1-5% is moderate with occasional spontaneous bleeding and prolonged bleeding with surgery or minor trauma.[4] Those with mild hemophilia A have a factor VIII level of 5% to 40% and may experience severe bleeding after surgery or major trauma, but risk of spontaneous bleeding is low.[4]

The current standard of care for severe hemophilia A is regular administration of prophylactic CFCs or other hemostasis products to prevent bleeding.[3] This prophylaxis is recommended prior to the age of 3 years to prevent both acute bleeds and the long-term development of hemarthroses and joint disease.[3] Many CFCs have a short half-life, leading to breakthrough bleeding as factor levels fall close to baseline between intravenous administration of factor VIII.[3] Newer formulations of CFCs with an increased half-life and the use of monoclonal antibodies allow for extended intervals between administrations. Some patients develop inhibitors to factor VIII and require other therapy such as emicizumab.[4] Outcomes used when caring for patients and researching interventions for hemophilia A tend to include annualized bleeding rate (ABR), response to treatment (e.g., number of CFC infusions or dose required to resolve a bleed or time from last infusion to bleeding episode), need for other therapies, and quality of life.[3] There are no clear minimum clinically important differences (MCIDs) for these outcomes. The Haem-A-Qol is a common questionnaire used for assessment of health-related quality of life.[5] It has been validated in adult patients ≥ 17 years old with hemophilia.[5] Questions use a 5-point Likert-type frequency scale (1=never, 2=rarely, 3=sometimes, 4=often, 5=all the time).[5] Higher total scores indicate more impairment and the maximum score is 100.[5] There are 10 different domains (e.g., physical health, sports & leisure, work & school) with varying numbers of items in each domain.[5]

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:
Valoctocogene roxaparvovec-rvox (ROCTAVIAN) is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with severe hemophilia A, with factor VIII activity < 1 IU/dL without pre-existing adeno-associated virus serotype 5 (AAV5) antibodies detected by a Food and Drug Administration (FDA)-approved test.[6] The functional copy of a transgene is transcribed in the liver hepatocytes with a liver-specific promoter to result in the expression of the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). The hFVIII-SQ is meant to replace the missing coagulation factor VIII in people with hemophilia A.[6]

Valoctocogene roxaparvovec-rvox approval was based on one trial (GENEr8-1) in adult men (n=134) with severe hemophilia A (factor VIII activity < 1 IU/dL).[2] Those with factor VIII inhibitors, AAV5 antibodies, and risk factors or active liver disease were excluded.[2] Patients with human immunodeficiency virus (HIV) were excluded by protocol amendment after hepatoxicity was seen in a patient on efavirenz in a different valoctocogene study (**Table 2)**.[2] This single-arm, open-label, multi-center phase 3 study assessed the effect of a single-infusion gene therapy treatment in improving factor VIII activity levels during weeks 49 to 52 post-infusion compared to a baseline period as the primary endpoint.[2] Additional endpoints included annualized factor VIII use and annualized treated bleeding rate. Baseline levels for these were determined using historical medical records or information gathered during the 270-902 study. After gene therapy treatment, the factor VIII use and the number of bleeding episodes requiring factor VIII treatment were patient reported at each visit as captured in patient diary. Baseline factor VIII use and bleeding episodes in a subset of the modified intent-to-treat population came from study records in patients who had rolled over from the non-interventional 270-902 study and had at least 6 months of data. [2] This non-interventional study prospectively recorded bleeding episodes, factor VIII infusion information, and patient reported outcomes in severe hemophilia A patients and had the same study sponsor as the GENEr8-1 trial. At baseline, most patients had zero (72.4%) or one (12.7%) problem joint. Enrolled patients had a median of 121.1 factor VIII infusions and 2.3 bleeds annualized each year. The annualized mean rate for factor infusion and bleeds were higher than the median (137.5 infusions/year and 5.4 bleeds/year) which may indicate a skewed population distribution or outliers with more frequent bleeding and infusions.[2] Two patients with HIV were enrolled prior to the protocol change, and 14.9% and 30.6% had a history of hepatitis B and C infections, respectively.[2] All participants were male sex and primarily White (71.6%).[2]

The modified intent-to-treat (mITT) population included all patients receiving valoctocogene roxaparvovec-rvox and without HIV. At week 49 to 52, the average factor VIII activity level was improved from less than 1 IU/dL at baseline to a mean of 42.9 IU/dL (standard deviation [SD] 45.5) and median of 23.9 IU/dL (interquartile range 11.9 to 62.3).[2] The secondary endpoints assessed in the rollover population found a 98.6% decrease (P<0.001) in mean annualized factor VIII concentrate use and mean change in bleeds of -4.1 annualized bleeds/yr (95% CI -5.3 to -2.8; P<0.001).[2]

An extension trial of the GENEr8-1 study reported outcomes out to week 104 where 132 of the original 134 participants remained in the study.[1] Based on feedback from the FDA, the primary endpoint of this 2-year extension analysis was amended to evaluate change in annualized treated bleeding events instead of factor VIII activity.[1] In people with data on factor utilization prior to treatment (n=112), the annualized bleeding rate compared to baseline was improved by an average of -4.1 bleeds/yr (95% CI -5.3 to -2.98, P<0.001) at 104 weeks.[1]

Studies are ongoing to evaluate continued durability of response over time and monitor for unknown side effects which could occur as gene therapy treatments are used more widely in clinical practice.[1] This trial was limited by the open-label, single arm design. Additionally, some outcomes such as factor VIII consumption from on demand use and treated bleeding events require a subjective assessment which increase risk of bias for this trial. The exclusion criteria around hepatotoxicity make safety and effectiveness uncertain in people with risk factors for liver injury. Those with increased alanine aminotransferase (ALT) who received glucocorticoids to protect against potential cytotoxicity did not seem to have reduced factor VIII activity compared to those who did not experience ALT increases. Valoctocogene roxaparvovec-rvox should not be used in those with pre-existing factor VIII inhibitors or AAV5 antibodies as therapy will not be effective for people with these characteristics.

Clinical Safety:

Valoctocogene roxaparvovec-rvox has contraindications for use with active infections (acute or chronic), known significant hepatic fibrosis or cirrhosis, or those with known hypersensitivity to mannitol.[6] Every participant experienced at least one adverse reaction; most were mild while 16.4% experienced serious adverse reactions.[2] Rise in ALT occurred in 85.8% of patients. There is concern that transduced hepatocytes may become targets for cellular cytotoxicity.[7] This appears to result in increased ALT and potential loss of transgene expression.[7] A glucocorticoid protocol, used to mitigate these concerns, was initiated in 79.1% of patients. In addition, 29.1% of patients received other immunosuppressants due to contraindications, side effects, or a poor/absent response from glucocorticoid treatment.[2] Eleven patients (8.2%) had a grade 3 ALT increase and 2 of these patients experienced serious elevations and required intravenous methylprednisolone.[2] The median corticosteroid treatment duration was 230 days, with 71.8% of patients receiving corticosteroids experiencing typical glucocorticoid side effects (e.g., Cushing's syndrome, acne, insomnia).[2] There were no deaths or withdrawals due to adverse events.[2] No patients reported thromboembolism although this is a hypothetical risk with increased factor levels and was included as a precaution in the product labeling.[6] Additional labeled warnings include theoretical risk of hepatocellular carcinoma and significant differences with measurements of factor VIII activity based on laboratory assay type and the reagents used. When transitioning from hemostatic agents, after receipt of valoctocogene roxaparvovec-rvox, patients should have factor VIII levels consistently measured with the same type of test and same reagents when possible.[2] More common adverse reactions include headache, nausea, vomiting, abdominal pain, and fatigue.[6] **Table 2** describes additional details of the phase 3 clinical trial including efficacy and safety data.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Clinically relevant bleeds
2) Quality of Life
3) Freedom from prophylactic factor therapy infusions
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in Factor VIII activity over 49 to 52 weeks

Table 1. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	• Adeno-associated virus serotype 5 (AAV5) based gene therapy vector. • Introduces a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). • Transcription of this transgene occurs within the liver resulting in the expression of hFVIII-SQ, which replaces the missing coagulation factor VIII.
Biodistribution	• Peak vector deoxyribonucleic acid (DNA) and shedding between days 1 to 9 post-dose and detectable in plasma up to 10 weeks.
Distribution and Protein Binding	• Highest vector DNA concentration in blood, followed by saliva, semen, stool, and urine.

Elimination	• For encapsidated (potentially transmissible) vector DNA, maximum time to first of 3 consecutive measurements below limit of detection or negative by the time of data cut was:
	  ○ 12 weeks in semen,
	  ○ 8 weeks in urine,
	  ○ 52 weeks in saliva, and
	  ○ 131 weeks in stool.
	• All patients achieved first of 3 consecutive measurements below the lower limit of quantification in semen by 36 week for vector DNA.
	• Magnitude and duration of shedding independent of attained factor VIII activity.

Immunogenicity	• All patients seroconverted to anti-AAV5 antibody positive within 8 weeks. • Titers peaked by 36 weeks. • Cellular immune response to AAV5 capsid peaked at week 2 (70%) and declined at week 26 (23%) and week 52 (17%).
Half-Life	Not applicable
Metabolism	Not applicable

Table 2. Comparative Evidence Table.[1,2]

Ref./ Study Design	Gene Therapy/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mahlangu et al. Ozelo et al. GENEr8-1 study NCT03370913 OL, SA, MC, Phase 3	1. Valoctocogene roxaparvovec-rvox $6x10^{13}$ vector genomes per kg as a single infusion Glucocorticoids (prednisone 60 mg daily tapered over minimum of 8 weeks) or other IS in response to ALT elevations Factor VIII prophylaxis continued x 4 wk then PRN	Demographics: -Mean age 31.7 years -Male 100% -White 71.6% -Asian 14.2% -Black 11.2% -Hispanic/Latino 5.2% -Hepatitis B 14.9% -Hepatitis C 30.6% -HIV 1.5% -0 Problem joints 72.4% -1 Problem joint 12.7% -Baseline bleeding and factor used data 9.2 mo Key Inclusion Criteria: -Men 18 years and older -Severe hemophilia A (factor VIII activity level < 1 IU/dL) -Regular exogenous factor VIII prophylaxis for at least 1 year -No history of Factor VIII inhibitors Key Exclusion Criteria: -Anti-AAV5 capsid antibodies -Significant liver dysfunction or fibrosis; cirrhosis -HIV (added after protocol amendment) -Willing to abstain from alcohol for at least 52 weeks following infusion -Chronic or active hepatitis B	ITT: 134 (all receiving gene therapy) mITT: 132 (ITT & HIV negative) Rollover: 112 (mITT & with at least 6 mo of prospectively collected bleeding and factor VIII usage data from 270-902 study) Attrition: 1 (LTFU at wk 66)	Primary Endpoint: Change from baseline in median factor VIII activity between 49-52 weeks post-treatment (mITT) Baseline: 1 IU/dL Treatment: Median 23.9 IU/dL (IQ, 11.9 to 62.3) Median Change: 22.9 IU/dL (IQ 10.9 to 61.3) Mean±SD: 42.9±45.5 IU/dL Mean Change: 41.9 IU/dL (95% CI 34.1 to 49.7; P<0.001) Median Factor VIII activity post-treatment 40 IU or greater: 37.9 % 5 IU to <40 IU: 50.0% <5 IU: 12.1% (<3 IU: 9.1%; subset of <5 IU) Primary endpoint (2-year extension): Change in annualized bleeding events at week 104 compared to baseline Change -4.1 (95% CI -5.4 to -2.8; P<0.001) Secondary Endpoints (rollover population): Change from baseline in annualized factor VIII concentrate consumption after week 4 Baseline:	NA NA NA	Adverse events: Any event: 100% Grade 3 (overall): 26.1% Grade 3 (ALT increase): 8.2% Grade 4: 0.7% TRAE ≥ 20%: ALT increase: 80.6% AST increase: 29.1% Nausea: 23.1% SAE: Any 16.4% ALT increase: 1.5% Diarrhea: 1.5% Gastroenteritis: 1.5% Rectal hemorrhage: 1.5% Deaths: None Infusion reactions: Systemic hypersensitivity: 5.2% Serious infusion-related reactions: 2.2%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Non-randomized, single arm design. Performance Bias: (Unclear) Open-label before and after study design; Objective measurements for primary outcome, though higher risk of bias for patient reported secondary endpoints of factor VIII use and bleeding events. Detection Bias: (Unclear) Objective measurements for primary outcome of activity level, though higher risk of bias for patient reported secondary endpoints of factor VIII use and bleeding events. Attrition Bias: (Unclear) Low overall attrition. Missing data imputed as LOCF for primary endpoint. Missing values for secondary endpoints imputed as zero. Reporting Bias: (Low) Protocol and study amendments available online. Other Bias: (Unclear) Study designed by sponsor with input from authors (some authors are employees of sponsor). Data collection and analysis performed by employees of the sponsor. First draft written by medical writer contracted by sponsor. Data-access plan was in place to minimize bias by limiting sponsor access to efficacy data before protocol-specified analyses were conducted. **Applicability**: Patient: Similar to disease population. Efficacy and safety in people with liver dysfunction or risk factors is unknown. Intervention: Dose based on phase 1/2 research. Comparator: Single-arm before/after design using prospectively gathered baseline data for most patients. No side by side comparison to existing standard of care or information on lifestyle/activity

		-Active hepatitis C or on antiviral therapy		Mean 3961.2±1751.5 IU/kg/yr Treatment: Mean 56.9 IU/kg/yr (98.6% reduction; P<0.001) Change from baseline in annualized number of treated bleeding events after week 4 Baseline: Mean 4.8±6.5 bleed/yr Treatment: 0.8 bleed/yr Change -4.1 (95% CI, -5.3 to -2.8; P<0.001)	NA			changes or differences between two time periods. Outcomes: Long-term durability unknown. Impact on quality of life was not evaluated. Setting: 48 sites in 13 countries worldwide, 15 US sites
Abbreviations: AAV5 = adeno-associated virus 5; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = Aspartate aminotransferase; CI = confidence interval; dL = deciliter; HIV = human immunodeficiency virus; IQ = interquartile; IS = immunosuppressants; ITT = intention to treat; IU = international unit; kg = kilogram; LOCF = last observation carried forward; LTFU = lost to follow up; MC = multi-center; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PP = per protocol; PRN = as needed; SA = single arm; SD = standard deviation; TRAE = treatment-related adverse event; wk = week.								

References:

1. Mahlangu J, Kaczmarek R, von Drygalski A, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. *N Engl J Med.* 2023;388(8):694-705.
2. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. *N Engl J Med.* 2022;386(11):1013-1025.
3. Lindsey W, Alexander C, Yang H, Grabowsky A. Gene therapies for hemophilia A and B. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2023.
4. DynaMed. Hemophilia A. EBSCO Information Services. Accessed August 13, 2023. Available at: https://www.dynamed.com/condition/hemophilia-a.
5. Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Haemophilia. 2015;21(5):578-584.
6. Roctavian (valoctocogene roxaparvovec-rvox) prescribing information. Biomarin Pharmaceuticals. June 2023. Available at: https://www.fda.gov/media/169937/download.
7. Long BR, Veron P, Kuranda K, et al. Early Phase Clinical Immunogenicity of Valoctocogene Roxaparvovec, an AAV5-Mediated Gene Therapy for Hemophilia A. *Mol Ther.* 2021;29(2):597-610.

Appendix 1: Prescribing Information Highlights

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

ROCTAVIAN (valoctocogene roxaparvovec-rvox) suspension for intravenous infusion
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. (1)

----------DOSAGE AND ADMINISTRATION----------
For one-time single-dose intravenous use only. (2)
- Perform baseline testing to select patients, including testing for pre-existing antibodies to adeno-associated virus serotype 5 (AAV5), factor VIII inhibitor presence, and liver health assessments. (2)
- The recommended dose of ROCTAVIAN is 6×10^{13} vector genomes (vg) per kg of body weight. (2.1)
- Start the infusion at 1 mL/min. If tolerated, the rate may be increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- ROCTAVIAN is a suspension for intravenous infusion. (3)
- ROCTAVIAN has a nominal concentration of 2×10^{13} vg valoctocogene roxaparvovec-rvox per mL, each vial contains an extractable volume of not less than 8 mL (16×10^{13} vg). (3)

----------CONTRAINDICATIONS----------
- Active infections, either acute or uncontrolled chronic. (4)
- Known significant hepatic fibrosis (stage 3 or 4), or cirrhosis. (4)
- Known hypersensitivity to mannitol. (4)

----------WARNINGS AND PRECAUTIONS----------
- Infusion-related reactions: Infusion reactions, including hypersensitivity reactions and anaphylaxis, have occurred. Monitor during and for at least 3 hours after ROCTAVIAN administration. If symptoms occur, slow or interrupt administration and give appropriate treatment. Restart infusion at slower rate once symptoms resolve. Discontinue infusion for anaphylaxis. (2.3, 5.1)
- Hepatotoxicity: Monitor alanine aminotransferase (ALT) weekly for at least 26 weeks and institute corticosteroid treatment in response to ALT elevations as required. Continue to monitor ALT until it returns to baseline. Monitor factor VIII activity levels since ALT elevation may be accompanied by a decrease in factor VIII activity. Monitor for and manage adverse reactions from corticosteroid use. (5.2)
- Thromboembolic events: Thromboembolic events may occur in the setting of elevated factor VIII activity above the upper limit of normal (ULN). Factor VIII activity above ULN has been reported following ROCTAVIAN infusion. Evaluate for risk factors for thrombosis including cardiovascular risk factors prior to and after ROCTAVIAN use and advise patients accordingly. (5.3)
- Monitoring laboratory tests: Monitor for factor VIII activity and factor VIII inhibitors. (5.4)
- Malignancy: Monitor for hepatocellular malignancy in patients with risk factors for hepatocellular carcinoma (e.g., hepatitis B or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, advanced age). Perform regular liver ultrasound (e.g., annually) and alpha-fetoprotein testing following administration. In the event that any malignancy occurs after treatment with ROCTAVIAN, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100. (5.5)

----------ADVERSE REACTIONS----------
- Most common adverse reactions (incidence ≥ 5%) were nausea, fatigue, headache, infusion-related reactions, vomiting, and abdominal pain. (6)
- Most common laboratory abnormalities (incidence ≥ 10%) were ALT, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), factor VIII activity levels, gamma-glutamyl transferase (GGT) and bilirubin > ULN. (6)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- For 6 months after administration, men must not donate semen, and men and their female partners must prevent or postpone pregnancy. (8.3)
- There is limited information on the safety and effectiveness of ROCTAVIAN in patients with HIV infection. (8.6)
- The safety and effectiveness of ROCTAVIAN in patients with prior or active factor VIII inhibitors have not been established. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2023

Valoctocogene roxaparvovec-rvox

Goal(s):

- Approve valoctocogene roxaparvovec-rvox (ROCTAVIAN) for conditions supported by evidence of benefit.

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Valoctocogene roxaparvovec (billed as pharmacy or physician 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 it the 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 for any diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have severe Hemophilia A with factor VIII activity of < 1 IU/dL?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation that the patient does not have factor VIII inhibitors?	**Yes:** Go to #6 Test date_____ Result_____	**No**: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient 18 years or older?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient tested negative for adeno-associated virus serotype 5 (AAV5) antibodies as measured by an FDA approved test?	**Yes**: Go to #8 Test date_____ Result_____	**No:** Pass to RPh. Deny; medical appropriateness
8. Has this patient had a liver health assessment (ALT, AST, bilirubin, alkaline phosphatase, INR, ultrasound or other radiologic assessment) and were all hepatic enzymes and hepatic radiological tests normal? Note: Mild enzyme elevations which are transient and resolved on repeat testing may answer "Yes" to this question.	**Yes**: Go to # 11	**No:** Go to #9
9. Does the patient have a history of severe liver fibrosis or cirrhosis?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Has the patient been evaluated and cleared for gene therapy treatment by a gastroenterologist or hepatologist?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient able and willing to abstain from alcohol for one year following receipt of gene therapy?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is there documentation that the patient does not have any active, acute or chronic infections, including HIV, hepatitis B, or hepatitis C?	**Yes**: Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is it anticipated that the patient will be able to safely use corticosteroids or other immunosuppressants for at least 8 weeks if needed?	**Yes**: Approve one lifetime does.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 10/23 (SF)
Implementation: TBD

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: SGLT2 Inhibitors

Date of Review: August 2023

Generic Name: bexagliflozin
Generic Name: sotagliflozin

Date of Last Review: October 2022
Dates of Literature Search: 08/01/2022 - 04/24/2023
Brand Name (Manufacturer): Brenzavvy (TheracosBio, LLC)
Brand Name (Manufacturer): Inpefa (Lexicon Pharmaceuticals, Inc.)
Dossiers Received: no

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for safety and harms of sodium-glucose co-transporter 2 (SGLT-2) inhibitors. The evidence for the new SGLT-2 inhibitors, bexagliflozin and sotagliflozin, will be evaluated and recommendations for place in therapy will be presented.

Plain Language Summary:
- This review looks at new research published for drugs called sodium-glucose co-transporter 2 (SGLT2) inhibitors. These medicines are used to lower blood sugar in people with type 2 diabetes. They have also shown to prevent damage to the heart and kidneys in people with and without diabetes.
- A high quality guideline from the National Institute for Health and Care Excellence recommends SGLT2 inhibitors for adults with chronic heart failure.
- Several different guidelines have made recommendations for the use of SGLT2 inhibitors in people with type 2 diabetes in addition to their ability to decrease blood sugar levels. These include evidence of benefit to the kidney and heart.
- There is a new drug approved by the Food and Drug Administration called bexagliflozin. The research on how well bexagliflozin lowers blood sugars showed bexagliflozin works the same as other SGLT2 inhibitors and has similar adverse reactions, such as yeast infections, bladder infections and increased urination. It was also found to lower blood sugars a similar amount as 2 other medicines used to manage type 2 diabetes called sitagliptin and glimepiride.
- There is a second new drug approved in this class called sotagliflozin. It has shown benefit in people with heart failure or in those with type 2 diabetes, chronic kidney disease and other cardiovascular risk factors, such as heart failure or high blood pressure. It has similar adverse events as other SGLT2 inhibitors, such as bladder infections, diarrhea and very low blood sugars.
- The Drug Use Research and Management Group recommends no changes to the preferred SGLT2 inhibitors in this class. The new drugs, bexagliflozin and sotagliflozin should go through the prior authorization process to ensure appropriate use.

Author: Kathy Sentena, PharmD

Research Question

1. In patients with type 2 diabetes (T2D), what is the comparative evidence for efficacy or harms of SGLT2 inhibitors for important outcomes (e.g., hemoglobin A1c [HbA1C], microvascular outcomes, macrovascular outcomes and mortality)?
2. Are there specific subpopulations (e.g., those with comorbidities) for which SGLT2 inhibitors may be better tolerated or more effective than other available antidiabetic therapies when used for glucose lowering?
3. What is the evidence for the effectiveness and harms of bexagliflozin in patients with T2D?
4. Are there specific subpopulations for which bexagliflozin may be specifically indicated, more effective, or associated with less harm?
5. What is the evidence for the effectiveness and harms of sotagliflozin in patients with HF or T2D, CKD and other CV risk factors?
6. Are there specific subpopulations for which sotagliflozin may be specifically indicated, more effective, or associated with less harm?

Conclusions:

- Included in this update are the following: 4 high quality guidelines, 3 new indications, one new safety warning, 3 randomized controlled trials and 2 new drug evaluations.
- National Institutes for Health and Care Excellence (NICE) guidance recommends the use of SGLT-2 inhibitors for adults with chronic heart failure (HF).[1]
- Updated guidelines by the Kidney Disease: Improving Global Outcomes (KDIGO) strongly recommend SGLT-2 inhibitors for adults with T2D and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) $\geq$ 20 ml/min per 1.73 m^2, with or without hyperglycemia (Strong recommendation).[2]
- The Canadian Cardiovascular Society strongly recommends the use of SGLT2 inhibitors, based on moderate evidence, for adults with T2D for the treatment of HF and CKD.[3]
- The American Diabetes Association (ADA) recommends the use of SGLT2 inhibitors for glucose lowering and for CV and renal benefits in those with T2D.[4,5]
- Dapagliflozin and empagliflozin received additional Food and Drug Administration (FDA) approved indications for reducing cardiovascular (CV) risk in adults.[6,7]
- Empagliflozin monotherapy and in combination with metformin, received approval for use in children and adolescents 10 years of age and older with T2D.[8]
- A safety warning was added to SGLT2 labeling due to a drug interaction with lithium causing reduced lithium concentrations.
- A new SGLT2 inhibitor, bexagliflozin, was approved in January of 2023.[9] Moderate-quality evidence showed bexagliflozin efficacy is similar to other SGLT2 inhibitors with HbA1c lowering of -0.38% to -0.48%. Active treatment comparisons found bexagliflozin to be non-inferior to sitagliptin and glimepiride (moderate quality of evidence). Common adverse events are female genital mycotic infections, urinary tract infection and increased urination.[9]
- Moderate-quality evidence shows sotagliflozin reduces the risk of CV death, hospitalization for HF and urgent HF visits in adults with HF or T2D, CKD and other CV risk factors.[10] Sotagliflozin is not approved for glucose lowering at this time. Adverse reactions are similar to other SGLT2 inhibitors. When studied in patients with type 1 diabetes (T1D), sotagliflozin had an increased incidence of diabetic ketoacidosis (DKA) compared to placebo.
- Limitations to the data include lack of ethnic diversity and the enrollment of populations that are older than those in the fee-for-service (FFS) Medicaid program.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on a review of recent clinical evidence.
- Update prior authorization (PA) criteria to allow for preferred SGLT2 therapies to be used first-line in treatment of T2D.
- Maintain bexagliflozin and sotagliflozin as non-preferred.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- The SGLT2 inhibitor class was reviewed in October of 2022. The committee voted to maintain the PA criteria for preferred SGLT2 inhibitors as second line therapy after metformin in patients with diabetes and update the PA to clarify that renal function should be evaluated on an annual basis.
- Evidence was presented that demonstrated that SGLT2 inhibitors were more effective than placebo in people with T2D and atherosclerotic cardiovascular disease (ASCVD) or who were at high risk of ASCVD for the following outcomes: CV death or hospitalization for heart failure (HF), all-cause mortality, major adverse cardiovascular events (MACE), and hospitalizations for HF or emergency department visits for HF.

Background:

Approximately 287,000 adult Oregonians have T2D.[11] It is estimated that over 38,000 of these patients are Oregon Health Plan (OHP) members and over 10,000 Oregon FFS members have a T2D diagnosis.[11] The OHP paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012.[11] The overall cost to the state is estimated at $3 billion a year.[11] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2D by 2050.[12] Despite a variety of treatment options, a significant number of patients fail to meet HbA1c goals within 3 years of being diagnosed and 50% of patients require combination therapy to control their T2D.[13,14]

Underlying characteristics that lead to hyperglycemia and T2D are insulin resistance and impaired insulin secretion. While evidence has shown the importance of lifestyle modifications, such as diet and exercise changes, antidiabetic treatments are necessary to reduce glucose levels in most patients with T2D.[15] Pharmacotherapy improves hyperglycemia by increasing glucose uptake, increasing glucose secretion and/or increasing insulin sensitivity. Goal glucose levels are dependent upon patient characteristics, such as age and comorbidities; however, guidelines recommend a goal HbA1c of less than 7% for most patients but a range of less than 6.5% to less than 8% may be appropriate in certain patients. Currently available classes of non-insulin antidiabetic agents are: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), insulins, meglitinides, SGLT2 inhibitors, sulfonylureas, thiazolidinediones, bile acid sequestrants, dopamine-2 agonists and amylin mimetics. Current evidence and guidelines recommend metformin as a first-line treatment in most patients with T2D due to its safety profile, low risk of hypoglycemia and potential CV benefit.[16–18] In patients with CV or renal comorbidities some guidelines recommend the use of therapies such as SGLT2 inhibitors and GLP-1 RAs, that have evidence of CV and renal benefits, as first line therapy.[4,5] There is no consensus on a universally recognized second-line treatment, and therefore, selection should depend on the degree of glucose lowering required to assist in obtaining goal HbA1c levels, patient specific characteristics including comorbidities, and harms of therapy.[16] People that may benefit from weight loss should consider SGLT2 inhibitors or GLP-1 RAs, which have high quality evidence demonstrating weight reductions with use.[17] This update will focus on new evidence for the use of SGLT2 inhibitors (**Table 1**).

Sodium glucose cotransporter-2 inhibitors block the reabsorption of glucose from the renal glomerular filtrate in the renal proximal tubule.[19] The result is a reduction in renal absorption of filtered glucose and increased urinary glucose excretion. An additional mechanism of action is reduced sodium reabsorption and increased sodium delivery to the distal tubule.[19] In addition to glucose lowering, some SGLT-2 inhibitors have evidence of reducing CV death (e.g., canagliflozin, dapagliflozin, and empagliflozin) and adverse renal outcomes in those with diabetic nephropathy and albuminuria (e.g., canagliflozin) in adults with T2D. Benefits of SGLT2 inhibitors have also been demonstrated in adults without diabetes with HF (e.g., dapagliflozin, empagliflozin) and in those with chronic kidney disease (e.g., dapagliflozin).

Table 1. Cardiovascular and Renal Outcomes for SGLT2 Inhibitors compared to Placebo[17,20]

	All-Cause Mortality	Stroke	CV Death/ CV Events	Myocardial Infarction	Hospitalization for Heart Failure	Chronic Kidney Disease
SGLT-2 Inhibitors	*No effect (moderate quality evidence)* Benefit: Empagliflozin Neutral: Canagliflozin Dapagliflozin	*No effect (low quality evidence)* Neutral: Canagliflozin Dapagliflozin Empagliflozin	*Reduced Risk (moderate quality evidence)* Benefit: Canagliflozin* Dapagliflozin* Empagliflozin∞*	*No effect (moderate quality evidence)* Neutral: Canagliflozin Dapagliflozin Empagliflozin	*Significant risk reduction (moderate quality evidence)* Benefit: Canagliflozin Dapagliflozin* Empagliflozin* Ertugliflozin	*Reduced risk of eGFR decline, end stage kidney disease CV death and hospitalization for HF in adults with* CKD *(moderate quality evidence)* Benefit: Dapagliflozin* Canagliflozin*

* FDA indicated for this outcome

Abbreviations: CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ER = extended release; GLP-1 = glucagon-like peptide 1; HR = heart failure; inj = injection; SGLT-2 = sodium-glucose cotransporter-2

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, HbA1c reduction, severe adverse events and hypoglycemia. Hemoglobin A1C reduction is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well. A clinically relevant change in HbA1c is considered to be a decrease of 0.3% or more.[21] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most antidiabetic treatments to control glucose levels long-term.

Abbreviated Drug Utilization Evaluation:

Ninety-five percent of SGLT-2 utilization is for preferred products: canagliflozin, dapagliflozin and empagliflozin. There were almost 100 claims for SGLT-2 inhibitors in fourth quarter of 2022, which represents a modest cost to the OHP. All SGLT-2 inhibitors require PA.

Methods:

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

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

Systematic Reviews:
After review, twenty one systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[22–27, 23,28–39, 40–42]

New Guidelines:
High Quality Guidelines:

NICE – Chronic Heart Failure in Adults
The National Institute for Health and Care Excellence updated guidance for the use of dapagliflozin and empagliflozin in 2021 and 2022, respectively, for the management of people with HF.[1] The recommendation is that those adults with chronic HF and reduced ejection fraction (i.e., ejection fraction less than 40%) should be offered SGLT-2 inhibitors, if appropriate based on patient specific factors, along with other HF medications (e.g., ACE inhibitors, ARBs, beta-blockers, mineralocorticoid receptor antagonists [MRAs] and angiotensin receptor/neprilysin inhibitor [ARNIs]).[1]

Specific recommendations for the management of HF with reduced ejection fraction from NICE include:[1]
- ACE and beta-blockers as first-line treatment.
- ARBs licensed for HF as an alternative to ACE inhibitors in people who are unable to tolerate an ACE inhibitor.
- MRAs, SGLT-2 inhibitors, and sacubitril/valsartan have demonstrated improved outcomes and should be added to optimize the standard of care if advised by a specialist.

KDIGO 2022 Clinical Practice Guideline
In 2022 KDIGO updated their 2020 recommendations with an emphasis on glucose lowering therapies in patients with CKD, highlighting the use of SGLT-2 inhibitors. Guideline methodology was well described; however, authors had a significant number of conflicts of interest.[2] Recommendations were graded from Grade A (high quality of evidence) to Grade D (very low quality of evidence).

Optimal management of people with diabetes and CKD has important consequences on minimizing kidney failure and CV events (e.g., myocardial infarction [MI], stroke, ischemia, and HF) and other diabetes-related complications.[2] SGLT-2 inhibitors are an important component of first-line drug therapy recommendations that also include metformin, renin-angiotensin-system [RAS] inhibitors and moderate- or high-intensity statin. In addition to the composite kidney outcomes, SGLT2 inhibitors conferred less annual eGFR decline and a reduction in albuminuria or decreased progression to severely increased albuminuria.[2]

Recommendations pertaining to SGLT-2 utilization:[2]
- SGLT-2 inhibitors should be used to treat people with T2D and CKD with an eGFR $\geq$20 ml/min per 1.73 m^2, with or without hyperglycemia (Strong recommendation; Grade 1A).
- In Patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2 inhibitor therapy, or who are unable to use those medications, a long-acting GLP-1 RA is recommended (Grade 1B).

Other Considerations with using SGLT-2 inhibitors in people with T2D and CKD[2]:
- People treated with other glucose lowering therapy should still be considered for treatment with an SGLT2.

- SGLT-2 inhibitors with evidence of kidney and CV benefit (e.g., canagliflozin 100 mg, dapagliflozin 10 mg and empagliflozin 10 mg) should be considered in treatment choice.
- SGLT-2 inhibitors should be held if the patient undergoes a prolonged fast, surgery or critical medical illness.
- For patients at risk of hypovolemia, consider decreasing dose of thiazide or loop diuretic dose before initiating SGLT-2 therapy and counsel patients on symptoms of volume depletion.
- Upon initiation of SGLT-2 therapy a reversible decrease in eGFR may occur and most likely therapy does not have to be discontinued.
- If a patient has been initiated on a SGLT-2 inhibitor, it may be continued even if the eGFR falls below of 20 ml/min per 1.73 m^2 unless it is not tolerated or kidney replacement therapy is initiated.
- SGLT-2 inhibitors have not been adequately studied in kidney transplant recipients.

The recommendation for the use of SGLT2 inhibitors is based on evidence of benefit that demonstrated kidney and CV protection.[2] Improved outcomes in patients with CKD using SGLT-2 inhibitors have been demonstrated in those without diabetes as well. There is insufficient evidence to recommend the use of SGLT-2 inhibitors in patients with type 1 diabetes (T1D).

2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 receptor agonists and SGLT2 inhibitors for Cardiorenal Risk Reduction in Adults

A 2022 guideline from the Canadian Cardiovascular Guideline updated recommendations for the use of SGLT2 inhibitors in patients with T2D.[3] Methods were clearly presented; however, all but three of 25 panel members had conflicts of interest. Recommendations were based on a high quality systematic review and meta-analysis. Recommendations were evaluated by the GRADE approach. Recommendations ranged from "strong" to "weak" based on the quality of evidence are are presented in **Table 2**.

Table 2. Recommendations for the Use of SGLT2 inhibitors for Cardiorenal Risk Reduction[3]

Recommendation	Rationale	Strength of recommendation; quality of evidence
SGLT2 inhibitors are recommended for adults with HF and an LVEF less than or equal to 40%	To reduce the risk of all-cause and CV mortality, hospitalization for HF and the composite end point of significant decline in eGFR progression to end-stage kidney disease or death due to kidney disease	Strong; moderate
SGLT2 inhibitors are recommended for adults with HF and LVEF greater than 40%	To reduce hospitalizations for HF	Strong; moderate
SGLT2 inhibitors are recommended for adults with CKD (UACR >20 mg/mmol and eGFR $\geq$25 ml/min/1.73m^2)	To reduce the composite of significant decline in eGFR, progression to end stage kidney disease, or kidney death, all cause and CV mortality, nonfatal MI, and hospitalization for heart failure.	Strong; moderate
SGLT2 inhibitors and GLP-1 RAs are recommended for adults with T2D and either established ASCVD or multiple risk factors for ASCVD	To reduce the risk of all-cause or CV mortality or MACE	Strong; moderate

SGLT2 inhibitors are recommended for adults with T2D and either established ASCVD or multiple risk factors for ASCVD	To reduce the risk of hospitalization for HF or the composite for significant decline in eGFR, progression to end stage kidney disease or kidney death	Strong; moderate
Abbreviations: ASCVD – atherosclerotic cardiovascular disease; CKD – chronic kidney disease; CV – cardiovascular; eGFR – estimated glomerular filtration rate; GLP-1 RA – glucagon-like peptide-1 receptor agonists; HF – heart failure; LVEF – left ventricular ejection fraction; MACE – major adverse cardiovascular events; SGLT2 – sodium-glucose co-transporter 2; T2D – type 2 diabetes; UACR – urine albumin-creatinine ratio		

ADA – Standards in Diabetes Update 2023

The annual update from the ADA on the standards of care in diabetes was published in January in 2023. New updates include recommendations for the use of SGLT2 inhibitors to slow progression of chronic kidney disease.

Pharmacotherapy recommendations include using therapies to achieve and maintain goal treatment levels. Choice of medications should include consideration of patient comorbidities and selecting therapies which provide benefit, such as weight management or reduction in cardiorenal risk. Recommendations for the use of SGLT2 inhibitors include the use of SGLT2 inhibitors that have demonstrated CV benefit, irrespective of glucose levels, in those who are high risk or have atherosclerotic disease CV disease, HF (with preserved or reduced ejection fraction), and/or CKD to reduce cardiorenal risk as part of their glucose lowering regimen (Grade A). Specifically SGLT2 inhibitors are recommended for people with T2D and diabetic kidney disease to reduce progression and CV events in those with an eGFR of 20 ml/min/1.73 m^2, or greater, and urinary albumin of 200 mg/g creatinine or greater (Grade A). This recommendation is also extended to those with an eGFR of 20 ml/min/1.73 m^2, or greater, and urinary albumin ranging from normal to 200 mg/g creatinine (Grade B). The use of SGLT2 inhibitors for CV risk reduction in people with T2D (with an eGFR of 20 ml/min/1.73 m^2 or greater) and diabetic kidney disease is also recommended (Grade A).

Canagliflozin, dapagliflozin and empagliflozin have evidence of CV benefit and canagliflozin and dapagliflozin have evidence for slowing the progression of diabetic kidney disease. Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin have demonstrated benefit for HF. SGLT2 inhibitors are also recommended for those for glycemic management (high recommendation) and for achievement and maintenance of weight management (intermediate recommendation). The glucose lowering effect of SGLT2 inhibitors is reduced in people with lower eGFR.

Combination therapy with a SGLT2 inhibitor (with demonstrated CV benefit) and a GLP-1 RA (with demonstrated CV benefit) may be considered in those with T2D and established atherosclerotic CV disease or multiple risk factors for atherosclerotic CV disease to help reduce the risk of adverse CV and kidney events (Grade A).

New Formulations or Indications:

Dapagliflozin (FARXIGA) – In May of 2023 dapagliflozin received an expanded indication to reduce the risk of CV death, HF hospitalizations, and urgent visits due to HF in all adult patients.[6] The expanded indication applies to patients with HF that have all ranges of ejection fractions.

Empagliflozin and metformin (SYNJARDY AND SYNJARDY XR) – In February of 2023 the combination product containing empagliflozin and metformin received an additional indication to reduce the risk of CV death and hospitalization for HF in adults with HF.[43] The new indication was based off previously presented trials, Emperor-preserved and Emperor-reduced.

Empagliflozin and metformin (JARDIANCE and SNJARDY) – In June of 2023 empagliflozin and empagliflozin/metformin were approved for the use in children and adolescents, 10 years and older with T2D, to improve blood sugar control as an adjunct to diet and exercise.[8] Evidence for use was demonstrated in a 26-week, placebo-controlled, randomized, double-blind study which evaluated the use of empagliflozin and linagliptin.

New FDA Safety Alerts:

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
All SGLT2 inhibitors	Not applicable	October 2023	Warnings	Risk of drug interactions with lithium, which may decrease lithium concentrations. Serum lithium levels should be monitored more frequently if initiating or changing doses of a SGLT2 inhibitor.

Randomized Controlled Trials:

A total of 76 citations were manually reviewed from the initial literature search. After further review, 73 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Soloman, et al[44] DELIVER DB, MC, PG, Phase 3, RCT	1. Dapagliflozin 10 mg orally once daily* 2. Placebo* * In addition to usual therapy Median study duration: 2.3 years	Adult patients, with or without diabetes, with HF and left ventricular ejection fraction of more than 40% N = 10,418	Composite of worsening HF (unplanned hospitalization for HF or urgent visit for heart failure) or CV death	1. 512 (16.4%) 2. 610 (19.5%) HR 0.82 (95% CI, 0.73 to 0.92) P<0.001	In patients with mildly reduced or preserved ejection fraction, dapagliflozin was more effective than placebo at reducing the risk of worsening HF or CV death (ARR 3.1%/NNT 33)
Laffel, et al[45] DINAMO DB, MC, PG, Phase 3, RCT	1. Empagliflozin 10 mg orally once daily* 2. Linagliptin 5 mg orally once daily 7. Placebo	Patients 10-17 years of age with a history of diabetes for at least 8 weeks before screening N = 158	Change from baseline in HbA1c at 26 weeks	1. -0.17% (pooled doses) 2. 0.33% 3. 0.68% Empagliflozin compared to placebo: Mean change -0.84% (95% CI, -1.50 to -0.19) P=0.012	In patients with a mean age of 14 years and obese, empagliflozin reduced HbA1c more than placebo or linagliptin.

	* Those who did not have and HbA1c < 7% by week 12 were underwent a second randomization at week 14 to either stay on 10 mg or increase to 25 mg 26 weeks			Linagliptin vs. placebo: Mean change -0.34% (95% CI, -0.99 to 0.30) P=0.29	
EMPA-KIDNEY Collaborative Group[46] EMPA-KIDNEY DB, MC, PC, Phase 3, RCT	1. Empagliflozin 10 mg orally once daily* 2. Placebo* * In addition to usual therapy Median follow-up: 2 years	Adults with chronic kidney disease who had an eGFR of at least 20 but less than 45 ml/min/1.73 m2 or an eGFR of at least 45 but less than 90 ml/min/1.73 m2 with an urinary to albumin-to-creatinine ratio of at least 200 N=6609	Composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml/min/1.73 m2, sustained decrease in eGFR of 40% or greater from baseline or death from renal causes) or death from CV disease	1. 432 (13.1%) 2. 558 (16.9%) HR 0.72 (95% CI, 0.64 to 0.82) P<0.001	Results were similar in those with or without diabetes. Empagliflozin was more effective than placebo at reducing progression of kidney disease or death from CV causes (ARR 3.8%/NNT 27)

Abbreviations: ARR = absolute risk reduction; DB = double-bind; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure, HR = hazard ratio; MC = multicenter; NNT = number needed to treat; PG = parallel group, RCT = randomized controlled trial

NEW DRUG EVALUATION: BEXAGLIFLOZIN

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Bexagliflozin (Brenzavvy®) is a SGLT-2 inhibitor approved for use as an adjunct to diet and exercise for controlling glucose levels in adults with T2D.[9] Approval was based on 6 phase 3 studies, in which 3 have been published.[47–49] The published trials, including a phase 2 trial, are described in Table 6. In these trials, bexagliflozin was compared to placebo in 2 trials and compared to active treatment, sitagliptin and glimepiride, in the remaining two. Participants in the trials had T2D with baseline HbA1c levels ranging from 7.98% to over 8.5%.[19] The average age of the participants was 61 years and predominately of White ethnicity.

All of the trials were small (n= 283 to 426). In one trial the participants had moderate renal impairment.[48] The primary outcome in all of the trials was change in HbA1c. Changes in body mass and the percent of patients obtaining an HbA1c <7% were relevant secondary endpoints.

Bexagliflozin lowered HbA1c in all the trials with difference from placebo ranging from 0.37% to 0.79%.[47–49] In the FDA Integrated review, the placebo-adjusted estimate of the treatment effect of bexagliflozin ranged from -0.38% to -0.48%.[19] Bexagliflozin was found to be non-inferior to both sitagliptin and glimepiride, as add-on therapy to metformin. Bexagliflozin demonstrated reductions in body mass in placebo and active treatment comparison trials ranging from -2.0 kg to -3.75 kg. The mean number of patients obtaining a HbA1c <7% was 34% with bexagliflozin vs. 21.5% for placebo (p-value not reported; secondary outcome).[48]

Limitations to the evidence include the data from small, short-term studies for the majority of the evidence. In the non-inferiority trial comparing bexagliflozin to glimepiride, the max dose of glimepiride was 6 mg daily, which is less than then maximum approved dose of 8 mg daily, which could underestimate the glucose lowering effects of glimepiride.

Clinical Safety:
The most common adverse reactions with bexagliflozin are female genital mycotic infections, urinary tract infection and increased urination.[8] Bexagliflozin should not be used in people with a GFR less than 30 mL/min/ 1.73 m2 and is contraindicated in people on dialysis. Any volume depletion should be corrected before treatment initiation. Severe adverse events include: ketoacidosis, lower limb amputations, volume depletion, urosepsis and pyelonephritis, hypoglycemia with insulin and insulin secretagogues concomitant use, and necrotizing fasciitis of the perineum, all of which are similar to other SGLT-2 inhibitors.[9] A summary of adverse reactions observed in clinical trials is presented in **Table 4**.

Table 4. Adverse Reactions in Adult with Type 2 Diabetes (+/- metformin) that Occurred in at Least 2% of Patients[9]

Adverse Reaction	Placebo (n=300)	Bexagliflozin (n=372)
Increased urination	3	7
Urinary tract infection	4	6
Female genital mycotic infection	0	6
Thirst	2	3
Vaginal pruritus	0	3
Male genital mycotic infection	1	2
Hypoglycemia	1	2

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Change in HbA1c
2) Cardiovascular mortality
3) All-cause mortality
4) Progression of renal disease
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in HbA1 over 24 to 60 weeks

Table 5. Pharmacology and Pharmacokinetic Properties.[9]

Parameter	
Mechanism of Action	Sodium-glucose co-transporter 2 inhibitor, which blocks the reabsorption of the majority of glucose from the renal glomerular filtrate in the renal proximal tubule. This reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, increasing urinary glucose excretion.
Oral Bioavailability	78%
Distribution and Protein Binding	93% protein bound to plasma protein Volume of distribution is 262 L
Elimination	51.1% in the feces and 40.5% in the urine
Half-Life	12 hours
Metabolism	Metabolized by UGT1A9 and to a lesser extent by CYP3A4

Abbreviations: CYP = cytochrome P450; L = liters; UGT = Uridine 5'-diphospho-glucuronosyltransferase.

Table 6. Comparative Evidence Table for Bexagliflozin.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Halvorsen, et al[2] (2019) DB, DD, MC, NI, PG, Phase 3, RCT	1. Bexagliflozin 20 mg 2. Sitagliptin 100 mg * On background metformin in both arms 24-weeks	Demographics: Age: 59.4 years Male: 64.1% Asian: 16.1% White: 81.8% Disease duration: 8.79 years Baseline HbA1c: 7.99% Key Inclusion Criteria: - T2DM - ≥18 years of age - Metformin dose of 1500 mg or more - HbA1c 7% - 11% - BMI of ≤ 45 kg/m2 Key Exclusion Criteria: - T1DM - Pregnant or breastfeeding - Pancreatitis - Genitourinary infections	ITT: 1. 192 2. 194 PP: 1. 180 2. 189 Attrition: 1. 12 (6.3%) 2. 5 (2.6%)	Primary Endpoint: Mean change from baseline in HbA1c at week 24: 1. Bexagliflozin: -0.74% 2. Sitagliptin: -0.82% MD 0.08% (95% CI, -0.07 to 0.22%) NI achieved; prespecified margin was 0.35% Secondary Endpoints: Fasting blood glucose: 1. Bexagliflozin: -1.82 mmol/L 2. Sitagliptin: -1.44 mmol/L MD -0.37 (95% CI, -0.70 to -0.05) P=0.0123 Body mass: 1. Bexagliflozin: -3.35 kg/m2 2. Sitagliptin: -0.81 kg/m2	NA NA NA	Severe Adverse Events: 1. Bexagliflozin: 7 (3.7%) 2. Sitagliptin: 4 (2.1%) Hypoglycemia: 1. Bexagliflozin: 6 (3.1%) 2. Sitagliptin: 10 (5.2%) Nasopharyngitis: 1. Bexagliflozin: 15 (7.9%) 2. Sitagliptin: 25 (13.0%) Treatment Discontinuations due to AE: 1. Bexagliflozin: 6 (3.1%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Computer generated random assignment based on an interactive web response system. Baseline characteristics were similar between groups. Performance Bias: (Low) All patients took two identical investigational products. Detection Bias: (Unclear) Not described. Attrition Bias: (Low) Attrition was low in both groups. Reporting Bias: (Low) Study protocol followed as outlined. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to White males with moderately uncontrolled diabetes as an adjunct to metformin therapy. This population is older than the Oregon FFS demographic. Intervention: The intervention is appropriate. Bexagliflozin 20 mg was studied in phase 2 studies. Comparator: Sitagliptin 100 mg is an appropriate comparator. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents.

				MD -2.54 (95% CI, -3.15 to -1.92) P<0.0001		2. Sitagliptin: 1 (0.5%)		Setting: 52 sites across the United States, Czech Republic, Hungary, Spain, Poland and Japan.
2. Allegretti, et al[48] DB, MC, PC, PG, Phase 3, RCT	1. Bexagliflozin 20 mg 2. Placebo 24 weeks	Demographics: Mean Age: 69.6 yrs Male: 62.8% White: 54.8% Asian: 38.5% CKD stage 3a: 166 CKD stage 3b: 146 Mean duration of diabetes: 16 years Mean baseline HbA1c: 7.98% Insulin use: 56% Metformin use: 41.7% Key Inclusion Criteria: - Ages 20 years or older - Patients with CKD stage 3a or 3b - T2DM - HbA1c 7.0% to 10.5% - GFR 30-59 ml/min/1.73m2 - BMI 45 kg m2 or less - Taking oral hypoglycemic agents without changes in the previous 8 weeks Key Exclusion Criteria: - T1DM - History of hypoglycemia more than 1 episode a week - Cancer (not in remission), MI, stroke or hospitalization for unstable angina/HF within previous 3 months	ITT: 1. 157 2.155 PP: 1. 152 2.144 Attrition: 1. 4 (3%) 2. 7 (5%)	Primary Endpoint: Change in HbA1c from baseline to week 24: Bexagliflozin: -0.61% Placebo: -0.24% MD -0.37% (95% CI, -0.20 to -0.54%) P <0.001 Secondary Endpoints: Changes in body weight at 24 weeks: Bexagliflozin: -2.0 kg Placebo: -0.39 kg MD -1.61 kg (95% CI, -1.00 to -2.2) P <0.001 Percent of Patients Achieving a HbA1c <7%: Bexagliflozin: 52 (34.2%) Placebo: 32 (21.5%) p-value not reported	NA NA NA	Severe Adverse Events: 1. Bexagliflozin: 11 (7.0%) 2. Placebo: 9 (6%) Treatment Discontinuations due to AE: 1. Bexagliflozin: 1 (1%) 2. Placebo: 4 (3%) Hypoglycemia: 1. Bexagliflozin: 39 (25%) 2. Placebo: 38 (25%) Urinary Tract Infections: 1. Bexagliflozin: 11 (7%) 2. Placebo: 5 (3%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1 ratio via a central interactive web response system. Performance Bias: (Low) Investigators, patients and sponsors blinded to treatment allocation. Allocation codes managed by statistician not involved in the study operations. Detection Bias; (Unclear) Not described. Attrition Bias: (Low) Low attrition. Results analyzed with ITT and LOCF. Reporting Bias: Study protocol followed as outlined. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to patients with long-term diabetes that are moderately controlled with CKD stage 3a or 3b. Intervention: Bexagliflozin 20 mg is appropriate Comparator: Placebo comparison is appropriate; however, active treatment comparison would be more helpful in determining place in therapy. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents. Setting: 54 sites in the United States, Spain, France and Japan.

3. Halvorsen, et al (2023)[49] DB, DD, MC, NI, PG, Phase 3, RCT	1. Bexagliflozin 20 mg 2. Glimepiride 2-6 mg (titrated up if SMG measurements were >100 mg/dL) 96 weeks	Demographics: Mean Age: 59.6 yrs Male: 58.2% White: 94.4% Asian: 3.1% Mean duration of diabetes: 5.8 years Body mass index: 89.09 kg Baseline FPG: 9.62 mmol/L (173 mg/dL) Baseline HbA1c: 8.01% Metformin use: 64.3% Key Inclusion Criteria: - Ages 18 years or older - Inadequately controlled on metformin 1500 mg daily for at least 8 weeks - Not taking more than one other OHA - T2DM - HbA1c 7.0% to 10.5% - GFR 30-59 ml/min/1.73m^2 - BMI 45 kg m^2 or less - Taking oral hypoglycemic agents without changes in the previous 8 weeks Key Exclusion Criteria: - T1DM or maturity onset diabetes of the young - History of genitourinary infections - Cancer, uncontrolled hypertension, eGFR less than 60 mL/min/1.73 m^2	ITT: 1. 213 2. 213 PP: 1. 180 2. 177 Attrition: 1. 33 (15.5%) 2. 36 (17%)	Primary Endpoint: Change in HbA1c from baseline to week 60: 1. Bexagliflozin: -0.70% 2. Glimepiride: -0.66% MD -0.05% (95% CI, -0.21 to 0.11%) Prespecified margin of 0.35% for the upper boundary of the 95% CI was met for noninferiority Secondary endpoints; Body mass changes at week 60 in those that with a BMI of 25 kg /m2 or greater: 1. Bexagliflozin: -3.75 kg 2. Glimepiride: 0.6 kg MD -4.31 kg (95% CI, -5.10 to -3.52) P<0.0001	NA NA	Severe Adverse Events: 1. Bexagliflozin: 25 (12%) 2. Glimepiride: 26 (12%) Treatment Discontinuations due to AE: 1. Bexagliflozin: 8 (3.8%) 2. Glimepiride: 11 (5.2%) Hypoglycemia: 1. Bexagliflozin: 36 (16.9%) 2. Glimepiride: 71 (33.3%) Urinary Tract Infections: 1. Bexagliflozin: 25 (11.7%) 2. Glimepiride: 10 (4.7%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized via an interactive web-response system. There were more females in the bexagliflozin arm. Performance Bias: (Low) All patients received identical products as a placebo and active therapy Detection Bias: (High) An independent data and safety monitoring committee reviewed unblinded data for safety and efficacy issues and a blinded clinical endpoint committee adjudicated major CV events. Attrition Bias: (high) Greater than 10% attrition. Results analyzed with ITT and missing data imputed via multiple imputations. Reporting Bias: Study protocol followed as outlined. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to patients who were predominately white, inadequately controlled by metformin who are overweight or obese. Intervention: Bexagliflozin 20 mg is appropriate Comparator: Glimepiride 2-6 mg. The maximum dose of glimepiride is 8 mg so the bexagliflozin efficacy could potentially be underestimated. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents. Setting: 38 sites in the United States, Germany, Poland and Spain.

4. Halvorsen, et al[37] (2019) DB, MC, PG, Phase 2, RCT	1. Bexagliflozin 20 mg 2. Placebo 96 weeks	Demographics: Mean Age: 55.6 yrs Male: 41% White: 77.7% Mean duration of diabetes: 7.47 years Body mass index: 30.1 kg m2 Baseline FPG: 9.44 mmol/L (169.9 mg/dL) Baseline HbA1c < 8.5%: 65% Baseline HbA1c ≥ 8.5%: 35% Key Inclusion Criteria: - Ages 18 years or older - T2DM - HbA1c 7.0% to 10% - FPG < 250 mg/dl if treatment naïve or < 240 mg/dl if taking only oral hypoglycemic agent. - BMI 45 kg m2 or less Key Exclusion Criteria: - Parenteral antidiabetic medication - eGFR < 50 ml/min/1.73 m2 - History of genitourinary infections - Abnormal LFTs - Cancer, uncontrolled hypertension	ITT: 1. 145 2. 138 PP: 1. 126 2. 122 Attrition: 1. 33 (13.1%) 2. 16 (11.6%)	Change in HbA1c at 24 weeks: 1. Bexagliflozin: -0.28% 2. Placebo: 0.51% MD -0.79% (95% CI, -0.53 to -1.06%) P<0.0001 Secondary endpoints; Body mass changes at week 60 in those that with a BMI of 25 kg /m2 or greater: 1. Bexagliflozin: -2.63 kg 2. Placebo: 0.67 kg MD -1.96 kg (95% CI, -5.10 to -3.52) P<0.0001	NA NA	Severe Adverse Events: 1. Bexagliflozin: 4 (2.8%) 2. Placebo: 12 (8.5%) Treatment Discontinuations due to AE: 1. Bexagliflozin: 2 (1.4%) 2. Placebo: 0 (0%) Hypoglycemia: 1. Bexagliflozin: 24 (16.6%) 2. Placebo: 25 (17.7%) Urinary Tract Infections: 1. Bexagliflozin: 21 (14.5%) 2. Placebo: 29 (20.6%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized via an interactive web-response system using a computer generated sequence. There were more females in the bexagliflozin arm. Performance Bias: (Unclear) Not described. Detection Bias: (High) Unblinded data and safety monitoring board to review study data. Attrition Bias: (High) Greater than 10% attrition. Results analyzed with ITT and missing data with LOCF. Reporting Bias: One site had to be closed due to improbable data. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to patients who were predominately white females who are obese who have been previously treated with antidiabetic therapy. Intervention: Bexagliflozin 20 mg is appropriate Comparator: Placebo is appropriate; however, active treatment comparison would be more helpful in determining place in therapy. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents. Setting: 27 sites in the United States, Columbia and Mexico.

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = double-blind; DD = double-dummy; eGFR = estimated glomerular filtration rate; ITT = intention to treat; LOCF = last observation carried forward; MC = multi-center; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PG = parallel group; PP = per protocol, RCT = randomized controlled trial

NEW DRUG EVALUATION: SOTAGLIFLOZIN

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Sotagliflozin (Inpefa®) is a SGLT2 inhibitor indicated to reduce the risk of CV death, hospitalization for HF and urgent HF visits in adults with HF or T2D, CKD and other CV risk factors. Sotagliflozin inhibits both SGLT2 and SGLT1.[10] Inhibition of SGLT1 reduces intestinal absorption of glucose and sodium, which may lead to diarrhea. The inhibition of SGLT2 reduces renal absorption of glucose and sodium leading to downregulation of sympathetic activity. The exact mechanism conferring CV benefit with the SGLT2 inhibitor class is not fully know but is thought to be due to changes in volume status/diuresis.[51] Sotagliflozin is initiated as a 200 mg dose before the first meal of the day and increased to 400 mg daily if tolerated.[10]

Sotagliflozin was studied for HF, CKD, and T1D in 7 phase 3 trials (Table 9). Sotagliflozin was approved in Europe as an adjunct to insulin therapy to improve glucose control in people with T1D and later withdrawn due to commercial reasons.[52] The FDA did not approve sotagliflozin for glucose lowering in patients with T1D due to the incidence of DKA.[53] The trials will be discussed below based on indication. The SOLOIST and SCORED trials were used for FDA approval.[51,54]

The SCORED trial was a phase 3, placebo-controlled randomized trial in 10,584 patients with T2D, CKD (eGFR 25 to 60 ml/min/1.73 m^2) and at risk for CV disease. The mean age was 69 years, majority of participants were white (83%), taking glucose lowering medication (97%), had poorly controlled diabetes with an mean HbA1c of 8.3% at risk of CV disease (89%) or had HF (31%).[54] Those with a history of DKA were excluded. The primary outcome was a composite of total CV death from CV causes, hospitalizations for HF and urgent visits for HF. Sotagliflozin was found to lower the risk for the primary endpoint with 5.6 events/100 patient-years compared to 7.5 events/100 patient-years for placebo (HR 0.74; 95% CI, 0.63 to 0.88; p<0.001).[54]

In a second phase 3 trial, sotagliflozin was studied in patients (n=1222) with T2D and worsening HF who had been admitted to the hospital, HF unit, infusion center or emergency department.[51] Patients were a median age of 70 years old, predominately White (93%) with a baseline eGFR of 50 ml/min/1.73 m^2, baseline HbA1c of 7.2%, taking glucose lowering medication (85%) and any renin-angiotensin-aldosterone system (RAAS) inhibitor (91%).[51] Exclusion criteria included need for oxygen therapy, systolic blood pressure of less than 100 mg Hg, need for intravenous inotropic or vasodilator therapy (excluding nitrates) and currently on IV diuretic therapy. The primary endpoint is was total number of deaths from CV causes and hospitalizations and urgent visits for HF. Sotagliflozin reduced the primary endpoint more than placebo, 245 events compared to 355 (HR 0.67; 95% CI, 0.52 to 0.85; p<0.001).[51] Hospitalizations and urgent visits for HF were reduced with sotagliflozin, 194 events versus 297 for placebo (HR 0.64; 95% CI, 0.49 to 0.83; p<0.001).[51]

Sotagliflozin was studied in two trials in patients with T2D and renal disease.[55,56] One trial included patients with severe renal dysfunction (eGFR 30 to 59 mL/min/1.73 m^2) and the second trial included patients with stage 3 chronic kidney disease. The placebo-adjusted HbA1c reduction was -0.1% to -0.46% for sotagliflozin in placebo-controlled trials in patients with renal disease, which was not statistically significant from placebo.[55,56] The glucose lowering effect is attenuated in patients with reduced renal function. Small decreases in eGFR were seen in patients with CKD3 but returned toward baseline.

Sotagliflozin was also studied in patients with T1D for glucose lowering; however, it is not approved for this indication at this time. The 3 inTandem trials had the same study design and evaluated the efficacy and safety of sotagliflozin in people with T1D on insulin.[57–59] All trials were phase 3, placebo-controlled, double-

blind trials. In the InTandem1 trial participants were randomized to sotagliflozin 200 mg and 400 mg with a baseline HbA1c of 7.57%, average age of 46.1 years and BMI of 29.66 kg/m^2.[57] The inTandem2 study enrolled participants in Europe and Israel with a baseline HbA1c of 7.75%, mean of age of 41.2 years and BMI of 22.77 kg/m^2.[58] The inTandem3 trial enrolled people with uncontrolled T1D (mean HbA1c 8.2%) taking insulin who were also overweight (mean BMI 28 kg/m^2).[59] The primary outcome was change in HbA1c from baseline in all 3 trials, in which sotagliflozin reduced HbAC1 by -0.35% to -0.79% versus placebo.

Trials in participants with T1D were of short duration so it is unknown if glucose lowering could be sustained long-term. Trials conferring CV benefit were studied in patients who were older and at high risk of developing a CV event. The benefits seen in the CV composite outcomes were driven by reductions in HF hospitalizations. Across all trials, sotagliflozin was associated with weight loss of -1.0 kg to -3.45 kg.

Clinical Safety:
Sotagliflozin use has similar adverse events as other SGLT2 inhibitors. In placebo controlled trials adverse events that occurred in 5% or more of patients include the following: urinary tract infection, volume depletion, diarrhea, and hypoglycemia (**Table 7**).[10] Serious adverse events which occurred with sotagliflozin are ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with insulin and insulin secretagogues, necrotizing fasciitis and genital mycotic infections.

Table 7. Adverse Events Occurring in 2% or more of Patients Treated with Sotagliflozin versus Placebo[10]

Adverse Reaction	SOLOIST Trial		SCORED Trial	
	Placebo (n=611)	Sotagliflozin (N=605)	Placebo (N=5,286)	Sotagliflozin (N=5,291)
Urinary tract infection	7.2%	8.6%	11.0%	11.5%
Volume depletion	8.8%	9.3%	4.0%	5.2%
Diarrhea	4.1%	6.9%	6.0%	8.4%
Hypoglycemia	2.8%	4.3%	7.9%	7.7%
Dizziness	2.5%	2.6%	2.8%	3.3%
Genital mycotic infection	0.2%	0.8%	0.9%	2.4%

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Change in HbA1c
2) Cardiovascular mortality
3) All-cause mortality
4) Progression of renal disease
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Composite of total CV deaths from CV causes, hospitalizations for HF, and urgent visits for HF
2) Change in HbA1c over 24 weeks

Table 8. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Inhibition of SGLT1 and SGLT2. Inhibition of SGLT2 reduces renal absorption of glucose and sodium, which lowers pre-load, and afterload of the heart and reducing sympathetic activity. Blocking SGLT1 causes reduction in intestinal glucose absorption, which may cause diarrhea. The exact mechanism of the CV benefit is unknown.
Oral Bioavailability	25%
Distribution and Protein Binding	Distribution is 9000 L and 93% protein bound
Elimination	Urine 57% and Feces 37%
Half-Life	5-10 hours
Metabolism	Metabolized by UGT1A9 and to a lesser extend CYP3A4

Abbreviations: L = liter; SGLT1 = sodium-glucose cotransporter-1; SGLT2 = sodium glucose cotransporter-2

Table 9. Comparative Evidence Table for Sotagliflozin.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
HEART FAILURE TRIALS								
1. Bhatt, et al[10] SCORED DB, MC, PC, Phase 3, RCT	1. Sotagliflozin 200 mg* 2. Placebo * Increased to 400 mg if tolerated Median follow-up: 16 months	Demographics: Mean Age: 69 yrs Male: 55% White: 83% Asian: 7% Ejection fraction 40% or less or hospitalization for heart failure during previous 2 years: 20% History of HF: 31% CV risk factors: 89% Previous MI: 20% Baseline eGFR: 44 ml/min/1.73 m^2 Baseline HbA1c: 8.3% Any glucose-lowering medication: 97% Key Inclusion Criteria: - 18 years of age and older - T2D - HbA1c of 7% or higher - CKD (25 to 60 min/ml/1.73 m2) - Additional CV risk factors (e.g., at least one major CV risk factor in those 18 years and older, or at least 2 minor CV risk factors in those 55 years or older Key Exclusion Criteria: - History of diabetic ketoacidosis - Antihyperglycemic treatment (if applicable) that has been unstable in the 12 weeks prior to study initiation - Use of other SGLT2 inhibitor currently or within 1 month of screening - Lower extremity complications - Uncontrolled hypertension - End-stage HF	ITT: 1. 5292 2. 5292 PP: 1. 5232 2. 5210 Attrition: 1. 60 (1.1%) 2. 82 (1.5%)	Primary Endpoint: Composite of total CV deaths from CV causes, hospitalizations for HF, and urgent visits for HF: 1.Sotagliflozin: 5.6 events per 100 patient-years 2. Placebo: 7.5 events per 100 patient-years HR 0.74 (95% CI, 0.63 to 0.88) P<0.001 Secondary Endpoint: Total number of hospitalizations for heart failure: 1. Sotagliflozin: 3.5 events per 100 patient-years 2. Placebo: 5.1 events per 100 patient-years HR 0.67 (95% CI, 0.55 to 0.82) P<0.001 Deaths from CV causes: 1. Sotagliflozin: 2.2 events per 100 patient-years 2. Placebo: 2.4 events per 100 patient-years HR 0.90 (95% CI, 0.73 to 1.12) P=0.35	NA NA NS	Urinary tract infection: 1. Sotagliflozin: 610 (11.5%) 2. Placebo: 585 (11.1%) P=0.45 Diarrhea: 1. Sotagliflozin: 448 (8.5%) 2. Placebo: 315 (6.0%) P<0.001 Volume Depletion: 1. Sotagliflozin: 278 (5.3%) 2. Placebo: 213 (4.0%) P=0.003 Serious treatment emergent adverse events: 1. Sotagliflozin: 1236 (23.4%) 2. Placebo: 1331 (25.2%) P=0.03 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin: 112 (2.1%) 2. Placebo: 94 (1.8%) P=0.21	NA ARR 2.5%/ NNH 40 ARR 1.3%/ NNH 77 ARR 1.8%/ NNH 56 NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization done by interactive response technology. Baseline characteristics were well matched. Performance Bias: (Low) Matched placebo indistinguishable from sotagliflozin. Investigators blinded to treatment assignment. Detection Bias: (Low) Adjudication committee to evaluate primary endpoint assigned in a blinded manner. Attrition Bias: (Low) Results analyzed via an ITT analysis. Attrition was low in both treatment groups. Reporting Bia: (High) Primary endpoint changed during trial. Trial ended early due to loss of funding. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: Results are most applicable to older patients with T2D and chronic kidney disease and at risk of CV disease. This demographic is older than the average Medicaid enrollee. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Composite outcomes may overestimate treatment effect of sotagliflozin. Outcomes are appropriate. Setting: 54 countries including the United States.

2. Bhatt, et al[51] SOLOIST-WHF DB, MC, PC, Phase 3, RCT	1. Sotagliflozin 200 mg* 2. Placebo * Increased to 400 mg if tolerated Median follow-up: 9 months	Demographics: Median Age: 70 yrs Male: 66.4% White: 93% Black: 4% Ejection fraction 50% or less: 79% Median Baseline eGFR: 50 ml/min/1.73 m^2 Baseline HbA1c: 7.2% Median body-mass index: 31 kg/m^2 Any glucose-lowering medication: 85% Any RAAS inhibitor: 91% Key Inclusion Criteria: - 18 to 85 years - hospitalized due to signs and symptoms of heart failure and received treatment with IV diuretic therapy - T2D or laboratory evidence to support a T2D diagnosis - Elevated natriuretic peptide levels (at least 150 pg/ml B-type natriuretic peptide or at least 600 pg/ml for N-terminal pro-B type natriuretic peptide - not on oxygen therapy - systolic BP of 100 mg Hg or greater - not on IV inotropic or vasodilator therapy (excluding nitrates) - transitioned from IV to oral diuretic therapy Key Exclusion Criteria: - End-stage HF or recent acute coronary syndrome - Stroke - PCI or coronary bypass - eGFR of 30 ml/min/1.73 m^2 or less	ITT: 1. 608 2. 614 PP: 1. 588 2. 591 Attrition: 1. 20 (3.3%) 2. 23 (3.7%)	Primary Endpoint: Total number of deaths from CV causes and hospitalizations and urgent visits for HF : 1. Sotagliflozin: 245 events (51.0%) 2. Placebo: 355 events (76.3%) HR 0.67 (95% CI, 0.52 to 0.85) P<0.001 Secondary Endpoints: Hospitalizations and urgent visits for heart failure: 1. Sotagliflozin: 194 events (40.4%) 2. Placebo: 297 (63.9%) HR 0.64 (95% CI, 0.49 to 0.83) P<0.001 Deaths from CV causes: 1. Sotagliflozin: 51 events (10.6%) 2. Placebo: 58 events (12.5%) HR 0.84 (95% CI, 0.58 to 1.22) P=0.36	NA NA NS	Urinary tract infection: 1. Sotagliflozin: 29 (4.8%) 2. Placebo: 31 (5.1%) Diarrhea: 1. Sotagliflozin: 37 (6.1%) 2. Placebo: 21 (3.4%) Hypotension: 1. Sotagliflozin: (6.0%) 2. Placebo: 28 (4.6%) Serious treatment emergent adverse events: 1. Sotagliflozin: 235 (38.8%) 2. Placebo: 251 (41.1%) Treatment discontinuations due to AE: 1. Sotagliflozin: 29 (4.8%) 2. Placebo: 23 (3.8%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized centrally via an interactive-response technology and stratified by LVEF and geographic region. Performance Bias: (Low) Double-blind design with placebo matched tablets. Detection Bias: (low) Independent data monitoring committee and independent clinical endpoint adjudication committee that evaluated events in a treatment-blinded manner. Attrition Bias: (Low) Results analyzed by ITT analysis and low attrition. Reporting Bias: (High) Primary endpoint was changed mid-trial and trial was ended early due to loss of funding from sponsor. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T2D recently hospitalized for worsening heart failure Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Composite outcomes may overestimate treatment effect of sotagliflozin. Outcomes are appropriate. Setting: Thirty-two countries with 72 (6%) patients enrolled in US centers.

TYPE 1 DIABETES TRIALS								
3. Buse, et al[57] inTandem1 DB, PC, Phase 3. RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks * All patients underwent a 6-week insulin optimization phase	Demographics: Median Age: 46.1 yrs Male: 48.3% White: 92.2% Black: 3.5% Hispanic: 3.8% Baseline HbA1c: 7.57% Mean weight (kg): 86.92 Mean body mass index: 29.66 kg/m^2 Insulin dose: 65.36 IU/day Key Inclusion Criteria: - T1D treated with insulin - Age 18 years and over - HbA1c 7.0 % to 11.0% Key Exclusion Criteria: - Use of other antidiabetic therapies - Severe hypoglycemic episode within 1 month - Beta-hydroxybutyrate >0.6 mmol/L	ITT: 1. 263 2. 262 3. 268 PP: 1. 236 2. 240 3. 236 Attrition: 1. 27 (10.3%) 2. 22 (8.4%) 3. 32 (11.9%)	Mean placebo-adjusted change in HbA1c from baseline at 24 weeks: 1. Sotagliflozin 200 mg: -0.37% 2. Sotagliflozin 400 mg: -0.35% Sotagliflozin 200 mg vs. placebo: LSM -0.37% (95% CI, -0.48 to -0.25); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -0.35% (95% CI, -0.47 to -0.24); P<0.001 Secondary outcomes (at week 24): Composite of the proportion of patients with HbA1C <7%, no episode of severe hypoglycemia and no episode of diabetic ketoacidosis: 1. Sotagliflozin 200 mg: 33.46% 2. Sotagliflozin 400 mg: 43.51% 3. Placebo: 21.64% Sotagliflozin 200 mg vs. placebo: LSM 11.82% (95% CI, 3.90 to 19.73); P=0.002 Sotagliflozin 400 mg vs. placebo: LSM 21.87% (95% CI, 13.72 to 30.02); P<0.001 Placebo-adjusted change from baseline in body weight: 1. Sotagliflozin 200 mg: -2.35 kg 2. Sotagliflozin 400 mg: -3.45 kg Sotagliflozin 200 mg vs. placebo: LSM -2.35 kg (95% CI, -2.85 to -1.85); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -3.45 kg (95% CI, -3.95 to -2.94); P<0.001	NA NA NA NA NA NA	Urinary tract infection: 1. Sotagliflozin 200: 26 (9.9%) 2. Sotagliflozin 400: 11 (4.2%) 3. Placebo: 19 (17.1%) Genital mycotic infections: 1. Sotagliflozin 200: 24 (9.1%) 2. Sotagliflozin 400: 34 (13.0%) 3. Placebo: 9 (3.4%) Diarrhea: 1. Sotagliflozin 200: 22 (8.4%) 2. Sotagliflozin 400: 27 (10.3%) 3. Placebo: 18 (6.7%) Volume Depletion: 1. Sotagliflozin 200: 8 (3.0%) 2. Sotagliflozin 400: 4 (1.5%) 3. Placebo: 4 (1.5%) Serious adverse events: 1. Sotagliflozin 200: 27 (10.3%) 2. Sotagliflozin 400: 29 (11.1%) 3. Placebo: 20 (7.5%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 4 (1.5%) 2. Sotagliflozin 400: 4 (1.5%) 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 13 (4.9%) 2. Sotagliflozin 400: 17 (6.5%) 3. Placebo: 11 (4.1%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 1 (0.4%) 2. Sotagliflozin 400: 0 (0%) 3. Placebo: 2 (0.7%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Randomization not described. Performance Bias: (Unclear) Double-blind design stated but no details provided. Detection Bias: (Low) Independent data monitoring committee was blinded to treatment status. Attrition Bias: (High) Results analyzed by mITT analysis with missing observations imputed as non-responders. High attrition in the sotagliflozin 200 mg and placebo groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T1D receiving insulin and who were overweight. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: 75 sites in the United States and Canada.

4. Danne, et al[58] inTandem2 DB, PC, Phase 3, RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks * All patients underwent a 6-week insulin optimization phase	Demographics: Median Age: 41.2 yrs Male: 51.9% White: 96.2% Black: 1% Hispanic: 18% Baseline HbA1c: 7.75% Mean weight (kg): 81.66 Mean body mass index: 27.77 kg/m^2 Insulin dose: 61.17 IU/day Key Inclusion Criteria: - see above Key Exclusion Criteria: - see above	ITT: 1. 261 2. 263 3. 258 PP: 1. 235 2. 236 3. 238 Attrition: 1. 26 (10.0%) 2. 27 (10.3%) 3. 20 (7.8%)	Mean placebo-adjusted change in HbA1c from baseline at 24 weeks: 1. Sotagliflozin 200 mg: -0.37% 2. Sotagliflozin 400 mg: -0.35% Sotagliflozin 200 mg vs. placebo: LSM -0.37% (95% CI, -0.48 to -0.25); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -0.35% (95% CI, -0.47 to -0.24); P<0.001 Secondary outcomes: Composite of the proportion of patients with HbA1C <7%, no episode of severe hypoglycemia and no episode of diabetic ketoacidosis at week 24: 1. Sotagliflozin 200 mg: 31.42% 2. Sotagliflozin 400 mg: 32.32% 3. Placebo: 15.12% Sotagliflozin 200 mg vs. placebo: LSM 16.3% (95% CI, 8.79 to 23.82) P<0.001 Sotagliflozin 400 mg vs. placebo: LSM 17.20% (95% CI, 9.67 to 24.73); P<0.001 Placebo-adjusted change from baseline in body weight at week 24: 1. Sotagliflozin 200 mg: -1.98 kg 2. Sotagliflozin 400 mg: -2.58 kg Sotagliflozin 200 mg vs. placebo: LSM -1.98 kg (95% CI, -2.53 to -1.44); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -2.58 kg (95% CI, -3.12 to -2.04); P<0.001	NA NA NA NA NA NA	Urinary tract infection: 1. Sotagliflozin 200: 11 (4.2%) 2. Sotagliflozin 400: 18 (6.8%) 3. Placebo: 13 (5%) Genital mycotic infections: 1. Sotagliflozin 200: 24 (9.2%) 2. Sotagliflozin 400: 29 (11%) 3. Placebo: 6 (2.3%) Diarrhea: 1. Sotagliflozin 200: 12 (4.6%) 2. Sotagliflozin 400: 19 (7.2%) 3. Placebo: 9 (3.5%) Volume Depletion: 1. Sotagliflozin 200: 6 (2.3%) 2. Sotagliflozin 400: 2 (0.8%) 3. Placebo: 1 (0.4%) Serious adverse events: 1. Sotagliflozin 200: 26 (10%) 2. Sotagliflozin 400: 21 (8%) 3. Placebo: 17 (6.6%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 4 (1.5%) 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 7 (2.7%) 2. Sotagliflozin 400: 12 (4.6%) 3. Placebo: 6 (2.3%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 0 3. Placebo: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized centrally by an interactive voice/web response system Performance Bias: (Low) Double blind design that extended to investigators, patient, sponsor or designee. Detection Bias: (Unclear) Independent data monitoring committee with unknown blinding status. Attrition Bias: (High) Results analyzed by mITT analysis with missing observations imputed as non-responders. High attrition in the active treatment groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T1D receiving insulin and who were overweight. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: Nineteen countries with 96 study sites in Europe and Israel.

5. Garg, et al InTandem3 DB, MC, PC, PG, Phase 3, RCT	1. Sotagliflozin 400 mg daily 3. Placebo Study duration: 24 weeks	Demographics: Median Age: 43 yrs Male: 49.7% White: 88% Hispanic: 7% Baseline HbA1c: 8.2% Mean body-mass index: 28.2 Duration of diabetes: 20 yrs. Daily total insulin dose: 0.70 IU/kg Key Inclusion Criteria: - T1D - stable insulin use - HbA1c. 7.0% to 11.0% - BMI at least 18.5 Key Exclusion Criteria: - Severe hypoglycemia - Diabetic ketoacidosis - eGFR 45 ml/min/1.73 m^2	mITT: 1. 700 2. 705 PP: 1. 601 2. 602 Attrition: 1. 99 (14%) 2. 103 (15%)	HbA1c levels lower than 7% at week 24 (with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization): 1. Sotagliflozin 400 mg: 200 (28.6%) 2. Placebo: 107 (15.2%) MD 13.4 (95% CI, 9.0 to 17.8) P<0.001 Secondary Endpoints (at week 24): Change from baseline in HbA1c: 1. Sotagliflozin: -0.79% 2. Placebo: -0.33% LSMD 0.46% (CI not provided) P<0.001 Change from baseline in body weight: 1. Sotagliflozin: -2.21 kg 2. Placebo: 0.77 kg LSMD -2.98 kg (95% CI, -3.31 to -2.66); P<0.001 Change from baseline SBP (for those with SBP >130 at baseline): 1. Sotagliflozin: -9.2 mmHg 2. Placebo: -5.7 mmHg LSMD -3.5 mmHg (95% CI, -5.7 to -1.3); P=0.002	NA NA NA NA	Urinary tract infection: 1. Sotagliflozin: 25 (3.6%) 2. Placebo: 27 (3.8%) Genital mycotic infections: 1. Sotagliflozin: 45 (6.4%) 2. Placebo: 15 (2.1%) Diarrhea: 1. Sotagliflozin: 29 (4.1%) 2. Placebo: 16 (2.3%) Volume Depletion: 1. Sotagliflozin: 13 (1.9%) 2. Placebo: 2 (0.3%) Serious adverse events: 1. Sotagliflozin: 48 (6.9%) 2. Placebo: 23 (3.3%) Diabetic ketoacidosis: 1. Sotagliflozin: 21 (3.0%) 2. Placebo: 4 (0.6%) Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin: 44 (6.3%) 2. Placebo: 16 (2.3%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin: 21 (3%) 2. Placebo: 17 (2.4%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized centrally by an interactive voice/web response system Performance Bias: (Low) Double blind design that extended to investigators, patient, sponsor or designee. Detection Bias: (Unclear) Independent data monitoring committee with unknown blinding status. Attrition Bias: (High) Results analyzed by mITT analysis with missing observations imputed as non-responders. High attrition in both groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T1D receiving insulin and who were overweight. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: Nineteen countries with 133 study sites.

RENAL TRIALS								
6. Cherney, et al[55] (2021) DB, MC, PC, PG, Phase 3, RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks	Demographics: Median Age: 67 yrs Male: 48.8% White: 81.9% Black: 5.8% Hispanic: 38.6% Mean baseline HbA1c: 8.1% Mean body mass index: 31.6 kg/m^2 Insulin use: 80.1% Antihypertensive use: 97% Mean eGFR: 24 ml/min/1.73 m^2 CDK3A: 50.1% CDK3B: 49.9% Key Inclusion Criteria: - T2D - CKD - eGFR 15 to 30 ml/min/1.73 m^2 - Age 18 years and over - HbA1c 7.0 % to less than 11.0% Key Exclusion Criteria: - history of DKA - severe hypoglycemic - BMI of 20 kg/m^2 or less or >45 kg/m^2 - SBP <120 mmHg or diastolic BP <60 mmHg - dialysis - renal disease requiring immunosuppressive therapy	ITT: 1. 92 2. 92 3. 93 PP: 1. 64 2. 70 3. 66 Attrition: 1. 28 (30.4%) 2. 22 (24%) 3. 27 (29%)	HbA1c reduction at 26 weeks (sotagliflozin 400 mg dose only): 1. Sotagliflozin 400 mg*: -0.4% 2. Sotagliflozin 200 mg: -0.07% 3. Placebo: -0.1% Sotagliflozin 200 mg vs. placebo: LSMD 0.05% (95% CI, -0.3 to 0.4) P=0.812 Sotagliflozin 400 mg vs. placebo: LSMD -0.3% (95% CI, -0.6 to 0.05); P=0.096 Secondary Endpoints: Percent of patients achieving a HbA1c of <7% at week 26: 1. Sotagliflozin 200 mg: 16.3% 2. Sotagliflozin 400 mg: 17.4% 3. Placebo: 4.3% Sotagliflozin 200 mg vs. placebo: LSMD 12% (95% CI, -3.5 to 20.6) P=0.007 Sotagliflozin 400 mg vs. placebo: LSMD 13% (95% CI, 4.3 to 21.8) P=0.004 Placebo-adjusted change from baseline in body weight at week 24: 1. Sotagliflozin 200 mg: -0.4 kg 2. Sotagliflozin 400 mg: -1.0 kg 3. Placebo: 0.4 kg Sotagliflozin 200 mg vs. placebo: LSMD -0.8 kg (95% CI, -2.2 to 0.6) P=0.24 Sotagliflozin 400 mg vs. placebo: LSMD -1.4. kg (95% CI, -2.8 to -0.01); P=0.049	NA NA ARR 12/ NNT 9 ARR 13/ NNT 8 NA NA	Urinary tract infection: 1. Sotagliflozin 200: 16 (17%) 2. Sotagliflozin 400: 9 (10%) 3. Placebo: 18 (19.4%) Genital mycotic infections: 1. Sotagliflozin 200: 1 (1.1%) 2. Sotagliflozin 400: 0 3. Placebo: 0 Diarrhea: 1. Sotagliflozin 200: 5 (5.3%) 2. Sotagliflozin 400: 5 (5.6%) 3. Placebo: 3 (3.2%) Volume Depletion: 1. Sotagliflozin 200: 6 (6.4%) 2. Sotagliflozin 400: 1 (1.1%) 3. Placebo: 4 (4.3%) Serious adverse events: 1. Sotagliflozin 200: 18 (19.1%) 2. Sotagliflozin 400: 20 (22.2%) 3. Placebo: 21 (22.6%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 0 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 2 (2.1%) 2. Sotagliflozin 400: 1 (1.1%) 3. Placebo: 1 (1.1%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 3 (3.2%) 3. Placebo: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Randomization not described. Performance Bias: (Unclear) Double blind design but no details were provided. Detection Bias: (Unclear) Not described. Attrition Bias: (High) Results analyzed by mITT analysis. High attrition in all groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T2D and severe renal impairment (eGFR 30 to 59 ml/min/1.73 m^2). Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: 15 countries and 92 centers in North and South America, Europe, and Asia.

7. Cherney, et al[56] (2023) DB, MC, PC, PG, Phase 3, RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks (26 week treatment and 26 week extension)	Demographics: Median Age: 69.5 yrs Male: 56% White: 84.6% Black: 5.2% Hispanic: 25.2% Mean baseline HbA1c: 8.3% Mean body mass index: 32.4 kg/m^2 Insulin use: 64.3% Antihypertensive use: 96.6% Mean eGFR: 45.0 ml/min/1.73 m^2 Key Inclusion Criteria: - T2D - Stage 3 CKD - eGFR 30 to 59 ml/min/1.73 m^2 - Age 18 years and over - HbA1c 7.0 % to less than 11.0% Key Exclusion Criteria: - history of DKA - severe hypoglycemic - BMI of 20 kg/m^2 or less or >45 kg/m^2 - SBP >180 mmHg or diastolic BP >100 mmHg - reversible renal failure	ITT: 1. 267 2. 260 3. 260 PP: 1. 233 2. 222 3. 225 Attrition: 1. 34 (12.7%) 2. 38 (14.6%) 3. 35 (13.4%)	HbA1c reduction at 26 weeks: 1. Sotagliflozin 400 mg*: -0.46% 2. Sotagliflozin 200 mg: -0.32% 3. Placebo: -0.22% Sotagliflozin 200 mg vs. placebo: LSMD -0.10% (95% CI, -0.25 to 0.05) P=0.2095 Sotagliflozin 400 mg vs. placebo: LSMD -0.24% (95% CI, -0.39 to 0.09) P=0.0021 Secondary Endpoints: Percent of patients achieving a HbA1c of <7% at week 26: 1. Sotagliflozin 200 mg: 19.4% 2. Sotagliflozin 400 mg: 20.8% 3. Placebo: 13.5% Sotagliflozin 200 mg vs. placebo: LSMD 6% (95% CI, -0.2 to 12.2); P=0.0614 Sotagliflozin 400 mg vs. placebo: LSMD 7.4% (95% CI, 1.1 to 13.7); P=0.0230 Placebo-adjusted change from baseline in body weight at week 24: 1. Sotagliflozin 200 mg: -1.7 kg 2. Sotagliflozin 400 mg: -1.2 kg 3. Placebo: -0.4 kg Sotagliflozin 200 mg vs. placebo: LSMD -1.3 kg (95% CI, -1.9 to -0.6); P<0.0001 Sotagliflozin 400 mg vs. placebo: LSMD -0.8. kg (95% CI, -1.5 to -0.2); P=0.0155	NA NA NS ARR 7.4/ NNT 14 NA NA	Urinary tract infection: 1. Sotagliflozin 200: 34 (12.7%) 2. Sotagliflozin 400: 28 (10.8%) 3. Placebo: 27 (10.4%) Genital mycotic infections: 1. Sotagliflozin 200: 4 (1.5%) 2. Sotagliflozin 400: 5 (1.9%) 3. Placebo: 2 (0.8%) Diarrhea: 1. Sotagliflozin 200: 19 (7.1%) 2. Sotagliflozin 400: 24 (9.2%) 3. Placebo: 15 (5.8%) Volume Depletion: 1. Sotagliflozin 200: 8 (3.0%) 2. Sotagliflozin 400: 10 (3.8%) 3. Placebo: 4 (1.5%) Serious adverse events: 1. Sotagliflozin 200: 43 (16.1%) 2. Sotagliflozin 400: 44 (16.9%) 3. Placebo: 48 (18.5%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 0 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 18 (6.7%) 2. Sotagliflozin 400: 31 (11.9%) 3. Placebo: 13 (5.0%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 1 (0.4%) 2. Sotagliflozin 400: 3 (1.2%) 3. Placebo: 2 (0.8%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Randomization not described. Performance Bias: (Unclear) Double blind design but no details were provided. Baseline characteristics were well matched between groups. Detection Bias: (Unclear) Not described. Attrition Bias: (high) Results analyzed by mITT analysis and missing data was imputed by the multiple imputation methods. Attrition was high in all groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T2D that is not well controlled and chronic kidney disease (eGFR 30 to 59 ml/min/1.73 m^2). Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: 150 sites in North and South America, Europe, and Asia.

Key: * Primary endpoint was comparison between the 400 mg dose only.
Abbreviations: ARR = absolute risk reduction; BMI = body mass index; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; DB = double-blind; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; ITT = intention to treat; IV = intravenous; LSMD = least squares mean difference; LVEF = left ventricular ejection fraction; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = controlled; PCI = percutaneous coronary intervention; PP = per protocol; RAAS = renin-angiotensin-aldosterone system; RCT = randomized controlled trial; T1D = type 1 diabetes; T2D = type 2 diabetes

References:

1. National Institute for Health and Care Excellence. Chronic heart failure in adults. Quality Standard. June 29, 2023. Available at: www.nice.org.uk/guidance/qs9. Accessed May 15, 2023. Published online 2023.

2. Rossing P, Caramori ML, Chan JCN, et al. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney International*. 2022;102(5):S1-S127. doi:10.1016/j.kint.2022.06.008

3. Mancini GBJ, O'Meara E, Zieroth S, et al. 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults. *Can J Cardiol*. 2022;38(8):1153-1167. doi:10.1016/j.cjca.2022.04.029

4. ElSayed NA, Aleppo G, Aroda VR, et al. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2023. *Diabetes Care*. 2023;46(Supplement_1):S158-S190. doi:10.2337/dc23-S010

5. ElSayed NA, Aleppo G, Aroda VR, et al. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2023. *Diabetes Care*. 2023;46(Supplement_1):S191-S202. doi:10.2337/dc23-S011

6. Farxiga (dapagliflozin) [prescribing information]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. April 2022.

7. Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT. Boehringer Ingelheim Pharamceuticals, Inc. January 2020.

8. Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.

9. Brenzavvy (bexagliflozin prescribing information). Marlborough, MA; TheracosBio, LLC. January 2023.

10. Inpefa (sotagliflozin [prescribing information]. The Woodlands, TX; Lexicon Pharmaceuticals, Inc. May 2023.

11. Oregon Health Authorit. Oreogn Diabetes Report - A report on the burden of diabetes in Oregon and progress on the 2009 strategic plan to slow the rate of diabetes. Published online January 2015. http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Diabetes/Documents/OregonDiabetesReport.pdf

12. Centers for Disease Control and Prevention Press Release. Number of Americans with Diabetes Projected to Double or Triple by 2050. Published online 2010. Accessed July 23, 2013. http://www.cdc.gov/media/pressrel/2010/r101022.html

13. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149. doi:10.2337/dc14-2441

14. Redmon B, Caccamo D, Flavin P. Diagnosis and management of type 2 diabetes mellitus in adults. *Institute for Clincal Systems Improvement*. Published online July 2014. https://www.icis.org/_asset/3rrm36/Diabetes.pdf

15. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *JAMA*. 2017;318(7):637-646. doi:10.1001/jama.2017.10169

16. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. *NICE Guideline*. 2022;NG28.

17. American Diabetes Association. Pharmacological Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2022. Diabetes Care 2022;45:S125-S143.

18. Lin GA, Brouwer E, Nikitin D, et al. Tirzepatide for Type 2 Diabetes; Final Report. *Institute for Clinical and Ecomomic Review*. Published online February 15, 2022.

19. Food and Drug Administration. Bexagliflozin Integrated Review (Application number: 214373Orig1s000). Center for Drug Evaluation and Research. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/214373Orig1s000IntegratedR.pdf. Accessed June 3, 2023.

20. American Diabetes Association Professional Practice Committee. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45:S175-S184. *Diabetes Care*. 2022;45(Supplement_1):S175-S184. doi:10.2337/dc22-S011

21. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. [Review]. *Annals of Internal Medicine*. 2016;164(11):740-751. doi:10.7326/M15-2650

22. Zheng XD, Qu Q, Jiang XY, Wang ZY, Tang C, Sun JY. Effects of Dapagliflozin on Cardiovascular Events, Death, and Safety Outcomes in Patients with Heart Failure: A Meta-Analysis. *American Journal of Cardiovascular Drugs*. 2021;21(3):321-330. doi:10.1007/s40256-020-00441-x

23. Butt JH, Docherty KF, Claggett BL, et al. Association of Dapagliflozin Use With Clinical Outcomes and the Introduction of Uric Acid-Lowering Therapy and Colchicine in Patients With Heart Failure With and Without Gout: A Patient-Level Pooled Meta-analysis of DAPA-HF and DELIVER. *JAMA Cardiology*. 2023;8(4):386-393. doi:10.1001/jamacardio.2022.5608

24. Chen MB, Wang H, Zheng QH, Xu HL, Cui WY. Effect of sodium-dependent glucose transporter inhibitors on glycated hemoglobin A1c after 24 weeks in patients with diabetes mellitus: A systematic review and meta-analysis. *Medicine*. 2021;100(1):e24101. doi:10.1097/MD.0000000000024101

25. Zhou B, Shi Y, Fu R, et al. Relationship Between SGLT-2i and Ocular Diseases in Patients With Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Endocrinology*. 2022;1:907340. doi:10.3389/fendo.2022.907340

26. Fakhrolmobasheri M, Abhari AP, Manshaee B, et al. Effect of sodium-glucose cotransporter 2 inhibitors on insulin resistance; a systematic review and meta-analysis. *Acta Diabetologica*. 2023;60(2):191-202. doi:10.1007/s00592-022-01981-1

27. Mori Y, Duru OK, Tuttle KR, et al. Sodium-Glucose Cotransporter 2 Inhibitors and New-onset Type 2 Diabetes in Adults With Prediabetes: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Journal of Clinical Endocrinology & Metabolism*. 2022;108(1):221-231. doi:10.1210/clinem/dgac591

28. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nature Medicine*. 2022;28(9):1956-1964. doi:10.1038/s41591-022-01971-4

29. Younes AM, Salem M, Maraey A, et al. Safety outcomes of SGLT2i in the heart failure trials: A systematic review and Meta-analysis. *International Journal of Cardiology*. 2022;1:51-56. doi:10.1016/j.ijcard.2022.06.059

30. Patoulias D, Dimosiari A. Meta-analysis Addressing the Cardiovascular Safety of Bexagliflozin in Patients With Type 2 Diabetes Mellitus. *American Journal of Cardiology*. 2022;1:178-179. doi:10.1016/j.amjcard.2022.05.005

31. Zhou B, Shi Y, Fu R, et al. Relationship Between SGLT-2i and Ocular Diseases in Patients With Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Endocrinology*. 2022;1:907340. doi:10.3389/fendo.2022.907340

32. Ahmad Y, Madhavan MV, Stone GW, et al. Sodium-glucose cotransporter 2 inhibitors in patients with heart failure: a systematic review and meta-analysis of randomized trials. *European Heart Journal Quality of Care & Clinical Outcomes*. 2022;8(4):383-390. doi:10.1093/ehjqcco/qcab072

33. Xu X, Xu W, Zhuo Q, Yan Y. The efficacy and safety of dapagliflozin combined with oral hypoglycemic agents in patients with type 2 diabetes: a systematic review and meta-analysis. *Annals of Palliative Medicine*. 2022;11(3):1028-1037. doi:10.21037/apm-22-121

34. Shi FH, Li H, Yue J, et al. Clinical Adverse Events of High-Dose vs Low-Dose Sodium-Glucose Cotransporter 2 Inhibitors in Type 2 Diabetes: A Meta-Analysis of 51 Randomized Clinical Trials. *Journal of Clinical Endocrinology*. 2020;105(11). doi:10.1210/clinem/dgaa586

35. Ong HT, Teo YH, Teo YN, et al. Effects of Sodium/Glucose Cotransporter Inhibitors on Atrial Fibrillation and Stroke: A Meta-Analysis. *Journal of Stroke & Cerebrovascular Diseases*. 2022;31(1):106159. doi:10.1016/j.jstrokecerebrovasdis.2021.106159

36. Hu X, Yang Y, Hu X, et al. Effects of sodium-glucose cotransporter 2 inhibitors on serum uric acid in patients with type 2 diabetes mellitus: A systematic review and network meta-analysis. *Diabetes, Obesity & Metabolism*. 2022;24(2):228-238. doi:10.1111/dom.14570

37. Chenchula S, Varthya SB, Padmavathi R. Rationality, Efficacy, Tolerability of Empagliflozin Plus Linagliptin Combination for the Management of Type 2 Diabetes Mellitus: A Systematic Review of Randomized Controlled Trials and Observational Studies. *Current Diabetes Reviews*. 2022;18(4):e100921196392. doi:10.2174/1573399817666210910165402

38. Egolum UO, Cates DW, McGraw-Senat C, Ling H. Impact of Dapagliflozin on Mortality in Patients With Heart Failure and Reduced Ejection Fraction: A Meta-analysis. *American Journal of Therapeutics*. 2022;29(5):e578-e579. doi:10.1097/MJT.0000000000001354

39. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400(10354):757-767. doi:10.1016/S0140-6736(22)01429-5

40. Neuen BL, Oshima M, Agarwal R, et al. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials. *Circulation*. 2022;145(19):1460-1470. doi:10.1161/CIRCULATIONAHA.121.057736

41. Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400(10365):1788-1801. doi:10.1016/S0140-6736(22)02074-8

42. Mannucci E, Gallo M, Giaccari A, et al. Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: An updated meta-analysis of randomized controlled trials with external adjudication of events. *Diabetes, Obesity and Metabolism*. 2023;25(2):444-453. doi:10.1111/dom.14888

43. Synjardy (empagliflozin and metformin) [prescribing information]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals, Inc. February 2023.

44. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286

45. Laffel LM, Danne T, Klingensmith GJ, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. *The Lancet Diabetes & Endocrinology*. 2023;11(3):169-181. doi:10.1016/S2213-8587(22)00387-4

46. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233

47. Halvorsen YD, Lock JP, Zhou W, Zhu F, Freeman MW. A 24-week, randomized, double-blind, active-controlled clinical trial comparing bexagliflozin with sitagliptin as an adjunct to metformin for the treatment of type 2 diabetes in adults. *Diabetes Obes Metab*. 2019;21(10):2248-2256. doi:10.1111/dom.13801

48. Allegretti AS, Zhang W, Zhou W, et al. Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD. *Am J Kidney Dis*. 2019;74(3):328-337. doi:10.1053/j.ajkd.2019.03.417

49. Halvorsen YD, Lock JP, Frias JP, et al. A 96-week, double-blind, randomized controlled trial comparing bexagliflozin to glimepiride as an adjunct to metformin for the treatment of type 2 diabetes in adults. *Diabetes Obes Metab*. 2023;25(1):293-301. doi:10.1111/dom.14875

50. Halvorsen YDC, Walford GA, Massaro J, Aftring RP, Freeman MW. A 96-week, multinational, randomized, double-blind, parallel-group, clinical trial evaluating the safety and effectiveness of bexagliflozin as a monotherapy for adults with type 2 diabetes. *Diabetes Obes Metab*. 2019;21(11):2496-2504. doi:10.1111/dom.13833

51. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021;384(2):117-128. doi:10.1056/NEJMoa2030183

52. EMA. Zynquista. European Medicines Agency. Published February 27, 2019. Accessed July 7, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/zynquista

53. Dunleavy, K K, 2022 08:55am. Persistent Lexicon still working to get an audience with FDA on Type 1 diabetes prospect. Fierce Pharma. Published December 1, 2022. Accessed July 7, 2023. https://www.fiercepharma.com/pharma/persistent-lexicon-still-working-get-audience-fda-type-1-diabetes-drug-sotagliflozin

54. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med*. 2021;384(2):129-139. doi:10.1056/NEJMoa2030186

55. Cherney DZI, Ferrannini E, Umpierrez GE, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and severe renal impairment. *Diabetes Obes Metab*. 2021;23(12):2632-2642. doi:10.1111/dom.14513

56. Cherney DZI, Ferrannini E, Umpierrez GE, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease. *Diabetes Obes Metab*. 2023;25(6):1646-1657. doi:10.1111/dom.15019

57. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. *Diabetes Care*. 2018;41(9):1970-1980. doi:10.2337/dc18-0343

58. Danne T, Cariou B, Banks P, et al. HbA1c and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. *Diabetes Care*. 2018;41(9):1981-1990. doi:10.2337/dc18-0342

59. Garg SK, Henry RR, Banks P, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. *N Engl J Med*. 2017;377(24):2337-2348. doi:10.1056/NEJMoa1708337

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
canagliflozin	INVOKANA	TABLET	Y
dapagliflozin propanediol	FARXIGA	TABLET	Y
empagliflozin	JARDIANCE	TABLET	Y
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapagliflozin/metformin HCl	XIGDUO XR	TAB BP 24H	N
dapagliflozin/saxagliptin HCl	QTERN	TABLET	N
empaglifloz/linaglip/metformin	TRIJARDY XR	TAB BP 24H	N
empagliflozin/linagliptin	GLYXAMBI	TABLET	N
empagliflozin/metformin HCl	SYNJARDY XR	TAB BP 24H	N
empagliflozin/metformin HCl	SYNJARDY	TABLET	N
ertugliflozin pidolate	STEGLATRO	TABLET	N
ertugliflozin/metformin	SEGLUROMET	TABLET	N
ertugliflozin/sitagliptin phos	STEGLUJAN	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Solomon, Rudolf A de Boer , David DeMets , et al

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

Methods: We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

Results: Over a median of 2.3 years, the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

Conclusions: Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.).

Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial

Lori M Laffel, Thomas Danne, Georgeanna J Klingensmith, et al

Background: The incidence of type 2 diabetes in young people is increasing, but treatments remain limited. We aimed to assess the efficacy and safety of an empagliflozin dosing regimen versus placebo and linagliptin versus placebo on glycaemic control in young people with type 2 diabetes.

Methods: In this double-blind, placebo-controlled trial done in 108 centres in 15 countries, participants with type 2 diabetes (aged 10-17 years; HbA_{1c} 6·5-10·5% [48-91 mmol/mol]) who had been previously treated with metformin or insulin were randomly assigned (1:1:1) to oral empagliflozin 10 mg, oral linagliptin 5 mg, or placebo. Participants in the empagliflozin group who did not have HbA_{1c} below 7·0% (<53 mmol/mol) by week 12 underwent a second double-blinded randomisation (1:1) at week 14, either remaining on 10 mg or increasing to 25 mg. Participants in the placebo group were randomly reassigned (1:1:1) in a double-blinded manner at week 26 to linagliptin 5 mg or one of the empagliflozin doses (10 mg or 25 mg). Investigators were masked throughout the trial and received assignments of blinded medication kits through interactive response technology for all participants at the initial randomisation and for the re-randomisations at weeks 14 and 26. The primary outcome was change from baseline in HbA_{1c} at 26 weeks. For empagliflozin, results were based on a pooled analysis for all participants on empagliflozin. Safety was assessed until week 52. This trial is registered with ClinicalTrials.gov, NCT03429543.

Findings: Between April 26, 2018, and May 26, 2022, of 262 screened participants, 158 (60%) were randomly assigned to treatment (53 [34%] to placebo, 52 [33%] to empagliflozin 10 mg, and 53 [34%] to linagliptin). For the primary outcome, the adjusted mean HbA_{1c} change from baseline at week 26 was -0·84% [-9·2 mmol/mol] in the empagliflozin pooled group versus placebo (95% CI -1·50 to -0·19 [-16·4 to -2·1]; p=0·012); the corresponding change from baseline for linagliptin versus placebo was -0·34% [-3·8 mmol/mol; 95% CI -0·99 to 0·30 [-10·8 to 3·3]; p=0·29). Adverse events occurred in 34 (64%) participants in the placebo group, 40 (77%) in the empagliflozin pooled group, and 37 (71%) in the linagliptin group, up to week 26. Of these, severe adverse events were reported in two (4%) participants in the placebo group, one (2%) in the empagliflozin pooled group, and one (2%) in the linagliptin group. Hypoglycaemia was the most frequently reported adverse event with higher rates for those on active drug treatment compared with placebo. No severe hypoglycaemia cases were reported.

Interpretation: Empagliflozin provided clinically relevant placebo-corrected reductions in HbA_{1c}, whereas linagliptin did not, and might offer a new treatment option for young people with type 2 diabetes.

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group; William G Herrington, Natalie Staplin, et al

Background: The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a broad range of such patients.

Methods: We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

Results: A total of 6609 patients underwent randomization. During a median of 2.0 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P = 0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or

death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.
Conclusions: Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 24, 2023

Search Strategy:

#	Searches	Results
1	canagliflozin.mp. or Canagliflozin/	1732
2	dapagliflozin.mp.	2543
3	empagliflozin.mp.	2675
4	ertugliflozin.mp.	254
5	bexagliflozin.mp.	14
6	1 or 2 or 3 or 4 or 5	5620
7	limit 6 to (english language and humans and yr="2022 - 2023")	798
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	76

Appendix 4: Prescribing Information Highlights

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

BRENZAVVY (bexagliflozin) tablets, for oral use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
BRENZAVVY is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitation of Use: Not recommended in patients with type 1 diabetes mellitus. May increase the risk of diabetic ketoacidosis in these patients (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose: 20 mg once daily, taken in the morning, with or without food. Do not crush or chew the tablet. (2.2)
- Assess renal function before initiating BRENZAVVY and as clinically indicated. Correct volume depletion before initiating (2.1)
- Not recommended if eGFR less than 30 mL/min/1.73 m^2. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 20 mg (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to bexagliflozin or any excipient in BRENZAVVY
- Patients on dialysis (4)

----------WARNINGS AND PRECAUTIONS----------
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.1)
- *Lower limb amputation:* Consider factors that may increase the risk for amputations before initiating BRENZAVVY. Monitor patients for signs and symptoms of infection or ulcers of the lower limbs, and discontinue if these occur (5.2).
- *Volume depletion:* May result in acute kidney injury. Before initiating BRENZAVVY, assess and correct volume status in patients with impaired renal function or low systolic blood pressure, elderly patients or patients on diuretics. Monitor for signs and symptoms during therapy (5.3)
- *Urosepsis and pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination with BRENZAVVY (5.5)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males treated with SGLT2 inhibitors. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment (5.6).
- *Genital mycotic infection*: Monitor and treat as appropriate. (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 5%) are female genital mycotic infections, urinary tract infection and increased urination (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TheracosBio at 1-855-273-6928 (1-855-BRENZAV) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. BRENZAVVY is not recommended during the second and third trimesters of pregnancy (8.1)
- *Lactation:* Not recommended when breastfeeding. (8.2)
- *Geriatric patients:* Higher incidence of adverse reactions related to volume depletion. (5.3, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function (5.3, 8.6)
- *Hepatic Impairment:* Not recommended for patients with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2023

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

INPEFA™ (sotagliflozin) tablets, for oral use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
INPEFA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- heart failure (1) or
- type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors (1)

----------DOSAGE AND ADMINISTRATION----------
Correct volume status before starting INPEFA at 200 mg daily and titrate to 400 mg as tolerated. (2.2) In patients with decompensated heart failure, begin dosing when patients are hemodynamically stable. (2.1)

Withhold INPEFA at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg and 400 mg (3)

----------CONTRAINDICATIONS----------
- History of serious hypersensitivity reaction to INPEFA. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:* Consider ketone monitoring in patients with type 1 diabetes mellitus and consider ketone monitoring in others at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue INPEFA if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.1)
- *Volume Depletion:* Before initiating, correct volume status. Monitor for signs and symptoms of hypotension during therapy. (5.2)
- *Urosepsis and Pyelonephritis:* Monitor for signs and symptoms during therapy and treat promptly. (5.3)
- *Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:* Lower dose of insulin or insulin secretagogue may be required. (5.4)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)*: Monitor for pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. Discontinue INPEFA and treat urgently. (5.5)
- *Genital Mycotic Infections*: Monitor and treat as appropriate. (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 5%) are urinary tract infection, volume depletion, diarrhea, and hypoglycemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lexicon at 1-855-330-2573 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Digoxin: Monitor digoxin levels. (7.1)
Uridine 5'-diphospho-glucuronosyltransferase Inducers (e.g., rifampin): Sotagliflozin exposure is reduced. Consider monitoring of clinical status. (7.2)
Lithium: Monitor serum lithium concentrations. (7.3)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
Lactation: INPEFA is not recommended when breastfeeding. (8.2)
Geriatrics: Higher incidence of adverse reactions related to volume depletion. (5.2, 8.5)
Renal Impairment: Higher incidence of adverse reactions related to volume depletion. (5.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 05/2023

Appendix 5: Key Inclusion Criteria

Population	People with T2D, heart failure and chronic kidney disease
Intervention	SGLT2 inhibitors
Comparator	Placebo or active treatment
Outcomes	HbA1c, worsening cardiac or renal disease, mortality
Timing	Not applicable
Setting	Outpatient

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- Preferred therapies are: canagliflozin, dapagliflozin and empagliflozin
- All non-preferred SGLT-2 inhibitors require a PA

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

~~**Table 1**. Approved Indications for SGLT2 Inhibitors (in addition to glucose lowering)~~

~~Drug Name~~	~~CV risk reduction in patients with T2D and established CV disease~~	~~Reduction in risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria >300 mg/day~~	~~Reduction in risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in patients with CKD at risk of progression~~	~~HF risk reduction in patients with T2D and established CV disease or multiple CV risk factors~~	~~HF risk reduction in patients with HF~~
~~Canagliflozin~~	~~X~~	~~X~~			
~~Dapagliflozin~~			~~X~~	~~X~~	~~X (HFrEF)~~
~~Empagliflozin~~	~~X~~				~~X (HFrEF & HFpEF)~~
~~Ertugliflozin~~					

Abbreviations: CKD – chronic kidney disease; CV – cardiovascular; eGFR – estimated glomerular filtration rate; HF – heart failure; HFrEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; T2D – type 2 diabetes

Approval Criteria		
1. What is the diagnosis being treated?Is this a request for renewal of a previously approved prior authorization?	Record ICD10 code **Yes:** Go the **Renewal Criteria** **No:** Go to #2	
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient qualify for the requested therapy based on diagnoses and requirements in Table 1?	**Yes:** Go to #5	**No:** Go to #4
2. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have type 2 diabetes?	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does the patient have heart failure and is requesting an SGLT-2 inhibitor with demonstrated cardiovascular benefit (e.g., dapagliflozin, empagliflozin, or sotagliflozin)? 5.4.(document contraindication, if any)	**Yes:** Approve for up to 12 months**Yes:** Go to #5	**No:** Go to #5**No:** Pass to RPh. Deny and recommend trial of metformin. See below for metformin titration schedule.

Approval Criteria		
5. Does the patient have chronic kidney disease and is requesting an SGLT-2 inhibitor with demonstrated renal and cardiovascular benefits (e.g., dapagliflozin)? ~~Is the request for a SGLT2 inhibitor (including combination products) and there is a documented estimated glomerular filtration rate (eGFR) within the last 12 months showing the product is not contraindicated?~~ ~~Products listed below should not be used in the following patients:~~ ~~Canagliflozin and on dialysis, or~~ ~~Empagliflozin and on dialysis , or~~ ~~Dapagliflozin on dialysis, or~~ ~~Ertugliflozin and eGFR <30 mL/min/ 1.73 m^2?~~	**Yes:** Approve for up to 12 months~~**Yes:** Approve for up to 12 months~~	**No: No:** Pass to RPh. Deny; medical appropriateness~~**No:** Pass to RPh. Deny; medical appropriateness~~

~~Renewal Criteria~~		
~~1. Is the request for the renewal of a SGLT2 inhibitor (including combination products) and there is a documented eGFR within the last 12 months showing the product is not contraindicated? :~~ ~~Products listed below should not be used in the following patients:~~ ~~• Canagliflozin and on dialysis, or~~ ~~• Empagliflozin and on dialysis, or~~ ~~• Dapagliflozin and on dialysis, or~~ ~~• Ertugliflozin and eGFR <30 mL/min/ 1.73 m^2?~~	~~**Yes:** Approve for up to 12 months~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

~~**Initiating Metformin**~~

~~1. Begin with low dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.~~
~~2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).~~
~~3. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.~~
~~4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.~~

~~Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.~~

P&T Review: *10/23 (KS),* *10/22 (KS), 8/21 (KS), 8/20 (KS), 6/20, 7/18, 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *TBD;* *1/1/23; 9/1/20; 8/15/18; 10/13/16; 2/3/15; 1/1/14*

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Alzheimer's Disease Drugs

Date of Review: October 2023

Generic Name: lecanemab-irmb

Date of Last Review: October 2021
Dates of Literature Search: 07/01/2021 – 06/22/2023
Brand Name (Manufacturer): Leqembi (Eisai Inc)
Dossier Received: yes

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

Purpose for Class Update:
To review new evidence for efficacy and harms of the new monoclonal antibody agent, lecanemab, in the treatment of Alzheimer's dementia (AD). This review will also evaluate the evidence for other agents approved to treat AD and update prior authorization criteria as needed.

Plain Language Summary:
- This review looks at new evidence for medicines that are used for Alzheimer's disease.
- Alzheimer's disease (AD) is a condition that makes it difficult for a person think, remember, speak, and complete daily activities of life.
- About 1-2% of people over the age of 65 years have AD, but it becomes more common with increasing age.
- There is no cure for AD at this time, but there are some medicines called acetylcholinesterase inhibitors (ACHEIs) that work to increase levels of chemical messengers in the brain. These medicines may help people with AD think or speak more clearly or make them able to take better care of themselves. However, these medicines may only have a small benefit and usually work for a short amount of time (6 to 9 months). Also, these medicines may cause upset stomach, weight loss, or stomach pain/cramping.
- A review found that stopping ACHEIs (donepezil, galantamine, rivastigmine) within 2 months after starting treatment may make a person not able to think as well. The effects of stopping these ACHEI medicines 3-11 months after starting is unclear. There is some good evidence that at 12 months or after, stopping an ACHEI medicine may make a person less able to be active or take care of themselves than if they kept taking it.
- A different review looked at ACHEIs in people not able to think clearly because of low blood flow to the brain. The review found that donepezil 10 mg daily and galantamine 16 mg to 24 mg daily helped improve thinking ability. There was also good evidence that donepezil 10 mg daily may slightly improve a person's ability to care for themselves, but the individual is unlikely to notice the change.
- A new medicine, lecanemab (LEQEMBE), is used to treat patients with mild AD to help clear the brain of harmful proteins that might worsen AD. However, patients taking lecanemab may have a high risk of developing brain swelling or brain bleeding side-effects when using this drug, so treatment must be closely watched. At this time, there is not good evidence that these types of medicines help a patient think more clearly, remember or help them do daily tasks.

Author: Dave Engen, PharmD

- The Drug Use Research and Management group recommends that lecanemab be available for use under the Oregon Health Plan fee-for-service program if the prescriber can explain that it is needed, and that it will likely be safe and work for their patient. This process is called prior authorization.

Research Questions:

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

Conclusions:

- This update includes information from two high-quality systematic reviews[1,2] and two randomized control trials (RCTs).[3,4] There is low quality evidence from a systematic review that, compared to continuation of AChEIs, discontinuation of AChEI treatment may be associated with worse cognitive function based on standardized scales [which include the Alzheimer's Disease Assessment Scale-Cognitive subscale/11 (ADAS-Cog/11) and Mini-Mental State Examination (MMSE)/Standardized MMSE (SMMSE)] at up to 2 months (standardized mean difference (SMD) -0.42, 95% confidence interval (CI) -0.64 to -0.21), but the effect over 3-11 months is very uncertain (SMD -0.40, 95% CI -0.87 to 0.07; 3 RCTs; very low quality evidence).[1]
- Discontinuation of an AChEI (compared to continuing treatment) likely resulted in:
    - greater functional impairment at 12 months (MD -3.38 Bristol Activities of Daily Living Scale (BADLS) points, 95% CI -6.67 to -0.10) based on moderate quality evidence.[1]
    - little to no change in neuropsychiatric status at 12 months (MD -0.87 Neuropsychiatric Inventory (NPI) points; 95% CI -8.42 to 6.68) based on low quality evidence.[1]
    - worse cognitive function at 12 months (MD -2.09 Standardized Mini-Mental State Examination (SMMSE) points, 95% CI -3.43 to -0.75) based on moderate quality evidence.[1]
- There was high-quality evidence that at 24 weeks donepezil 10 mg daily and galantamine 16 mg to 24 mg daily at 26 weeks resulted in a modest beneficial effect on cognition compared to placebo in people with vascular cognitive impairment (VCI) as measured by the ADAS-Cog 11 tool (donepezil: MD -2.18 [95% CI −3.87 to −0.47]; galantamine: MD -1.84 [95% CI −3.63 to −0.14]).[2] There was moderate-quality evidence from 2 RCTs that donepezil 10 mg daily may slightly improve functional performance based on the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), although the size of the change is unlikely to be clinically important (MD −0.95 [95% CI −1.73 to −0.17]).[2] Galantamine 16 mg to 24 mg, donepezil 10 mg, and rivastigmine may be associated with slightly more adverse events compared to placebo based on low-quality evidence.[2]
- The Food and Drug Administration (FDA) recently approved donepezil once-weekly transdermal patch formulation.[8]
- The FDA issued a safety alert for worsening symptoms of extrapyramidal disorders with galantamine and amyloid-related imaging abnormalities with aducanuamb-avwa.[9,10]
- Lecanemab is an anti-amyloid beta (Aß) monoclonal antibody that received approval in January 2023 for the treatment of early AD.[6] One phase 2b, dose-finding trial (Study 201) and one phase 3 RCT (Study 301) compared lecanemab to placebo and were evaluated for FDA approval.[3-7]
    - In Study 201 lecanemab 10 mg/kg biweekly dosing regimen was unable to meet its prespecified primary endpoint as it failed to show a significant difference from placebo in the Alzheimer's Disease Composite Score (ADCOMS) cognitive function assessment. The ADCOMS contains 12 items that include components of the ADAS-Cog, MMSE, and Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) cognitive and functional ability total scores.

- In Study 301, the CDR-SB score from baseline favored lecanemab compared to placebo (mean difference [MD] 0.45; 95% CI, -0.67 to -0.23; P<0.001; insufficient evidence) at 18 months.[7] There were statistically significant changes in the secondary outcome measures of ADAS-Cog14 score (MD -1.44; 95% CI, -2.27 to -0.61; insufficient evidence), the ADCOMS (MD -0.05; 95% CI, -0.074 to -0.027; insufficient evidence), the ADCS-MCI-ADL (MD 2.0; 95% CI, 1.2 – 2.8; insufficient evidence) for lecanemab-treated groups compared to placebo (P<.001 for all). A substudy of amyloid burden on Positron Emission Tomography (PET) reported that brain amyloid burden showed a statistically significant dose- and time- dependent amyloid reduction with lecanemab therapy compared to placebo at 18 months (adjusted mean difference -59.12 [95% CI, -62.64 to -55.60; p<0.001]; insufficient evidence).[7] There is insufficient evidence to assess the clinical significance of these endpoints and whether changes in amyloid levels has an effect on cognitive decline.
    - The most common adverse events associated with lecanemab were infusion reactions, ARIA-H ("hemorrhage" including combined cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis), ARIA-E (edema/effusion), headache and falls.[4-7] Long-term clinical outcomes including mortality have not been studied with lecanemab.
    - Evidence for lecanemab comes from trials enrolling predominately people who identify as White, with mild AD, and between 50-90 years of age.[2,3] There is insufficient evidence on efficacy or harms data for people who identify as Black (only 2% of enrolled participants) and other important factors such as ethnicity and socioeconomic status or with health concerns such as people with a risk of bleeding, [2,3]
- Patients with AD who were homozygotes for the Apolipoprotein E4 (ApoE4) genotype had a greater risk of ARIA compared to heterozygotes and noncarriers when treated with either aducanumab or lecanemab.[7,10]

Recommendations:
- Create a new PDL class: Monoclonal Antibodies for Alzheimer's Disease.
- Designate lecanemab as non-preferred on the preferred-drug list (PDL).
- Implement prior authorization (PA) criteria for lecanemab and update existing criteria as proposed (**Appendix 5**).

Summary of Prior Reviews and Current Policy
- Therapies FDA-approved for the treatment of AD were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in October 2021.
- Previous evaluations concluded that there was insufficient evidence for the treatment of AD beyond 6 months.
- There was low to moderate quality evidence that acetylcholinesterase inhibitors (ACHEIs) improved outcomes of cognition in patients with mild to moderate AD compared to placebo but insufficient evidence that one agent was more efficacious or safer than another. ACHEIs and memantine also demonstrated modest but persistent improvements in cognition, activities of daily living, and behavior in patients with moderate to severe AD. In patients with severe AD, there was low-quality evidence that donepezil improved outcomes of function. The overall magnitude of benefit with ACHEIs for improvements in cognition and function was relatively small.
- None of the approved medications had been shown to stop or reverse the underlying process of AD or have any impact on important clinical outcomes such as mortality, disability, or institutionalization in patients with AD.
- There are numerous AChHEIs and memantine formulations available on the preferred drug list (PDL) that do not require PA (**See Appendix 1**)
- There is insufficient evidence that use of aducanumab in patients with AD has any clinically meaningful impact on symptoms, cognitive or functional improvement, quality of life, or disease progression based on a review of evidence presented to the P&T committee in October 2021.
- Aducanumab treatment resulted in an increased incidence of amyloid-related imaging abnormalities (ARIA) including brain microhemorrhage and edema compared to placebo.

- There was insufficient evidence to verify long-term safety of aducanumab, which is especially a concern in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding.
- No comparative efficacy or safety data were available for aducanumab versus other agents used to treat AD.

Background:
Alzheimer's disease (AD) is a progressive condition of neurological degeneration and memory impairment that primarily affects the elderly.[11] Alzheimer's dementia is a complex disorder that may be the result of numerous factors such as genetics, environmental stimuli, age, and education.[11] Generally, AD is characterized by deterioration of cognitive and reasoning skills, poor coordination and muscle function, personality changes, and an incapability of autonomous self-care.[11] Common neurological manifestations of AD include episodic memory impairment, a decline in visual-spatial perception, a reduced capability to learn, problem-solve, and complete mathematical calculations, a decreased ability to think in abstract, and overt lapses in judgement.[11] Alzheimer's dementia is the most common form of dementia and accounts for 60-80% of all dementia cases.[11] The prevalence of AD appears to increase dramatically with age.[11,12] The percentage of people with AD is around 5% for ages 65 to 74 years but increases to almost 14% for those aged 75 to 84 years.[11,12] By 85 years of age and older, around one-third of the population is estimated to have some form of AD.[11,12] Currently in the United States, an estimated 6 million people aged 65 or older have AD and it is projected that by 2060 the number may surge to almost 14 million.[12] Studies are inconclusive whether the incidence of AD differs among men and women, but there is some evidence to suggest a disproportionately higher incidence among Black, African and African American persons than other racial or ethnic groups.[11]

The diagnosis of AD may be challenging and often requires a review of clinical findings, medical history, and brain imaging.[11-13] Evaluation involves ascertainment of medical history from the patient and family member (or caregiver) along with a cognitive and neurologic examination.[12-14] The clinical spectrum of AD may range from asymptomatic to severe impairment.[11-14] Early disease without symptoms may be characterized as preclinical AD.[11-14] As neuronal injury and amyloid develops, there may be subtle decline in memory, organization, and mood where the patient would be diagnosed with mild cognitive impairment (MCI).[12] Medications that could cause cognitive impairment should be discontinued where possible and behavioral symptoms treated.[15] The American Academy of Neurology also recommends that clinicians assess for MCI with validated tools and monitor the cognitive status of their patients with MCI over time.[15] In patients with MCI, slight cognitive changes and short-term memory loss are evident, but there is generally little to no substantial impairment of social function or activities of daily living (ADL).[16,17] When changes in personality, speech, and cognition occur that result in functional impairment, a clinical diagnosis of AD is often made.[16,17] AD may be classified as mild, moderate, or severe depending upon the extent that cognitive decline interferes with ADLs.[13] Early-onset AD (EOAD) is rare and generally manifests before 65 years of age.[12] Mutations in the genes for amyloid precursor protein, presenilin 1, or presenilin 2 usually cause EOAD.[12,18] Late-onset AD (LOAD) affects most (greater than 95%) people with AD and typically occurs after 65 years of age.[12] Attempts to screen for AD and related dementia have been unable to show a positive impact on disease prevention or in measures of health-related quality of life.[33,34]

There have been several factors identified that increase the risk of AD development.[12,18] Advanced age, family history/genetics, Down syndrome, previous head trauma, and environmental pollutants may predispose individuals to AD.[12,18] Among the roughly 30 genes linked to AD, the ε4 allele of the Apolipoprotein E gene (ApoE4) has been one of the strongest risk factors.[12,19] Although estimates vary between studies and ethnicities, the ApoE4 allele is often present in more than 50% of AD patients but found in only about 15% of healthy older controls.[19,20] Modifiable risk factors for AD may include low education level, diabetes mellitus, hypertension, and a sedentary lifestyle.[16,17] Alzheimer's dementia generally has a slow onset and progresses gradually over many months or years.[13]

Although the precise cause of AD is not well understood, there are common neuropathogenic aspects such as amyloid-beta (Aβ) and tau protein that have been the focus of most modern research.[20,21] Physiologic amounts of Aβ peptide enhance memory, and tau protein appears to have an important role in neuronal

microtubule assembly .[20,21,23] However, an imbalance of these key proteins by overproduction or dysregulation may lead to accumulation of plaques and neurofibrillary tangles.[21-23] Aβ plaques exist in many different conformational states (monomers, oligomers, protofibrils, and insoluble fibrils) and some forms may be more neurotoxic than others.[21] Studies of the Arctic Alzheimer Mutation (AβPP E693G) have reported observance of high levels of soluble Aβ protofibrils in people with AD.[20-22] High levels of amyloid-beta increases glycogen synthase kinase 3B and phosphorylates tau.[20,23] It has been hypothesized that as amyloid beta aggregates and triggers tau phosphorylation, it leads to neurofibrillary tangle (NFT) formation, followed by synapse degradation and disruption of neuron signaling, and eventual neuronal destruction and death.[20,24] Whether tau tangle pathology precedes AB plaque formation is still under investigation.[20-22] Nevertheless, a direct correlation between mean plaque count and cognitive performance is controversial as at least one study has shown that in about one-quarter of elderly deaths with significant plaque accumulation, the individuals were not cognitively impaired.[20] Regardless of the root cause, neuronal damage results in widespread neurotransmitter deficiencies including those involved in the cholinergic pathway.[25-27] With less acetylcholine released from presynaptic neurons, the availability of neurotransmitters such as serotonin and norepinephrine involved in memory and mood are hindered, and AD symptoms worsen.[25-27]

A variety of brain imaging techniques are available to help confirm the presence of AD.[28-31] Classic magnetic resonance imaging (MRI) is useful in detection of low oxygen levels and reduced brain blood flow commonly observed in patients with AD.[30,31] Aβ plaques and NFTs are easily visible with Positron Emission Tomography (PET) neuroimaging.[29-31] PET scans help reveal glucose metabolism in the brain and may also be useful to establish biomarkers of amyloid burden in the progression of AD.[29,30] The standardized uptake value ratio (SUVR) is a method to quantify the degree of radioactive tracer uptake in the subject's brain. For imaging with amyloid and tau, SUVR is commonly calculated using the unaffected cerebellum as a reference.[49] Accumulation of tau may also be measured in the cerebral spinal fluid (CSF) and can serve as a biomarker of neuronal degeneration.[20,32] Detection of low levels of Aβ 42 or elevated hyperphosphorylated tau in the CSF are trademarks of AD.[28] Changes in brain amyloid may be measured by PET and converted into a Centiloid scale for comparison of data (100 points possible; 0=healthy, high certainty amyloid negative; 100=typical of AD).[5,32]

Since there is no known cure for AD, treatment involves symptom management and strategies to reduce long-term clinical decline.[12] A multifactorial approach will generally involve nonpharmacologic and behavioral interventions as well as pharmacotherapy.[12] Current FDA-approved therapies for AD include ACHEIs, the N-methyl-D-aspartate (NMDA) antagonist memantine, and the human monoclonal antibodies.[13,23,35] ACHEIs function to increase acetylcholine in the central nervous system via suppression of the metabolizing enzyme acetylcholinesterase.[13] ACHEIs (e.g. donepezil, galantamine, rivastigmine) are typically used as first-line therapy in mild to moderate dementia to alleviate AD symptoms.[13,15] Memantine blocks the excitatory effects of glutamate by the preferential binding to NMDA receptor channels to facilitate synaptic transmission, neuronal growth and differentiation.[13] Memantine may be used as monotherapy in people with moderate AD who are intolerant or have contraindications to ACHEI therapy, or it may be used alone or in combination with ACHEI in patients with severe AD.[13.20] The newer monoclonal antibodies are approved for mild AD and target the aggregated forms of amyloid beta plaques which includes soluble oligomers and insoluble fibrils.[36] Widespread use of monoclonal antibodies in patients with AD has been limited likely due to unknown clinical advantages and high cost. Overall, ACHEIs, NMDA antagonists, and monoclonal antibodies have reported only modest treatment effects in different stages of AD.[13] The oral and topical FDA-approved agents for AD along with their dosing and individual properties are listed in **Table 1**.

Table 1. FDA-Approved Pharmacologic Treatments for Dementia Attributed to Alzheimer Disease [6,13,37]

Generic Name	Brand Name	Typical Dose/Route/Frequency	FDA Approved AD Indication	Advantages	Safety Concerns
Donepezil	Aricept™, Aricept ODT™	5 mg or 10 mg orally once daily	Mild to Moderate	Prescriber familiarity; generic, orally	Nausea, vomiting, loss of appetite, increased frequency of bowel

		10 mg or 23 mg orally once daily	Moderate to Severe	disintegrating tablet available	movements, vivid dreams, insomnia; use with caution in patients with peptic ulcer disease, respiratory disease, seizure disorder, and urinary tract obstruction; contraindicated in patients with bradycardia
Galantamine	Razadyne™	4 mg orally twice daily	Mild to Moderate	Solution and generic formulation available	
Rivastigmine	Exelon™	1.5 mg orally twice daily; max dose 6 mg orally twice daily	Mild to Moderate	Patch and generic formulation available	
Memantine	Namenda™	5 mg orally once daily up to target max 10 mg orally twice daily	Moderate to Severe	May use as monotherapy or in combination with ACHEI; generic formulation available	Headache, constipation, confusion, and dizziness; use with caution in patients with cardiovascular disease, seizure disorder, and severe hepatic and renal impairment
	Namenda XR™	7 mg orally once daily up to target max 28 mg once daily	Moderate to Severe	May use as monotherapy or in combination with ACHEI	
Memantine + Donepezil	Namzaric™	If stabilized on donepezil 10 mg and NOT on memantine: Memantine ER 7 mg/donepezil 10 mg once daily in the evening up to target memantine ER 28 mg/ donepezil 10 mg once daily	Moderate to Severe	Combination for reduced pill burden	All of the above
Aducanumab	Aduhelm™	10 mg/kg once every 4 weeks	Mild	Unknown	ARIA including brain edema and microhemorrhage; cerebral hemorrhage; seizures
Lecanemab	Leqembe™	10 mg/kg once every 2 weeks			

Abbreviations: ACHEI=acetylcholinesterase inhibitor; AD=Alzheimer's dementia; ARIA=Amyloid-related imaging abnormalities; ER=extended release; FDA = Food and Drug Administration; max =maximum; kg=kilogram; mg=milligram; ODT=orally disintegrating tablet; XR = extended release

Much of contemporary AD drug therapy research has focused on immunotherapy targeted at accumulation of beta amyloid plaques in an attempt to reduce neuronal toxicity and possibly improve synaptic function.[23] Several MABs have been developed to either decrease amyloid beta production, hinder beta-amyloid aggregation, or increase amyloid beta clearance, but none of these agents have been able to demonstrate a definitive clinical benefit associated with changes in amyloid beta levels.[23] These agents differ in selectivity for Aβ polymorphic variants and their epitopes.[38] However, studies with amyloid modifying therapies and specifically amyloid-beta targeting MABs (e.g. bapineuzumab, aducanumab, lecanemab) have revealed their own unique safety risks collectively known as ARIA.[39,40] ARIA may be observed in patients who have undergone a MAB infusion as a result of anti-Aβ autoantibody development in the CSF.[39,40] MRI with ARIA findings may reveal brain swelling or microhemorrhages referred to as ARIA-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H), respectively.[39,41] ARIA may present with headache, confusion, visual changes and gait difficulty usually observed between the first and third therapy infusion.[41] Serious ARIA symptoms may include seizures, encephalopathy, stupor, and focal neurologic deficits. For patients with moderate or severe ARIA detected via imaging or who develop symptoms, anti-amyloid MAB therapy should be suspended and monitored closely until ARIA-E resolves or ARIA-H stabilizes.[35] Not all people with AD develop ARIA after amyloid modifying therapy, but a number of drug trials have suggested that side effect profiles may not only differ between various agents, but also whether patients are ApoE4 carriers or non-carriers.[19,40] In studies of patients treated with aducanumab and lecanemab, carriers of the ApoE4 genotype had a much greater frequency

of ARIA (particularly at higher doses) than non-carriers, and the rates were even higher for ApoE4 homozygotes than heterozygotes.[40] The risk of ARIA for these agents, notably for those with the ApoE4 genotype, is listed as a warning and precaution in the FDA labeling.[7,10]

Clinically important outcomes in AD include mortality, cognitive function, quality of life/independence, functional performance in activities of daily living (ADL), behavioral disturbances, and serious adverse events.[43] Several exams and scales have been used to monitor AD progression and to assess the effectiveness of clinical interventions in AD treatment. Due to the progressive nature and highly variable range of symptoms in AD, clinicians have found it difficult to establish and agree upon thresholds for minimal clinically important differences (MCIDs) in many AD therapy outcomes.[17] The SMMSE and MMSE are similarly designed and commonly used scales to assess cognitive impairment in AD (30 points possible, higher is better, MCID defined as 1 to 3 points) which includes multiple areas (e.g. orientation to time and place, registration, attention/calculation, recall, language, and visual construction).[44,45] Both scales have a range from 0 to 30 points possible and scoring is grouped into levels of severity based on cognitive impairment (≥25 = normal cognition; 21-24 = mild AD; 11-20 = moderate AD; and 10 or less = severe dementia).[44-46] Factors such as education level may influence SMMSE/MMSE scoring.[44-46] Although some studies have reported the minimum clinically important difference thresholds for the SMMSE/MMSE to be 1.4 points, a recent Cochrane review did not find any evidence to support the MMSE as a stand-alone test for early prediction of dementia development in people with mild cognitive impairments (MCI).[45] In mild AD, studies have used the Clinical Dementia Rating Scale (CDR) which include the CDR-Sum of Boxes (CDR-SB) and Global CDR Score (CDR-GS) that measure cognitive and functional impairment in AD.[48] The CDR assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-controlled interviews with the patient and a reliable companion or informant.[48] A qualified rater uses the interview data and clinical judgment to assign scores for each domain.[48] The CDR-GS ranges from 0 to 3 and dementia rating may be scored as none (0), questionable cognitive impairment/very mild dementia (0.5), mild cognitive impairment/mild dementia (1), moderate dementia (2), and severe dementia (3).[48] The CDR-SB score has a range from 0 (normal) to 18 (severe dementia).[42] A CDR-SB score of 0 is considered normal while the higher scores may be characterized in the following manner: 0.5-4.0 = questionable cognitive impairment to very mild dementia; 4.5-9.0 = mild dementia; 9.5-15.5 = moderate dementia; 16.0-18.0 = severe demetia.[42] The FDA has accepted the CDR-SB as a valid primary endpoint for clinical trials in patients with early AD due to its psychometric properties and its ability to assess both cognitive and functional disability.[42,48] An increase of 1- to 2-points on the CDR-SB was found to be clinically significant by the National Alzheimer's Coordinating Centers (NACC) Uniform Data Set (UDS).[42] Other validated instruments for AD outcome assessment include the Functional Activities Questionnaire (FAQ; 30 points possible, lower score is better; MCID defined as 3 to 5 points), the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) for cognitive assessment in mild to severe AD (11 subject-completed tests and observer assessments of memory, language, and critical thinking; ADAS-Cog14 includes all 11 items plus a test of word recall, number cancellation, and a maze with a score ranging from 0-90 with higher scores reflecting greater impairment; MCID = 2 points for MCI due to AD and ≥3 points for mild AD, lower score better), the 24-item Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) instrument (range from 0 to 78; higher score is better; MCID not defined) or 18-item ADCS-ACL Mild Cognitive Impairment (MCI) instrument (range from 0 to 57; higher score better; MCID not defined), and the 40-question severe impairment battery (SIB; 100 points possible, lower score=worse; MCID not defined).[28,50-53] The Bristol Activities of Daily Living scale (BADLS) is a tool used in AD patients for assessment of functional ability. The BADLS was developed for self-completion by caregivers of patients with dementia to assess basic activities of daily living (ADL) and instrumental ADLs. The BADLS has 20 questions rated on a 4-point scale with possible scores from 0 points (no help required) to 3 points (unable even with supervision) with a range 0 – 60 points (MCID = 3.5 points).[62] Quality of life in patients with AD may be measured with the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS; 16 items, range 0 to 54, higher scores = more severe impairment).[54] A two-point difference on the ADFACS between cognitively normal people and those with mild cognitive impairment in Alzheimer's disease may be clinically significant according to some research.[54] The ADCOMS is a manufacturer-developed 12-item weighted combination of items from 3 commonly used clinical scales: 4 items from the ADAS-Cog (delayed word recall, orientation, word recognition, and word finding), two items from the MMSE (orientation to time and drawing), and 6 items from the CDR-SB (personal care, home and hobbies, community affairs, judgment and

problem solving, orientation, and memory).[55] More studies are needed to evaluate whether the ADCOMS may be recognized as a valid clinical tool for assessment of MCI due to AD and dementia.[55,56]

Although the FDA typically performs a risk-benefit assessment in their reviews, MCID thresholds have not always been required prior to approval.[43] In recent years, the FDA has granted accelerated approval for many drugs based on evidence from unpublished studies with smaller patient populations, limited follow-up, and intermediate biomarkers that currently do not have established clinical significance.[57] For example, the human monoclonal antibody aducanumab was studied in 2 phase 3 placebo-controlled RCTs (study 302 "EMERGE" and study 301 "ENGAGE") that included patients with MCI or mild dementia due to AD who had evidence of amyloid plaques verified via PET scan.[48,58] Study 302 demonstrated a modest but statistically significant benefit compared to placebo at week 78 for the primary outcome of CDR-SB (absolute difference -0.39 points; P=0.01), while study 301 failed to show benefit.[48,58] Neither trial was able to establish a clinically meaningful difference from placebo; however, aducanumab was shown to remove amyloid beta in both trials in a dose-dependent manner.[48,58] Adverse effects such as ARIA were reported in over 40% of trial participants who received the higher dose of aducanumab and 25% of these cases were symptomatic (e.g. confusion, dizziness, headaches).[48,58] Using brain AB plaque reduction as a biomarker, the FDA approved aducanumab based on the conclusion that this surrogate endpoint might predict a future clinical benefit.[48,58] However, regulatory reviews by Health Canada and the European Medicines Agency (EMA) found the trial data insufficient to support marketing approval and therefore aducanumab is not currently approved for use in Canada or Europe.[58]

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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:
Cochrane - Withdrawal or continuation of ACHEI or memantine or both, in people with dementia.[1]
A 2021 Cochrane review evaluated the effects of withdrawal or continuation of ACHEIs or memantine, or both, in people with dementia. Participants were adults (n=759) with dementia due to AD that ranged in severity from mild to very severe and who were being actively treated with ACHEIs.[1] Seven RCTs of 6 weeks to 12 months duration were included. Results were categorized into three outcome assessment time periods: short-term (≤2 months), medium-term (3 to 11 months), and long-term (12 months or more).[1] Six of the trials investigated the effects of stopping an ACHEI while one trial examined the discontinuation of either donepezil or memantine. The mean age range of participants was 72.7 to 89.2 years.[1] The primary endpoints were change from baseline in cognitive function (based on ADAS-Cog/11 and MMSE), neuropsychiatric and functional outcomes (NPI, BADLS, ADCS-ADL), rates of institutionalization, adverse events, dropout from trials, mortality, quality of life and care-related outcomes.[1]

Four studies found low quality evidence that discontinuation of ACHEI treatment may be associated with worse cognitive function within 2 months compared to continuation (standardized mean difference (SMD) -0.42, 95% CI -0.64 to -0.21), but the effect of discontinuation versus continuation over medium time periods

(within 3 to 11 months) is very uncertain.[1] One study with moderate quality evidence found that discontinuation of ACHEI likely results in reduced cognitive function at 12 months (MD -2.09 SMMSE points, 95% CI -3.43 to-0.75).[1] There was one study with moderate quality evidence that reported discontinuation of an ACHEI likely resulted in greater functional impairment than continuing treatment at 12 months or longer (MD -3.38 Bristol Activities of Daily Living Scale (BADLS) points, 95% CI -6.67 to -0.10).[1] Discontinuation was shown to possibly worsen of neuropsychiatric symptoms over the short term and medium time periods, but all evidence was considered to be of very low quality.[1] Moderate quality evidence from one study suggest that discontinuing an ACHEI is probably associated with worse cognitive function after long-term treatment (MD -2.09 Standardized Mini-Mental State Examination (SMMSE) points, 95% CI -3.43 to -0.75).[1] There was no clear evidence found to show that discontinuation had an effect on dropout from trials, deterioration in overall medical condition, adverse events, institutionalization, or mortality.[1] The authors were unable to determine whether the effects of ACHEI discontinuation differed according to dementia severity at baseline.[1]

Cochrane- ACHEIs for vascular dementia and other vascular cognitive impairments: a network meta-analysis[2]

A 2021 systematic review and network meta-analysis evaluated the role of treating vascular dementia and other vascular cognitive impairments (VCI) with ACHEIs.[2] Eight RCTs (n=4373) were included with durations from 24 to 26 weeks.[2] Studies included RCTs in which donepezil, galantamine, or rivastigmine were compared with placebo in participants who had vascular dementia or other VCI (excluding cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)).[2] Mean ages of participants were between 72.2 and 73.9 years. Only oral formulations were assessed.[2] The primary outcomes of interest were cognitive function (ADAS-Cog), clinical global impression, functional performance in ADL, and number of adverse events.[2] All included trials were manufacturer-sponsored with low to unclear risk of bias and evidence grading ranged from very low to high-quality.[2]

There was high-quality evidence for donepezil 10 mg daily at 24 weeks and galantamine 16 mg to 24 mg daily at 26 weeks which suggests a modest beneficial effect on cognition compared to placebo in people with VCI as measured by the ADAS-Cog tool (donepezil 10 mg: MD -2.18 [95% CI −3.87 to −0.47]; galantamine 16 to 24 mg: MD -1.84 [95% CI −3.63 to −0.14]).[2] There was moderate-quality evidence that donepezil 10 mg daily may slightly improve functional performance based on the ADFACS, although the size of the change is unlikely to be clinically important (2 trials, 813 participants: MD −0.95 [95% CI −1.73 to −0.17]; used last observation carried forward (LOCF).[2] Studies with rivastigmine showed no significant difference from placebo in cognition or functional performance in ADL based on low quality evidence. All Galantamine 16 mg to 24 mg daily, donepezil 10 mg daily, and rivastigmine may be associated with slightly more adverse events compared to placebo based on low-quality evidence.[2] There was no evidence of increased numbers of serious adverse events or deaths with any of the ACHEIs included in the review.[2]

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

New Guidelines:

None identified.

New Formulations or Indications:

A new once-weekly transdermal patch formulation of the ACHEI donepezil (ADLARITY) was approved in March 2022 for the treatment of mild, moderate, and severe dementia of the Alzheimer's type.[8] Donepezil received initial US approval in 1996 and is currently available generically in 5 mg, 10 mg, and 23 mg oral tablets as well as 5 mg and 10 mg oral disintegrating tablets.[8] ADLARITY was approved through FDA's 505(b)(2) regulatory pathway which enabled results from

previous studies with donepezil tablets to be compared with the transdermal patch formulation.[8] Pharmacokinetic data assessed over a 5-week period in 60 healthy volunteers demonstrated that the 5 mg/day or 10 mg/day weekly patch had similar bioavailability as the oral tablets.[8]

The most common adverse reactions occurring in healthy subjects receiving donepezil transdermal system 10 mg/day were headache (15%), application site pruritus (9%), muscle spasms (9%), insomnia (7%), abdominal pain (6%), application site dermatitis (6%), constipation (6%), diarrhea (4%), application site pain (4%), dizziness (4%), abnormal dreams (4%), and skin laceration (4%).[8] Following the removal of donepezil transdermal systems, some participants experienced skin irritation, including erythema (64.6%), papules (16.0%), and edema (0.4%), but none of the transdermal systems were discontinued because of skin irritation.[8] ADLARITY is contraindicated in those with hypersensitivity to donepezil or to piperidine derivatives or patients with a history of contact dermatitis with its use.[8]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, Contraindications)	Addition or Change and Mitigation Principles
Galantamine[9]	Razadyne; Razadyne ER	8/2021	Warning	An increase in cholinergic tone may worsen symptoms related to extrapyramidal disorders
Aducanumab-avwa[10]	Aduhelm	2/2023	Warning	Extensive changes to the warnings and precautions regarding ARIA-E and ARIA-H. See full prescribing information for details. *"ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. Rarely, fatal events have occurred in the setting of ARIA… When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur…. Consider testing for ApoE ε4 carrier status to inform the risk of developing ARIA when deciding to initiate treatment with ADUHELM."* *… although ARIA can occur in any patient treated with ADUHELM, there is an increased risk in patients who are ApoE-E4 homozygotes"*
Abbreviations: ApoE-E4= ARIA-E= amyloid-related imaging abnormalities-edema; ARIA-H=amyloid related imaging abnormalities-hemorrhage				

Randomized Controlled Trials:
A total of 144 citations were manually reviewed and excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

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

Clinical Efficacy:
Lecanemab (LEQEMBE) is the latest anti-amyloid beta (Aß) monoclonal antibody that received FDA approval in January 2023 for the treatment of early AD.[4] The safety and efficacy of lecanemab in patients with MCI due to AD or mild dementia due to AD was evaluated in 2 industry-sponsored studies.[4-6] Both studies were randomized, double blind, placebo controlled, parallel group, multicenter trials.[4-6] Study 201 was a phase 2b dose-finding trial (N=856) and study 301 was a phase 3 confirmatory study (N=1795). More details on study design and risk of bias are included in **Table 5**.

Study 201
The primary outcome in study 201 was the change from baseline in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months (week 53).[3-6] Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at Week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at Week 79.[3-6] The population included an equal amount of male and female patients age 50 to 90 years (mean 71.3 years) all with evidence of Aβ pathology via PET scan or CSF assessment.[3-6] At baseline, the patients had a mean CDRSB score of 2.9, and 60% of patients had a MMSE score between 22 and 26 (mild dementia) while 40% had an MMSE score between 27 and 30 (questionable to no dementia).[3-6] Participants included 71% ApoE e4 carriers and 29% were ApoE e4 non-carriers.[3-6] Over half (54%) of the patients were on concomitant ACHEIs and/or memantine at the start of the study.[3-6] Patients were excluded if they had any other memory impairment besides AD associated with cognitive impairment, history of cardiovascular disease (TIA, stroke), seizures, an uncontrolled bleed, uncontrolled diabetes, hypertension, evidence of brain microhemorrhage or edema.[3-6] Patients were randomized into one of 5 different biweekly or monthly treatment groups or placebo.[3-6] A study protocol amendment related to safety resulted in discontinuation of ApoE4 carriers who had been receiving lecanemab 10 mg/kg every two weeks for 6 months or less due to observations of high risk of developing symptomatic ARIA-E.[3-6] Due to the change, the lecanemab 10 mg/kg every two weeks arm contained only 30% ApoE4 carriers and 70% ApoE e4 non-carriers.[3-6] All subjects with ARIA-E as assessed by MRI discontinued lecanemab per protocol.

Lecanemab 10 mg/kg biweekly dosing regimen was unable to show a statistically significant difference on the ADCOMS compared to placebo at 12 months.[4-6] An amyloid PET substudy was performed with 315 patients where 277 were evaluated at week 79 (see **Table 5**). Given the study's primary endpoint failure, the FDA statistical reviewers cautioned that all secondary endpoints should be considered exploratory.[5]

Study 301
A phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel group confirmatory trial ("Clarity AD") evaluated the efficacy and safety of lecanemab 10 mg/kg IV every 2 weeks over 18 months in 1795 patients with early AD.[7] The primary efficacy endpoint was the change from baseline at 18 months in the CDR-SB score.[7] Change from baseline in the ADAS-Cog14 score, the ADCOMS, and the ADCS-MCI-ADL were secondary endpoints.[7] Efficacy analyses were performed in the modified intention-to-treat population, which was defined as participants who underwent randomization that received at least one dose

of lecanemab or placebo and who had a baseline assessment and at least one post-dose primary efficacy (CDR-SB) measurement.[4] A separate substudy was conducted to investigate amyloid burden on PET (n=698), tau pathology on PET (n=257), and AD CSF biomarkers (n=281).[7] Trial participants were required to have mild cognitive impairment as evidenced by an MMSE score of 22-30.[7]

At baseline, the mean CDR-SB score was 3.2, about 38% had mild dementia due to AD, and the rest were classified with MCI due to AD.[7] The patients ranged from 50-90 years of age (mean age 71 years). All patients had evidence of amyloid burden as confirmed by PET or CSF measurements of Aβ.[7] Almost 70% were ApoE4+ (carriers).[7] The mean MMSE score for participants was 25.5. About half the patients were on a medication for AD symptoms (ACHEIs, memantine, or both).[7] Over half (52%) of the patients identified as female, 77% White, 17% Asian, 12% Hispanic, and only 2% as Black.[7] The other baseline characteristics of the study participants were generally similar between trial groups.[7]

At 18 months, the adjusted least-squares mean change of the CDR-SB score from baseline favored lecanemab compared to placebo (MD -0.45; 95% CI, -0.67 to -0.23; P<0.001).[7] When separated by clinical subgroup, the reported mean difference from placebo in the CDR-SB score was -0.35 and -0.62 for MCI and mild AD, respectively. When reported by sex, the adjusted mean difference from placebo in the CDR-SB was -0.73 for males (statistically significant) but -0.20 for females (not statistically significant – via forest plot).[7] In the substudy of amyloid burden on PET, there was a change from baseline of -55.48 centiloids in the lecanemab group versus 3.64 centiloids in the placebo group (MD -59.15 centiloids; 95% CI, −62.64 to −55.60; P<0.001).[7] There were statistically significant changes in the other secondary outcome measures of ADAS-Cognitive subscale score (MD -1.44; 95% CI, -2.27 to -0.61), the ADCOMS (MD -0.05; 95% CI, -0.074 to -0.027,) , and the ADCS-MCI-ADL (MD 2.0; 95% CI, 1.2 – 2.8) for lecanemab-treated groups compared to placebo (P<.001 for all).[7] There is insufficient evidence to assess the clinical significance of these changes and whether changes in amyloid levels has an effect on cognitive decline.

Limitations: The FDA approved lecanemab based on one study that did not meet its own prespecified criteria for success and relied on a secondary surrogate endpoint that reviewers determined was reasonably likely to predict a clinical benefit. Study 301 was published after FDA approval and reported a modest but statistically significant benefit in reducing the CDR-SB score, but it fell short of the MCID threshold recognized in published literature. The clinical significance of less than half a point on an 18-point cognitive/functional clinical scale is unclear as previous studies have reported that 1 to 2 points represent the MCID in patients with mild AD.[53,59] Furthermore, it is unknown if the reported effects on cognition has an equal effect on women compared to men as there were between group differences in CDR-SB scores reported when results were analyzed by sex. People identifying as White were over-represented in the trials and people identifying as Black were vastly under-represented, thereby limiting the applicability of the study results in more diverse real-world populations. It is unknown if lecanemab has any benefit in moderate AD or if any reported benefit would be sustained if drug were discontinued. The impact of amyloid beta reduction on clinical outcomes is uncertain as there has been no conclusive evidence to support a relationship between reductions in amyloid plaque levels and clinically meaningful symptom improvements in AD or a slowing of cognitive or functional decline.[59] Longer, more robust trials are needed in order to provide definitive results in areas of clinical importance for individuals with early AD.[60, 61]

Clinical Safety:

For the phase 3 trial, the most common adverse events associated with the use of lecanemab were infusion reactions, ARIA-H (combined cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis), ARAI-E (edema/effusion), headache and falls.[7] Most of the infusion reactions were mild to moderate and occurred after administration of the first dose.[7] There were 6 (0.7%) deaths in the lecanemab group and 7 (0.8%) deaths in the placebo group, none of which were attributed to ARIA by the investigators.[7] For those patients who experienced ARIA-E, the majority (81%) had their first episode by the 11th dose of lecanemab.[7] In addition, of the 113 (12.6%) patients treated with lecanemab who developed brain edema, 25 (22%) developed symptoms.[7] There

were 126 (14%) serious adverse events in the lecanemab group compared to 101 (11.3%) in the placebo group.[7] Treatment-emergent adverse events occurred in 88.9% of lecanemab patients and in 81.9% of the placebo group.[7]

Table 3. Adverse Reactions[7]

	Lecanemab N=898 N (%)	Placebo N=897 N (%)
Infusion related reaction	237 (26.4)	66 (7.4)
ARIA-H (with brain microhemorrhage or hemosiderin deposits)	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
UTI	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of CNS	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)

The FDA has issued a boxed warning for increased risk of ARIA, including symptomatic ARIA, in ApoE4 homozygotes compared to heterozygotes and noncarriers.[6] Testing for ApoE4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.[6] Prescribers are instructed to obtain a recent (within one year) brain MRI prior to initiating treatment with lecanemab and ongoing MRIs prior to the 5th, 7th, and 14th infusions.[6] It is recommended that prescribers suspend dosing for patients with moderate to severe ARIA-E or ARIA-H observed on MRI or who are exhibiting clinical symptoms.[6] If the ARIA-E symptoms are mild (i.e. discomfort but no disruption of normal daily activity), prescribers may continue dosing based on clinical judgement.[6] Asymptomatic patients with mild ARIA-E or ARIA-A may continue supervised dosing.[6] Lecanemab FDA labeling contains a warning to also monitor for infusion related reactions including flu-like symptoms, nausea, vomiting, and changes in blood pressure.[6] Long-term clinical outcomes including mortality have not been studied with lecanemab.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Mortality
2) Cognitive Function
3) Quality of Life (e.g. physical/psychological autonomy)
4) Functional performance in activities of daily living (ADL)
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in CDR-SB from baseline at 18 months

Table 4. Pharmacology and Pharmacokinetic Properties.[4,6]

Parameter	
Mechanism of Action	IgG1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid-beta
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd=3.22 (3.15-3.28) L; no information available on protein binding
Elimination	No information on route of elimination; Clearance = 0.434 (0.420-0.451) L/day
Half-Life	5 to 7 days
Metabolism	Degraded by proteolytic enzymes

Abbreviations: IgG1 = Humanized immunoglobulin gamma 1; L = liter; N/A=not applicable; Vd = volume of distribution

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Swanson CJ et al. [Study 201][3,5-7] Phase 2b, DB, PC, RCT	1. lecanemab (LEC) 10 mg/kg every 2 weeks* 2. Placebo (PBO) every 2 weeks *=also studied LEC in 2.5 mg biweekly, 5 mg biweekly and monthly, and 10 mg monthly	Demographics: Mean age: 71.3 years Male: 50% MCI due to AD: 64% Mild AD: 36% ApoE4+ (carriers): 1. 30% 2. 71% Baseline MMSE: 22 to 26 = 60% 27-30 = 40% Mean MMSE: 25.7 CDR-SB: 2.9 Mean ADCOMS: 0.38 ACHEI and/or memantine: 54% Race, ethnicity: Not reported Key Inclusion Criteria: -MCI due to AD or mild AD dementia -Memory impairment -Positive brain amyloid via PET or CSF assessment of t-tau/Aβ (1-42) -Age ≥50 to ≤90 years -MMSE score ≥22 (screening) and ≤30 (baseline) -BMI >17 and <35% -Naïve to or on stable dose (12 weeks) of AD medications (AChEI and/or memantine) Key Exclusion Criteria: -Non-AD cognitive impairment or dementia -Hx of transient ischemic attacks, stroke, or seizures within 12 months -Psychiatric diagnosis or symptoms, suicidal ideation, drug or alcohol abuse/dependence -Brain lesions (e.g. > 4 micro-hemorrhages, microhemorrhage, superficial siderosis) -Immunological disease (uncontrolled or requiring biologics) -Bleeding disorder -Abnormal labs/testing including: TSH, low Vit B12, prolonged QTc, or HIV+	ITT: 1. 161* 2. 247 *=includes only 10 mg/kg biweekly dosing cohort; total receiving LEC=609 Attrition: 1. 74** (46%) 2. 68 (28%) **=for all doses	Primary Endpoint: Mean change from baseline in the ADCOMS at 12 months (≥25%): -not statistically significant at all doses studied Secondary Endpoints: Change from baseline in brain amyloid beta PET Centiloid compared to PBO: Composite SUVR 1. -0.306 2. 0.004 MD -0.31 (p<0.001) PET Centiloid 1. -72.5 2. 1.0 MD -73.5 (p<0.001) Change from baseline in CDR-SB at week 79: NS Change from baseline ADAS-Cog14 at week 79: -Only 10 mg/kg biweekly dose had statistically significant finding: MD -2.31 (90% CI, -3.91 to -0.72; p=0.02)	NA NA	Discontinuation due to adverse event: LEC = 92* (15.1%) PBO = 15 (6.1%) SAE: LEC = 86* (14.1%) PBO = 43 (17.6%) TEAE LEC = 452* (74.2%) PBO = 216 (88.2%) Deaths: LEC = 5* (0.8%) PBO = 2 (0.8%) ARIA-H LEC = 65* (10.7%) PBO = 13 (5.3%) ARIA-E LEC = 46* (7.6%) PBO = 2 (0.8) *=for all LEC doses	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization created by the IVRS. Baseline characteristics generally balanced except very low ApoE4 positive representation in lecanemab 10mg/kg biweekly group. Performance Bias: (Unclear) Identical vials with placebo injection dispensed by unblinded pharmacists. Detection Bias: (Unclear) All study personnel and subjects blinded with respect to the dose regimen (excluding pharmacists). Interim analysis conducted at 3-month intervals by unblinded external independent. statisticians. Protocol amended during study to discontinue ApoE4 carriers from lecanemab 10 mg/kg biweekly group. Attrition Bias: (High) Attrition in almost half of the high-dose lecanemab study arm discontinued treatment. Reporting Bias: (Low) Trial appeared to be conducted according to protocol and outcomes reported as pre-specified. Other Bias: (High) Funded by manufacturer; Most authors employed by manufacturer. **Applicability**: Patient: Race/ethnicity of participants not reported Intervention: Appropriate based on earlier phase testing Comparator: Placebo appropriate for safety/efficacy; aducanumab available as future comparator Outcomes: Mix of composite clinical scales and surrogate; Must establish surrogate amyloid lowering as clinically relevant; Longer term outcomes needed. Setting: US (80%), Canada (5%), Western Europe (9%), Asia (6%)

		-Uncontrolled T1DM or T2DM, HTN, CVD -Malignant neoplasms last 3 years -Severe visual or hearing impairment -GDS score ≥8						
2.van Dyck et al.[4] Phase 3, DB, PC, RCT	1. lecanemab 10 mg/kg every 2 weeks 2. Placebo	Demographics: Female:52% Mean age: 71 Race/ethnicity: -White 77% -Black 2% -Asian 17% -Other 4% Concomitant AD meds: 52-53% ApoE4+ (Carrier): 68-69% -Heterozygous carrier: 53% -Homozygous carrier: 15% CDR-SB: 3.2 Mean MMSE score: 25.5 MCI due to AD: 61-62% Mild AD dementia: 38% Key Inclusion Criteria: -Age 50-90 years old, -MCI due to AD w/mild dementia -Amyloid pathology confirmed by amyloid PET or CSF assessment of tau/Aβ (1-42) ratio -MMSE score of 22-30 -BMI 17 to 35% -If on approved concurrent AD therapy (e.g. memantine, AChEI or both) must be stable for 12 weeks before baseline Key Exclusion Criteria: -Any neurological condition that may be contributing to cognitive impairment above and beyond AD -history of TIAs/stroke or seizures within 12 months of screening -any interfering psychiatric diagnosis or symptoms -drug or alcohol abuse within prior 2 years -any uncontrolled medical condition that could affect safety or study assessment -contraindications to MRI scanning -clinically significant lesions on brain MRI at screening that could indicate a dementia	ITT 1. 898 2. 897 mITT: 1. 859 2. 875 Attrition: 1. 169 (18.8%) 2. 140 (15.6%)	Primary Endpoint: Change in CDR-SB from baseline at 18 months LEC: 1.21 PBO: 1.66 MD -0.45 (95% CI, −0.67 to −0.23; P<0.001) Secondary Endpoints: Change from baseline to 18 mo in amyloid burden on PET (centiloids) LEC: -55.48 PBO: 3.64 MD: −59.12 (95% CI, −62.64 to −55.60; P <0.001) Change from baseline to 18 mo in the ADAS-cog14 score: LEC: 4.14 PBO: 5.58 MD: −1.44 (95% CI, −2.27 to −0.61; P <0.001) Change from baseline to 18 mo in the ADCOMS LEC: 0.164 PBO: 0.214 MD −0.050 (95% CI, −0.074 to −0.027; P <0.001) Change from baseline to 18 mo in the ADCS-MCI-ADL score LEC: −3.5 PBO: −5.5	NA NA	Discontinuation due to adverse event: 1. 62 (6.9%) 2. 26 (2.9) SAE: 1. 126 (14.0%) 2. 101 (11.3%) TEAE 1. 798 (88.9%) 2. 735 (81.9%) Deaths: 1. 6 (0.7%) 2. 7 (0.8%) Infusion reactions: 1. 237 (26.4%) 2. 66 (7.4%) ARIA-H 1. 155 (17.3%) 2. 81 (9%) ARIA-E 1. 113 (12.6%) 2. 15 (1.7%) Headache 1. 100 (11.1%) 2. 73 (8.1%) Fall 1. 93 (10.4%) 2. 86 (9.6%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias:(Low) Centralized, computer-generated randomization scheme reviewed and approved by an independent statistician Performance Bias: (Unclear) High rates of infusion reactions in drug group versus placebo with blinding potentially broken during trial. Detection Bias: (Low) independent data and safety monitoring board experts in Alzheimer's disease and statistics reviewed unblinded safety data; independent medical monitoring team that were unaware of the trial-group assignments reviewed ARIA, infusion related reactions, and hypersensitivity reactions; clinical assessment raters were unaware of the safety assessments and the trial-group assignments. Attrition Bias: (High) dropout rate >10%; mITT for those who discontinued drug but remained in trial. Reporting Bias: (Low) Study protocol available and appeared to be followed with all pre-specified primary and secondary outcomes reported. Other Bias: (High) Funded by manufacturer; Most authors serve as consultants for manufacturer. **Applicability**: Patient: 70% patients screened were ineligible; Extensive exclusions of patients with comorbidities. People who identified as black or of other racial and ethnic groups were under-represented. Intervention: Dose and comprehensive safety monitoring (adverse events, vital signs, physical examinations, clinical laboratory variables, and 12-lead electrocardiograms) at specific intervals

		diagnosis besides AD -any interfering medications within prior 6 mos (immunosuppressants, immunoglobulins) -prior exposure to lecanemab -HIV+ -low vitamin B12 -GDS score ≥8 at screening -Pregnant or breastfeeding females		MD 2.0 (95% CI, 1.2 to 2.8; P <0.001)				during treatment appropriate based on previous Phase 2 studies. Comparator: Placebo appropriate given few standard treatment options that delay, halt, or reverse AD. Outcomes: CDR-SB not a standard outcome measure in AD; amyloid plaque reduction is a surrogate endpoint that does not have clear effects on cognition; no outcomes such as behavioral symptoms or time to institutionalization were studied. Setting: Sites in North America, Europe, Asia, and Australia
Abbreviations : ACHEI=acetylcholinesterase inhibitor; ADCS-MCI-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment; AD=Alzheimer's disease; ADCOMS= Alzheimer's Disease Composite Score; ARIA= amyloid-related imaging abnormalities; ApoE4=apolipoprotein E4;ARIA-E=ARIA with edema or effusions; ARIA-H ARIA with hemorrhage; ARR = absolute risk reduction; BMI=body mass index; CDR=clinical dementia rating; CDR-SB=CDR–Sum of Boxes; CI = confidence interval; CSF=cerebrospinal fluid; CVD=cardiovascular disease; GDS=Geriatric depression scale; Hx=history; ITT = intention to treat; HTN=hypertension; IVRS=Interactive Voice Response System; LEC=lecanemab; MAB=monoclonal antibody; MCI=mild cognitive impairment; MD=mean difference; mg=milligram; MMSE=Mini–Mental State Examination; mo=months; MRI=magnetic resonance imaging; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PET=Positron Emission Technology; PBO=placebo; PP = per protocol; SUVR=standardized uptake value ratio; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA=transient ischemic attack; TSH=thyroid stimulating hormone; Tx=treatment; vit=vitamin								

References:

1. Parsons C, Lim WY, Loy C, et al. Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia. *Cochrane Database Syst Rev*. 2021 Feb 3;2:CD009081.
2. Battle CE, Abdul-Rahim AH, Shenkin SD, Hewitt J, Quinn TJ. Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;2(2):CD013306.
3. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody [published correction appears in Alzheimers Res Ther. 2022 May 21;14(1):70]. *Alzheimers Res Ther*. 2021;13(1):80.
4. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023;388(1):9-21.
5. US Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Leqembi Summary Review. Accessed June 1, 2023.
6. US Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Leqembi Statistical Review. Accessed June 1, 2023.
7. Leqembi (lecanemab injection) [Prescribing Information]. Eisai Inc., Nutley, NJ. Jan 2023.
8. ADLARITY (donepezil transdermal system) [Prescribing Information] Corium, Inc., Grand Rapids, MI. March 2022.
9. Food and Drug Administration. Drug Safety-related Label Changes: Razadyne/Razadyne ER (galantamine) August 2021.
10. Food and Drug Administration. Drug Safety-related Label Changes: Aduhelm (aducanumab). February 2021.
11. Alzheimer's disease facts and figures, 2020. Alzheimer's & Dementia. 2020;16(3):391-460.
12. Atri A. The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. *Med Clin North Am*. 2019;103(2):263-293.
13. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. *JAMA*. 2019;322(16):1589-1599.

14. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimers Dement.* 2019;15(7):888-898.
15. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(3):126-135.
16. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2021;17(3):327-406.
17. Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. *J Am Board Fam Med.* 2012;25(3):367–382.
18. Vilatela ME, López-López M, Yescas-Gómez P. Genetics of Alzheimer's disease. *Arch Med Res*. 2012;43(8):622-631.
19. Liu CC, Kanekiyo T, Xu H, et al. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013;9(2):106-118.
20. Morley JE, Farr SA, Nguyen AD. Alzheimer Disease. *Clin Geriatr Med*. 2018 Nov;34(4):591-601.
21. Zheng X, Tang Y, Yang Q, et al. Effectiveness and safety of anti-tau drugs for Alzheimer's disease: Systematic review and meta-analysis. *J Am Geriatr Soc*. 2022;70(11):3281-3292.
22. O'Nuallain B, Freir DB, Nicoll AJ, Risse E, Ferguson N, Herron CE, Collinge J,Walsh DM. Amyloid β-protein dimers rapidly form stable synaptotoxic protofibrils. *J Neurosci*. 2010;30:14411–9.
23. Panza, F., Lozupone, M., Logroscino, G. et al. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. Nat Rev Neurol 15, 73–88 (2019).
24. Hardy J, Higgins G. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992;256(5054):184-185.
25. Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron*. 2014;82(4):756–771.
26. Kumar A, Singh A, Ekavali, M. A review on Alzheimer's disease pathophysiology and its management: An update. *Pharmacol Rep*. 2015;67(2):195–203.
27. Hampel H, Mesulam M-M, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain*. 2018;141(7):1917–1933.
28. AHRQ evidence report. Diagnosis and Treatment of Clinical Alzheimer's-Type Dementia. A Systematic Review. April 2020. https://effectivehealthcare.ahrq.gov/products/alzheimers-type-dementia/research. Accessed June 1, 2023.
29. Mosconi L, Tsui WH, Herholz K. Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med*. 2008;49:390–8.
30. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004;55:306–19.
31. Xia C, Makaretz SJ, Caso C, et al. Association of in vivo [18F]AV-1451 Tau PET imaging results with cortical atrophy and symptoms in typical and atypical Alzheimer disease. *JAMA Neurol*. 2017;74:427–36.
32. Karran, E., De Strooper, B. The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. *Nat Rev Drug Discov.* 21, 306–318 (2022).
33. Moyer VA, U.S. Preventive Services Task Force. Screening for cognitive impairment in older adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:791-797
34. Fowler NR, Perkins AJ, Gao S, et al. Risks and Benefits of Screening for Dementia in Primary Care: The Indiana University Cognitive Health Outcomes Investigation of the Comparative Effectiveness of Dementia Screening (IU CHOICE)Trial. *J Am Geriatr Soc*. 2020;68(3):535-543.
35. Cummings J, Aisen P, Apostolova LG, et al. Aducanumab: Appropriate Use Recommendations. *J Prev Alzheimers Dis*. 2021;8(4):398-410.
36. Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature.* 2016;537:50–56.
37. Aduhelm (aducanumab injection) [Prescribing Information]. Cambridge, MA. Biogen Inc. Feb 2023.
38. Arndt JW, Qian F, Smith BA, et al. Structural and kinetic basis for the selectivity of aducanumab for aggregated forms of amyloid-β *Sci Rep.* 2018;8(1):6412.
39. Sperling RA, Jack CR, Jr., Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimer's & dementia: the journal of the Alzheimer's Association*. 2011;7(4):367-385.

40. Filippi M, Cecchetti G, Spinelli EG, et al. Amyloid-Related Imaging Abnormalities and β-Amyloid–Targeting Antibodies: A Systematic Review. *JAMA Neurol*. 2022;79(3):291–304.
41. DiFrancesco J, Longoni M, Piazza F. Anti-Aβ autoantibodies in amyloid related imaging abnormalities (ARIA): candidate biomarker for immunotherapy in Alzheimer's disease and cerebral amyloid angiopathy. *Frontiers in Neurology*. 2015;6(207).
42. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2019;5:354-363.
43. Rentz DM, Wessels AM, Annapragada AV, et al. Building clinically relevant outcomes across the Alzheimer's disease spectrum. *Alzheimers Dement (N Y).* 2021;7(1):e12181.
44. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198
45. Arevalo-Rodriguez I, Smailagic N, Roqué-Figuls M, et al. Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*. 2021;7:Cd010783.
46. Perneczky R, Wagenpfeil S, Komossa K, et al. Mapping Scores Onto Stages: Mini-Mental State Examination and Clinical Dementia Rating. *Am J Geriatr Psychiatry*. 2006;14(2):139-144.
47. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2019;5:354-363.
48. US Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Aduhelm Medical Review. Accessed June 1, 2023.
49. Vemuri P, Lowe VJ, Knopman DS, et al. Tau-PET uptake: Regional variation in average SUVR and impact of amyloid deposition. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2017;6(1):21-30.
50. Marshall GA, Amariglio RE, Sperling RA, Rentz DM. Activities of daily living: where do they fit in the diagnosis of Alzheimer's disease? *Neurodegener Dis Manag*. 2012;2(5):483-491.
51. Lansdall CJ, McDougall F, Butler LM et al. Establishing Clinically Meaningful Change on Outcome Assessments Frequently Used in Trials of Mild Cognitive Impairment Due to Alzheimer's Disease. *J Prev Alzheimers Dis*. 2023;10(1):9-18.
52. Schrag A, Schott JM, Alzheimer's Disease Neuroimaging Initiative. What is the clinically relevant change on the ADAS-Cog? *J Neurol Neurosurg Psychiatry*. 2012;83(2):171-173.
53. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. *The Lancet Psychiatry*. 2021;8(11):1013-1016.
54. Manero RM, Casals-Coll M, Sánchez-Benavides Get al. Diagnostic Validity of the Alzheimer's Disease Functional Assessment and Change Scale in Mild Cognitive Impairment and Mild to Moderate Alzheimer's Disease. *Dement Geriatr Cogn Disord*. 2014;37(5-6):366–375.
55.Wang J, Logovinsky V, Hendrix SB, et al ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. *J Neurol Neurosurg Psychiatry*. 2016;87:993-999.
56. Tahami Monfared AA, Lenderking WR, Savva Y, et al. Alzheimer's Disease Neuroimaging Initiative. Assessing the Clinical Meaningfulness of the Alzheimer's Disease Composite Score (ADCOMS) Tool. *Neurol Ther*. 2022;11(3):1085-1100.
57. Naci H, Smalley KR, Kesselheim AS. Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration. *JAMA*. 2017;318(7):626-636.
58. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *J Prev Alzheimers Dis*. 2022;9(2):197-210.

59. Ackley SF, Zimmerman SC, Brenowitz WD, et al. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. *BMJ*. 2021;372:n805.
60. Decourt B, Boumelhem F, Pope ED 3rd, Shi J, Mari Z, Sabbagh MN. Critical Appraisal of Amyloid Lowering Agents in AD. *Curr Neurol Neurosci Rep*. 2021;21(8):39.
61. Tochel C, Smith M, Baldwin H, et al. What outcomes are important to patients with mild cognitive impairment or Alzheimer's disease, their caregivers, and health-care professionals? A systematic review. *Alzheimers Dement (Amst)*. 2019;11:231-247.
62. Bucks RS, Haworth J. Bristol Activities of Daily Living Scale: a critical evaluation. *Expert Rev Neurother.* 2002;2(5):669-676.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
donepezil HCl	DONEPEZIL HCL ODT	TAB RAPDIS	PO	Y
donepezil HCl	ARICEPT	TABLET	PO	Y
donepezil HCl	DONEPEZIL HCL	TABLET	PO	Y
galantamine HBr	GALANTAMINE ER	CAP24H PEL	PO	Y
galantamine HBr	RAZADYNE ER	CAP24H PEL	PO	Y
galantamine HBr	GALANTAMINE HBR	TABLET	PO	Y
memantine HCl	MEMANTINE HCL ER	CAP SPR 24	PO	Y
memantine HCl	NAMENDA XR	CAP SPR 24	PO	Y
memantine HCl	MEMANTINE HCL	SOLUTION	PO	Y
memantine HCl	MEMANTINE HCL	TAB DS PK	PO	Y
memantine HCl	NAMENDA	TAB DS PK	PO	Y
memantine HCl	MEMANTINE HCL	TABLET	PO	Y
memantine HCl	NAMENDA	TABLET	PO	Y
memantine HCl/donepezil HCl	NAMZARIC	CAP SPR 24	PO	Y
memantine HCl/donepezil HCl	NAMZARIC	CAP24 DSPK	PO	Y
rivastigmine	EXELON	PATCH TD24	TD	Y
rivastigmine	RIVASTIGMINE	PATCH TD24	TD	Y
rivastigmine tartrate	RIVASTIGMINE	CAPSULE	PO	Y
aducanumab-avwa	ADUHELM	VIAL	IV	N
donepezil HCl	ADLARITY	PATCH TDWK	TD	N
galantamine HBr	GALANTAMINE HYDROBROMIDE	SOLUTION	PO	N
lecanemab-irmb	LEQEMBI	VIAL	IV	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to June 22, 2023

1. donepezil.mp. or Donepezil/4901
2. galantamine.mp. or Galantamine/2583
3. rivastigmine.mp. or Rivastigmine/2220
4. memantine.mp. or Memantine/4410
5. aducanumab.mp./446
6. lecanemab.mp./114
7. Alzheimer disease.mp. or Alzheimer Disease/125290
8. alzheimers.mp./166073
9. 1 or 2 or 3 or 4 or 5 or 6/11885
10. 7 or 8/197593
11. 9 and 10/6469
12. limit 11 to (english language and full text and humans and yr="2021 -Current")/144

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LEQEMBI® (lecanemab-irmb) injection, for intravenous use
Initial U.S. Approval: 2023

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES
See full prescribing information for complete boxed warning.

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. Serious intracerebral hemorrhage greater than 1 cm have occurred in patients treated with this class of medications. (5.1, 6.1)

ApoE ε4 Homozygotes

Patients treated with this class of medications, including LEQEMBI, who are ApoE ε4 homozygotes have a higher incidence of ARIA, including symptomatic and serious ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. (5.1)

Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI. (5.1, 14)

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

Boxed Warning	7/2023
Indications and Usage (1)	7/2023
Dosage and Administration (2.3)	7/2023
Contraindications (4)	7/2023
Warnings and Precautions (5.1, 5.2, 5.3)	7/2023

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

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. (1)

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

- Confirm the presence of amyloid beta pathology prior to initiating treatment. (2.1)
- The recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks. (2.2)
- Obtain a recent baseline brain MRI prior to initiating treatment. (2.3, 5.1)
- Obtain an MRI prior to the 5th, 7th, and 14th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms. (2.3, 5.1)
- Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter. (2.5)

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

Injection:

- 500 mg/5 mL (100 mg/mL) solution in a single-dose vial (3)
- 200 mg/2 mL (100 mg/mL) solution in a single-dose vial (3)

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

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. (4)

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

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated. (2.3, 5.1)
- Infusion-Related Reactions: The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids. (5.2)

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

Most common adverse reactions (at approximately 10% and higher incidence compared to placebo): infusion-related reactions, amyloid related imaging abnormality-microhemorrhages, amyloid related imaging abnormality-edema/effusion, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2023

Appendix 4: Key Inclusion Criteria

Population	Patients with Alzheimer's Dementia
Intervention	Drugs Listed in Appendix 1
Comparator	Drugs listed in Appendix 1 or placebo
Outcomes	Function, symptoms, disease progression, quality of life, morbidity, mortality
Timing	Any duration
Setting	Outpatient

Monoclonal Antibodies for Alzheimer's Disease

Goal(s):
- To support medically appropriate and safe use of Alzheimer Dementia drugs (as designated by the FDA)
- To limit off-label use of Alzheimer's Dementia drugs

Length of Authorization:
- Up to 6 months

Requires PA:
- Pharmacy point-of-sale and physician-administered claims

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

Table 1. Dosing and ARIA Monitoring

Drug	MRI Timing for ARIA Monitoring	IV Infusion every 4 weeks	Dose
Aducanumab	90 days prior to Infusion 1	Infusion 1 and 2	1 mg/kg
	--	Infusion 3 and 4	3 mg/kg
	--	Infusion 5 and 6	6 mg/kg
	28 days prior to Infusion 7	Infusion 7 to 11	10 mg/kg
	28 days prior to Infusion 12	Infusion 12	10 mg/kg
	Annually	After infusion 12	10 mg/kg
Lecanemab	At least 28 days prior to infusion 1 (no longer than 1 year)	Infusion 1, 2, 3, and 4	10 mg/kg
	28 days prior to Infusion 5	Infusion 5 and 6	
	28 days prior to Infusion 7	Infusion 7 to 13	
	28 days prior to infusion 14	Infusion 14 and beyond	

ARIA = amyloid related imaging abnormalities; IV = intravenous; MRI = magnetic resonance imaging

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

Approval Criteria		
2. Is the drug to be used for treatment of a patient diagnosed with Alzheimer's Dementia **AND** has the prescriber ruled out other types of dementia (e.g., vascular dementia, Lewy body, and frontotemporal)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to Renewal Criteria	**No:** Go to #4
4. Is the therapy prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient between 50 and 90 years of age?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there documented evidence that the patient has **mild** cognitive impairment due to Alzheimer's disease or **mild** Alzheimer's dementia as evidenced by the following assessments performed within the last 6 months: • Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1.0 **AND** • Mini-Mental Status Exam (MMSE) score between 22 and 30 (inclusive) **AND** • Positron Emission Tomography (PET) scan positive for elevated amyloid beta plaque or presence of elevated amyloid and/or elevated phosphorylated tau confirmed in cerebrospinal fluid (CSF)?	**Yes:** Go to #7 Document test results and dates. _____	**No:** Pass to RPh. Deny; medical appropriateness There is insufficient evidence for use of this agent in treating moderate or severe AD

Approval Criteria		
7. Has the prescriber assessed and documented baseline disease severity within the last 6 months utilizing an objective measure/tool (e.g. Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version [ADCS-ADL-MCI], Clinical Dementia Rating-Sum of Boxes [CDR-SB], MMSE, or other validated AD monitoring tool)?	**Yes:** Record baseline measurement. _____ Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient received a baseline brain magnetic resonance imaging (MRI) within 90 days prior to initiating treatment with no evidence of pre-treatment localized superficial siderosis or brain hemorrhage?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the prescriber scheduled additional brain MRIs to be obtained as outlined in Table 1 to evaluate for the presence of asymptomatic amyloid related imaging abnormalities [**ARIA-E**]-edema (brain swelling) and/or [**ARIA-H**]-hemorrhage (brain bleeding or protein deposits on brain/spinal cord)?	**Yes:** Record scheduled appointment dates: _____ Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient been screened to ensure they are not currently receiving anticoagulant or antiplatelet therapy (excluding aspirin 81 mg)?	**Yes:** Go to #11.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Is there documentation based on medical records that the prescriber has tested the patient for the presence of apolipoprotein E4 (ApoE4) and, if a carrier, has discussed benefits and risks associated with therapy? Patient who are ApoE4 homozygotes have a higher risk of ARIA, including symptomatic, serious, and severe radiographic ARIA compared to heterozygotes and non-carriers.	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documented evidence that the patient has mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's dementia as evidenced by the following assessments performed within the last 30 days: • Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1.0; **AND** • Objective evidence of cognitive impairment at screening; **AND** • Mini-Mental Status Exam (MMSE) score between 22 and 30 (inclusive)	**Yes:** Go to #2 Document test results and dates: _____	**No:** Pass to RPh. Deny; medical appropriateness
2. Is there documented evidence of follow-up MRIs performed and/or scheduled as recommended in Table 1 for therapy safety surveillance?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documented evidence of amyloid beta reduction compared to baseline confirmed by post-infusion brain imaging or CSF testing?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Was there a serious adverse event (symptomatic moderate to severe ARIA-H or ARIA-E [brain microhemorrhage, superficial siderosis, or edema]) observed or reported with therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Has the patient received at least 6 months of uninterrupted therapy?	**Yes:** Go to #6	**No:** Approve remaining duration of the 6-month titration period
6. Is there documentation that, compared to baseline assessment, therapy has resulted in: • cognitive or functional improvement **OR** • disease stabilization **OR** • reduction in clinical decline compared to the natural disease progression? The same clinical measure used to assess AD (e.g., CDR-GS, MMSE, ADAS-Cog, ADCS-ADL-MCI, etc) is recommended to document clinical benefit.	**Yes:** Approve for up to 6 months Document benefit: _____	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 10/23;10/21 (DE)
Implementation: TBD

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

Drug Class Update: Vesicular Monoamine Transporter 2 Inhibitors

Date of Review: October 2023

Date of Last Review: January 2018
Dates of Literature Search: 11/07/2017 – 06/20/2023

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

Purpose for Class Update:
To review new evidence for the three vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine, deutetrabenazine, and tetrabenazine, approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of adults with tardive dyskinesia (TD) or Huntington's chorea (HC) due to Huntington's Disease (HD). Evaluate evidence for the safety and efficacy for tetrabenazine compendial supported off-label uses in people with TD or Tourette syndrome.

Plain Language Summary:
- This review looks at new evidence published since the last Pharmacy and Therapeutics Committee last reviewed the medicines used to treat tardive dyskinesia and repetitive movement disorders associated with Huntington's disease (also called chorea). Evidence for the use of these medicines for unusual muscle movement disorders such as Tourette syndrome will also be reviewed.
- People with tardive dyskinesia have unusual and uncontrolled muscle movements of the mouth, tongue, body, arms and legs. Examples of these movements are lip smacking, repeated chewing movements of the mouth and jaw, toe and finger tapping, and frequent eye blinking. Medicines used to treat nausea or mental health conditions (for example, bipolar disorder and schizophrenia) are known to cause tardive dyskinesia in some people.
- Two medicines, valbenazine (INGREZZA) and deutetrabenazine (AUSTEDO; AUSTEDO XR), are approved by the Food and Drug Administration to treat tardive dyskinesia. These medicines have been available in the United States since 2017.
- Huntington's Disease causes nerve cells in the brain to break down. This affects the body, mind and emotions. Symptoms include: trouble making decisions, memory lapses, mood swings, trouble sleeping, and fatigue. Huntington's disease is passed on in families, so if parents have the condition, their children will have a 50-50 chance of also having Huntington's disease. Genetic testing helps confirm if someone has Huntington's disease. Huntington's chorea are sudden, uncontrolled movements in the face, arms, and legs in people who have Huntington's disease. These irregular movements can make it difficult to eat, swallow, or speak.
- There are no medicines that help with all the symptoms of Huntington's disease. Two medicines, tetrabenazine (XENAZINE) and deutetrabenazine (AUSTEDO; AUSTEDO XR), are approved by the Food and Drug Administration to help treat Huntington's chorea.
- Tourette syndrome causes people to have tics. Tics are sudden twitches, movements, or sounds that people make repeatedly. Tetrabenazine (XENAZINE) has been used to manage tics associated with Tourette syndrome and tardive dyskinesia. The limited evidence supporting the use of tetrabenazine in these

conditions is based on individual patient reports and poorly conducted studies at risk for error. Studies with better quality looked at deutetrabenazine and valbenazine for helping to lessen tics associated with Tourette syndrome, and these studies did not show benefit from either medicine, but did show an increase in side effects.

- Valbenazine, tetrabenazine and deutetrabenazine can cause dizziness and drowsiness, so people should avoid activities requiring mental alertness such as operating a motor vehicle or hazardous machinery until they know how this drug makes them feel. Deutetrabenazine and tetrabenazine can increase the risk of depression and suicidal thoughts and behavior in people with Huntington disease. Close observation of patients for the emergence or worsening of depression or unusual changes in behavior should accompany the use of these medicines.
- Providers must explain to the Oregon Health Plan (OHP) why someone needs valbenazine, deutetrabenazine or tetrabenazine before the OHP fee-for-service program will pay for it. This process is called prior authorization.

Research Questions:

1. Do the VMAT2 inhibitors, valbenazine, deutetrabenazine, and tetrabenazine, differ in efficacy when use to treat patients with TD or HC?
2. Do the VMAT2 inhibitors differ in adverse events or tolerability when used for the treatment patients with TD or HC?
3. What is the evidence for the safety and efficacy of tetrabenazine in non-FDA approved, compendial indications such as Tourette syndrome or TD?
4. Are there subgroups of patients with TD or HC based on demographic characteristics (i.e., age, gender, race, ethnicity, comorbidities, disease duration or severity) in which one VMAT2 inhibitor may be associated with reduced effectiveness or greater harm than the other VMAT2 inhibitors used to manage these conditions?

Conclusions:

- Two high-quality systematic reviews were identified that evaluated the safety and efficacy of VMAT2 inhibitors in TD[1] or Tourette syndrome[2] since this drug class was last reviewed in January 2018. Three high-quality guidelines for management of TD associated with schizophrenia treatment[3,4] and treatment of HC[5] were identified.
- No head-to-head trials with VMAT2 inhibitors that evaluated comparative safety and efficacy in patients with TD or HC were identified. Therefore, there is insufficient evidence to broadly compare the VMAT2 inhibitors in terms of efficacy and safety in patients with TD or HC, or more specifically in populations based on age, gender, race or ethnicity.
- Evidence for the off-label use of tetrabenazine in managing tics associated with Tourette syndrome is of very low-quality from one retrospective, single-arm, open-label study in a small number of patients (n=17)[6] and another small, retrospective, open-label study (n=77).[7] Two randomized controlled trials (RCTs) evaluated the efficacy of deutetrabenazine in patients with Tourette syndrome; however, neither of these studies met the primary endpoint of change in the Yale Global Tic Severity Scale (YGTSS) from baseline over 8 to 12 weeks (see **Table 4**).[8,9]
- Currently, there are 3 FDA-approved medications to manage Tourette syndrome: pimozide, haloperidol, and aripiprazole; however, extrapyramidal side effects limit their use.[10] The 2019 American Academy of Neurology (AAN) guidance provides recommendations for treatment of tics in people with Tourette syndrome.[11] Due to insufficient evidence, no recommendations were made regarding the use of VMAT2 inhibitors in Tourette syndrome.[11] Recommendations based on moderate- to low-quality evidence were issued regarding the safety and efficacy of 2 alpha-adrenergic agonists (clonidine and guanfacine), antipsychotics, and topiramate in Tourette syndrome.[11]
- A 2018 Cochrane review evaluated evidence for therapies to treat TD.[1] This review found that the use of valbenazine may be effective in relieving the symptoms of TD.[1] One study found moderate-quality evidence of benefit for valbenazine compared with placebo (relative risk [RR] 0.63, 95% confidence interval [CI] 0.46 to 0.86, n=92).[1] However, due to the small sample size of the study, the certainty of these effects is unclear.[1]

- A 2022 meta-analysis evaluated evidence for the efficacy of VMAT2 inhibitors in treating chronic tic disorders including Tourette syndrome.[2] Five short-term RCTs compared valbenazine (n=3) or deutetrabenazine (n=2) with placebo in alleviating chronic tic disorders over 6 to 12 weeks.[2] No RCTs were identified to evaluate the safety and efficacy of tetrabenazine in chronic tic disorders. The change in tic symptom severity, as measured by the YGTSS, was not significantly different between valbenazine or deutetrabenazine and placebo (N = 583; mean difference [MD] = −0.71; 95% confidence interval [CI], −1.93 to 0.50; p=0.24; I^2 = 0%; high-quality evidence).[2] Participants taking valbenazine or deutetrabenazine were more likely to discontinue the study early for any reason than participants taking placebo (N = 626; odds ratio [OR] = 1.90; 95% CI, 1.14 to 3.18; p=0.01; I^2 = 3.2%; low-quality evidence and N = 626; OR = 2.67; 95% CI, 1.21 to 5.92; p=0.01; I^2 = 0%; moderate-quality evidence, respectively).[2]
- The American Psychiatric Association (APA) published updated guidance for schizophrenia treatment in 2020.[3] APA recommends that patients who have moderate to severe or disabling TD associated with antipsychotic therapy be treated with a VMAT2 inhibitor (strong recommendation; moderate-quality evidence).[3] In general, deutetrabenazine or valbenazine is preferred over tetrabenazine because there is more evidence to support their use.[3]
- In 2023 the Department of Veterans Affairs and the Department of Defense (VA/DoD) updated 2021 guidance for management of schizophrenia.[4] The clinical practice guideline was developed after a systematic review of recent evidence.[4] The guideline was revised to include a recommendation that suggests a trial of a VMAT 2 inhibitor for the treatment of tardive dyskinesia for individuals with schizophrenia and tardive dyskinesia (weak recommendation).[4] The Work Group's confidence in the quality of the evidence was low.[4]
- In 2019 the European Huntington's Disease Network (EHDN) commissioned an international task force to provide global evidence-based recommendations for treatment of HD.[5] Tetrabenazine is a first-line treatment for HC unless the patient suffers from poorly managed depression or suicidal thoughts (Grade A: high-quality evidence).[5]
- Valbenazine is appropriate in patients with hepatic dysfunction. Dosing adjustments for patients with moderate to severe hepatic impairment are included in the labeling.[12] In contrast, deutetrabenazine and tetrabenazine are contraindicated in patients with any hepatic impairment.[13,14] Patients who require doses of tetrabenazine greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers or extensive metabolizers by their ability to express the drug metabolizing enzyme, CYP2D6.[14] There is insufficient pediatric data for the use of VMAT2 inhibitors in this population, although tetrabenazine has been used off-label in children with Tourette syndrome.[15]
- A new extended-release formulation of deutetrabenazine (AUSTEDO XR) received FDA approval February 2023.[16] This formulation is taken once daily with or without food, unlike the immediate-release formulation, which must be taken twice daily with food.[16]
- In August 2023, the FDA approved an expanded indication for valbenazine (INGREZZA) to include chorea associated with HD.[12] Approval was based on results from a double-blind, placebo-controlled, phase 3 RCT (KINECT-HD) which evaluated the safety and efficacy of valbenazine in managing HC.[17] The primary endpoint was a least-squares mean (LSM) change in Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMC) score from baseline to week 12.[17] Least-squares mean changes in the UHDRS TMC score over 12 weeks were –4.6 for valbenazine and –1.4 for placebo (LSM mean difference = –3.2, 95% CI –4.4 to –2.0; p<0·0001).[17] The most commonly reported treatment-emergent adverse event was somnolence (ten [16%] with valbenazine, two [3%] with placebo).[17]

Recommendations:

- After review of clinical evidence, no changes are recommended to the Preferred Drug List (PDL).
- Revise prior authorization criteria (PA) to include a trial, contraindication, or hypersensitivity to alpha-adrenergic blockers, antipsychotics or topiramate before approving tetrabenazine to alleviate tics in people with Tourette syndrome and use of valbenazine in patients with HC.
- Review costs in the executive session.

Summary of Prior Reviews and Current Policy:

- The VMAT2 inhibitors were reviewed at the January 2018 Pharmacy and Therapeutics (P & T) committee meeting. Evidence for 2 new VMAT2 inhibitors, valbenazine and deutetrabenazine, which had recently received FDA approval for TD and management of HC, was presented.[18] Recommendations were based on low-quality quality evidence from small, short-term studies primarily funded by industry.[18] Prior to the approval of valbenazine and deutetrabenazine, the only FDA-approved VMAT2 inhibitor was tetrabenazine, which entered the market in 2008 for the use in patients with HC.[14]
- There was insufficient direct comparative evidence between VMAT2 inhibitors for efficacy outcomes in people with TD and HC or for treatment of dyskinesia associated with other conditions in adults (e.g., Parkinson's disease and Tourette syndrome).[18] There was insufficient evidence to evaluate long-term efficacy or safety of VMAT2 inhibitors and long-term data in larger populations were not available to determine the significance of harms observed in the short-term phase 3 trials.[18]
- After review of the evidence, the P & T Committee approved recommendations to create a new PDL class for VMAT2 inhibitors. Prior authorization criteria were implemented for valbenazine, deutetrabenazine, and tetrabenazine to ensure appropriate use (**Appendix 5**). All 3 medications are non-preferred (**Appendix 1**) on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- A comparison of all FDA-approved VMAT2 inhibitors is presented in **Table 1**. In the first quarter of 2023, there was no utilization of valbenazine or deutetrabenazine in the Oregon Health Plan (OHP) Fee-for-Service (FFS) program. One OHP FFS member who had a claim for tetrabenazine.

Table 1. Vesicular Monoamine Transporter 2 Inhibitors

Generic Name (BRAND NAME)	FDA-Approved Indication(s)	Dosing Frequency	Drug Interactions/Dosing Recommendations	Warnings/Precautions
Valbenazine (INGREZZA)[12]	• TD in adults • HC in adults	Once daily with or without food	Concomitant CYP2D6 and CYP3A4 inhibitors: Maximum recommended dose is 40 mg once daily.	• Avoid co-administration with MAOIs and strong CYP3A4 inducers • Avoid use in congenital long QT syndrome or arrhythmias associated with prolonged QT interval
Deutetrabenazine (AUSTEDO, AUSTEDO XR)[13,16]	• TD in adults • HC in adults	IR: Two times daily with food XR: Once daily with or without food	Concomitant CYP2D6 inhibitors: Maximum recommended dose is 36 mg per day.	• Hepatic impairment • Avoid use in congenital long QT syndrome or arrhythmias associated with prolonged QT interval • Avoid co-administration with MAOIs or reserpine • **Black Box Warning:** Depression and suicidality in people with HC
Tetrabenazine (XENAZINE)[14]	• HC in adults **Off-label uses cited in Micromedex: Tardive dyskinesia and Tourette syndrome*	Three times daily with or without food	Concomitant CYP2D6 inhibitors: Maximum recommended dose is 50 mg per day.	• Hepatic impairment • Avoid co-administration with MAOIs or reserpine • Avoid use in congenital long QT syndrome or arrhythmias associated with prolonged QT interval • **Black Box Warning:** Depression and suicidality in people with HC

Abbreviations: FDA = Food and Drug Administration; HD = Huntington's chorea; IR = immediate release; MAOIs = monoamine oxidase inhibitors; TD = Tardive dyskinesia; XR = extended release

Background:

Tardive Dyskinesia

Tardive dyskinesia is a delayed-onset, involuntary movement disorder which occurs in patients treated with dopamine receptor blocking agents (DRBAs), including anti-psychotic drugs (e.g., haloperidol, fluphenazine, risperidone), certain tricyclic antidepressants (e.g., amoxapine, amitriptyline), and some antiemetics (e.g., metoclopramide, prochlorperazine, promethazine).[19] Symptoms of TD include spontaneous, repetitive motions that commonly affect the muscles of the lower face and jaw and occur in an involuntary jerking or writhing fashion; patients may also have difficulty in walking, breathing and using their hands.[20] Tardive dyskinesia is one of many disorders thought to arise from dopamine receptor blockade, but it is distinct from other movement disorders such as Parkinson's disease, Tourette syndrome, and Huntington's chorea.[19] Genetic testing, neuroimaging, and other diagnostic work-ups may be necessary to rule out other causes of dyskinesia.[19] The Diagnostic and Statistical Manual of Mental Disorders definition for DRBA-induced TD requires exposure to a DRBA for at least 3 months (or 1 month in patients ≥ 60 years of age), presentation of symptoms within 4 weeks after withdrawal of an oral medication (or within 8 weeks of a depot medication), and persistence of symptoms for 1 month after discontinuation of offending agent.[21] Sudden withdrawal of a DRBA is suspected of triggering the development of TD, therefore, it is safer to taper the dosage of a DRBA before stopping it.[22]

The yearly rate of TD development in patients treated with DRBAs is approximately 2 to 5% with a 5-year incidence of approximately 20% to 25%.[23] It is estimated that 20 to 50% of patients treated with a DRBA will develop TD.[21] Neuroleptic-induced TD is higher in women, especially those middle-aged and elderly, where incidence rates may reach as much as 30% after 1 year of cumulative exposure.[19] TD may persist for years even after discontinuation of the DRBA, and in many cases, may not be reversible.[24] The debilitating effects of TD lead to increased mortality, decreased physical functioning, medication nonadherence, and a lower quality of life.[24]

Nonmodifiable patient-related and illness-related risk factors for TD include older age, female sex, White or Black race/ethnicity, longer illness duration, intellectual disability and brain damage, negative symptoms in schizophrenia, presence of mood disorders, cognitive symptoms in mood disorders, and genetic polymorphisms involving antipsychotic metabolism.[25] Modifiable comorbidity-related and treatment-related factors include diabetes, smoking, and alcohol and substance abuse, first generation antipsychotic versus second generation antipsychotic treatment, higher cumulative and current antipsychotic dose or antipsychotic plasma levels, early parkinsonian side effects, anticholinergic (e.g. benztropine) co-treatment, akathisia, and emergent dyskinesia.[25] If patients require continued treatment, then every effort should be made to switch to medication with lower risk of TD.[23] In the cases of antipsychotics, switching to clozapine or quetiapine may be considered because they have lower dopamine receptor affinity and relatively low risk of TD.[23] In cases of antiemetics, those without dopamine receptor blocking activity (e.g., ondansetron and trimethobenzamide) should be considered first-line.[23]

Tardive Dyskinesia Treatments: Valbenazine and Deutetrabenazine

Two VMAT2 inhibitors, valbenazine and deutetrabenazine, are FDA-approved treatments for TD.[12,13] The VMAT2 inhibitors interfere with dopamine uptake and storage in presynaptic vesicles, resulting in decreased dopamine available for release in the synapse, which opposes the increased dopaminergic activity caused by prolonged DRBA use.[20] Several characteristics differentiate these 2 medications, including drug interaction potential, dosing in special populations, and frequency of administration. Valbenazine metabolism can be affected by co-administration with strong CYP3A4 inhibitors, CYP3A4 inducers, and CYP2D6 inhibitors.[12] Drug interactions with deutetrabenazine have been identified only when co-administered with CYP2D6 inhibitors.[13] Patients with CYP2D6 genetic polymorphisms may demonstrate alterations in metabolism necessitating dose adjustments for both medications.[12,13] Another difference between these

medications are recommendations for use in hepatic impairment. Valbenazine is appropriate in patients with hepatic dysfunction and dosing adjustments for patients with moderate to severe hepatic impairment are included in the labeling.[12] In contrast, deutetrabenazine is contraindicated in patients with any degree of hepatic impairment.[13] Electrocardiogram (ECG) monitoring is recommended for both agents in patients at risk for QT prolongation (i.e. congenital long QT syndrome or history of cardiac arrhythmias).[12,13] Finally, valbenazine is dosed once daily versus immediate-release deutetrabenazine, which is dosed twice daily.[12,13] A new, extended-release formulation of deutetrabenazine (AUSTEDO XR) received FDA approval February 2023.[16] This formulation is taken once daily with or without food, unlike the immediate-release formulation, which must be taken twice daily with food.[16]

Assessment of Tardive Dyskinesia

The assessment of TD is challenging due to the variability in research criteria and different rating scales.[26] An accepted standard has been the 12-item Abnormal Involuntary Movement Scale (AIMS), developed by the U.S. National Institute of Mental Health.[27] The current standard in research is for the AIMS to be used by remote video raters who are experts in movement disorders.[28] The first 7 items of the AIMS rate dyskinetic movements in 7 different muscle groups or body areas using a 5-point scale (0 = none, 1 = minimal/extreme normal, 2 = mild, 3 = moderate, 4 = severe), with a total score ranging from 0 to 28.[27] Four of the items measure facial, lip, jaw, and tongue movements, one item is assigned to the upper extremities, one item is assigned to the lower extremities, and one item is assigned to the trunk.[27] The last 5 items assess the patient's awareness of their abnormal movements, functional impact, and severity of symptoms (global impression) and dental health status.[27] Higher scores indicate increased severity of TD symptoms.[27] The AIMS evaluation is suggested at least every 6 months for people taking antipsychotics.[29] However, there is not a well-established guideline for interpretation of AIMS scores, and there is criticism that it lacks sensitivity due to its limited range and non-specificity for movement frequency.[29] There is no minimal clinically effective difference (MCID) established and evidence has not demonstrated that improvement in the AIMs score translates into improved function or quality of life for patients with TD.[29] However, the first 7 items of the AIMS assessment were used as the primary outcome measure for the VMAT2 inhibitors approved by the FDA for the management of TD.[28] A 2-point decrease in AIMs severity score maybe considered clinically important, based on data analysis of the pivotal phase 3 RCTs that led to FDA approval of valbenazine and deutetrabenazine.[30,31]

Huntington's Disease

Huntington's Disease is a rare, incurable, inherited neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric dysfunction.[32,33] Symptoms of HD usually appear in middle-aged adults. The average duration of survival after clinical onset of symptoms ranges from 10 to 20 years.[33] One of the most recognized motor signs is chorea, characterized by unwanted muscle contractions that progress over time and interfere with activities of daily living.[34] Huntington's disease results from a gene abnormality of an exon 1 CAG (cytosine-adenine-guanine) amino acid sequence trinucleotide expansion in the huntingtin (HTT) gene on chromosome 4.[32] The mutant huntingtin accumulates within brain cells, causing cell toxicity and neuron dysfunction throughout the brain as the disease progresses.[34] Early stages of HD are often characterized by deficiencies in voluntary motor function while mid-stages are associated with more of an impact on motor coordination and function.[32] Optimization of quality of life is the focus of HD treatment through symptom management since there is no cure or treatment to slow progression for this disease.[32] The estimated incidence of HD is 3 to 7 per 100,000 people in western European populations.[35] This condition is less common in Japan, China, Finland and Africa.[35] In the OHP population (FFS and Coordinated Care Organizations), 148 people had claims for Huntington's disease from October 2021 to November 2022.

Management of Huntington's Chorea: Tetrabenazine and Deutetrabenazine

Tetrabenazine received FDA approval in 2008 for use in treating symptoms of chorea associated with HD and has been used off-label for severe TD; however, mixed efficacy and numerous safety concerns have limited its widespread use.[11] The use of tetrabenazine is limited by variable CYP2D6 metabolism which often results in dosing 3 times a day.[36] Tolerability is also an issue with tetrabenazine due to adverse effects such as sedation, fatigue, akathisia, anxiety and nausea.[36]

In the pivotal phase 3 trial of tetrabenazine in patients with HC, the tetrabenazine group experienced more adverse effects compared to the placebo group, with 90% of patients reporting a TEAE compared to 70% in the placebo group.[37] Tetrabenazine labeling has a black box warning due to risk of suicide and depression associated with its use in patients with HD.[14] Prior to the approval of deutetrabenazine in 2017, the only treatment approved for chorea symptoms associated with HD was tetrabenazine. Deutetrabenazine is an isomer of tetrabenazine. The substitution of deuterium for hydrogen in the tetrabenazine molecule produces a longer drug half-life, less frequent daily dosing, and reduced metabolism variability of deutetrabenazine. Deutetrabenazine labeling also has a black box warning due to risk of suicide and depression associated with its use in patients with HD.[13] There are no head to head trials of tetrabenazine and deutetrabenazine to evaluate comparative safety and efficacy in patients with HC.

Symptom Assessment of Huntington's Disease

The severity of HC and functional impact is measured by the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and is the main endpoint used in many trials.[38] The UHDRS-TMS motor scale uses 106 questions to measure chorea, Parkinsonism, dystonia, eye movements, and other signs of HD.[39] There are 31 items that are graded 0 (not affected) to 4 (most severely affected).[39] There is limited evidence that a 1-point increase in the UHDRS-TMS, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children.[39] In studies of patients with a diagnosis of HD, the mean annual change in patients UHDRS-TMS was 3.8 points.[39] The American Academy of Neurology (AAN) guidelines define the change in subscores of less than 1-point decrease in UHDRS as unimportant, 1 to less than 2-point decrease as modestly important, 2 to less than 3-point decrease as moderately important and more than a 3-point decrease as very important.[39]

The UHDRS total chorea score (UHDRS-TCS) is a subscore which rates facial, bucco-oral-lingual, trunk and extremity chorea. Standardized assessment of chorea based on the UHDRS-TCS subscore is determined by frequency and severity of chorea in 7 areas of the body by a scale of 0 to 28, with a higher number indicating worse disease.[39] This subscoring portion represents 23% of the overall UHDRS-TMS and is recommended for determining the impact of chorea symptoms over using the UHDRS-TMS.[38] The clinically important change for this endpoint has not been determined.[40]

Symptom Assessment Used for Both Tardive Dyskinesia and Huntington's disease

The patient's global impression of change (PGIC) is used to determine the patient's perspective on overall improvement in movement dysfunction.[41] This is a 1 to 7-point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".[41] The clinical global impression of change (CGIC) is a clinician perspective of the severity of the patient's symptoms utilizing the same scale as the PGIC.[41] Limitations to the CGIC is the reliance on provider recall of patient symptoms.[41] The CGI-TD score is used to rate the overall change in tardive dyskinesia symptoms on a scale from 1 ("very much improved") to 7 ("very much worse").[41] The 36-question short form (SF-36) quality of life assessment is also used with a higher score indicating an improved quality of life. A summary of outcome assessments for TD and HD are presented in **Appendix 3**.

Symptom Assessment of Tic Severity: Yale Global Tic Severity Scale

The YGTSS is a clinician-rated scale that measures tic severity and is commonly used as a primary outcome measure in RCTs.[42] The motor and phonic (i.e., coughing, throat clearing, grunting, blowing, squeaking) tics are rated separately on a 0 (none) to 5 (severe) scale across 5 dimensions: number, frequency, intensity, complexity, and interference.[42] The scores from each dimension (number, frequency, intensity, complexity, and interference) are summed to produce the Total Motor Tic score (range 0–25), the Total Phonic Tic score (range 0–25), and the combined Total Tic score (range 0–50).[42] The scale also includes a separate Impairment scale that reflects overall tic-related impairment (range 0–50).[42] Higher scores indicate more severe tics.[43] In 2021, a study evaluated 706 children and adolescents with Tourette syndrome to study the reliability of the YGTSS, and found that the YGTSS correlates well with the Clinical Global Impression Scale for tics.[44] The YGTSS may be insensitive to clinically meaningful tic reduction in patients with frequent severe symptoms while fluctuating

excessively in response to small changes in the symptoms of those with mild phonic tics.[2] Tic severity is only captured during the past 7 days and tic-related impairment is not incorporated into the Total Tic Score and requires separate assessment.[2] Despite these limitations, the YGTSS remains the gold standard for assessing tics and has reliably demonstrated the efficacy of other pharmacological agents typically used in the treatment of TS, including FDA-approved medications.[2]

Off-label Uses for Tetrabenazine: Tardive Dyskinesia and Tourette Syndrome

Tardive Dyskinesia

Tetrabenazine is only FDA-approved for management of HC, but it has been used off-label to manage TD.[14],[15] Low-quality evidence from a limited number of patients enrolled in 2 single-arm, open-label trials suggests that tetrabenazine may decrease the frequency and severity of movements in adults with TD.[45,46] The first study, published in 1999, included 20 patients with refractory TD and assessed AIMS as an outcome measure.[45] In addition to TD, 45% of patients also showed mild evidence of parkinsonism, and 25% had akathisia at baseline.[45] Participants in this study were diagnosed with a psychiatric disorder or symptoms (unspecified psychosis, schizophrenia, bipolar disorder, agitation), gastrointestinal disorder, or organic brain disorder.[45] Use of the DRBA was stopped in all cases. Cessation of antipsychotic medications is often not practical in patients with chronic psychotic disorders due to the risk of relapse, and it may have confounded treatment results due to unmasking or worsening of existing TD.[45] The mean dose of tetrabenazine was 60 mg daily with a mean treatment duration of 20 weeks.[45] TD severity was assessed by a single-blinded investigator who rated videos using the standardized AIMS, both at baseline and at approximately 3 months after starting treatment.[45] Improvement on the motor section of the AIMS was demonstrated at the end of treatment versus baseline values ($p < 0.001$) and no patient had unchanged or worsened TD.[45] Eleven patients rated themselves as markedly improved, 6 as moderately improved, and 2 as mildly improved.[45] The most common adverse events were sedation and parkinsonism observed in 25% of patients enrolled in the study.[45]

The second study was a 1988 publication of case series that included 23 patients with TD who were treated with tetrabenazine.[46] The mean total dose of tetrabenazine was 91 mg daily; however, duration of therapy was not reported.[45] Severity of involuntary movements was evaluated in three regions (face/mouth/tongue, trunk, limbs) using a 5-point involuntary movement scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) and video recordings were made for each patient before and during treatment.[46] At baseline, 83% of patients has a severity score of 3 or 4 (moderate/severe).[46] After treatment with tetrabenazine 87% of patients noted improved involuntary movement scores of 1 or 2 (none/minimal).[46] Side effects were minimal and the most common events were drooling (9%) and parkinsonism with tremor (4%).[46]

Tourette Syndrome

The primary clinical features of Tourette syndrome are tics, which vary in their severity.[43] Tics are involuntary or semi-involuntary, sudden, brief, intermittent, repetitive movements (motor) or sounds (phonic) and often stereotypical.[43] Behavioral therapy is considered first-line therapy for Tourette syndrome.[43] Currently, there are 3 FDA-approved medications to manage this condition: pimozide, haloperidol and aripiprazole; however, extrapyramidal side effects limit their use.[10] Tetrabenazine has been studied in several low-quality studies as an alternative to conventional neuroleptics because it does not cause tardive dyskinesia. In a retrospective, open-label, single-arm study, of 217 patients with movement disorders, 17 adults with Tourette syndrome received tetrabenazine at a dose of 81 mg daily (range 37.5 to 100 mg).[6] All of these patients had responded poorly to prior treatment with haloperidol or developed therapy-limiting adverse effects.[6] Tetrabenazine showed moderate reduction in abnormal movements in 4 patients (6%) and fair response in 11 patients (65%).[6] The most frequently reported adverse events in all patients (n=217) were parkinsonism, depression and anxiety, but were not classified by type of movement disorder. In

another retrospective, open-label study, 77 patients with Tourette syndrome (75.3% male), and a median age of 14 years, were treated with tetrabenazine for an average of 2 years.[7] The median dose of tetrabenazine was 50 mg daily (range: 6 to 125 mg).[7] Tetrabenazine showed a moderate to marked improvement in Tourette syndrome-related symptoms and functional improvement in 83% of patients.[7] Adverse events included drowsiness or fatigue (36%), nausea (10%), depression (9%), insomnia (8%), and parkinsonism (6.5%).[7] No RCTs have evaluated the safety and efficacy of tetrabenazine in Tourette syndrome. Two RCTs have been published which evaluate the efficacy of deutetrabenazine in patients with Tourette syndrome (see **Table 4**).[8,9] Neither of these studies met the primary endpoint of change in the YGTSS total tic severity score from baseline over 8 to 12 weeks.[8,9]

In 2019 the American Academy of Neurology (AAN) published practice guidance for treatment of tics in people with Tourett syndrome and chronic tic disorders.[11] Due to insufficient evidence, no recommendations were issued with respect to the use of VMAT2 inhibitors in managing tics associated with Tourette's syndrome. However, recommendations for the safety and efficacy of alpha-adrenergic agonists (clonidine and guanfacine), antipsychotics and topiramate were provided in the guidance.[11] The recommendations and supporting evidence are summarized below.

- *Physicians should prescribe alpha-adrenergic agonists for the treatment of tics when the benefits of treatment outweigh the risks (Level B recommendation).*[11]
  People with tics receiving clonidine are probably more likely than those receiving placebo to have reduced tic severity, and people with tics receiving guanfacine are possibly more likely than those receiving placebo to have reduced tic severity, with the majority of trials conducted in children.[11] In children with tics and comorbid attention-deficient/hyperactivity disorder (ADHD), clonidine and guanfacine have demonstrated beneficial effects on both tics and ADHD symptoms.[11] The effect size of clonidine and guanfacine on tics appears larger in children with tics and ADHD compared with individuals with tics without a comorbid diagnosis of ADHD.[11] Relative to placebo, clonidine is probably associated with higher rates of sedation, and guanfacine is probably associated with higher rates of drowsiness.[11]

- *Physicians may prescribe antipsychotics for the treatment of tics when the benefits of treatment outweigh the risks (Level C recommendation).*[11]
  Haloperidol, risperidone, and aripiprazole are probably more likely than placebo to reduce tic severity, and pimozide, ziprasidone, and metoclopramide are possibly more likely than placebo to reduce tic severity.[11] There is insufficient evidence to determine the relative efficacy of these drugs.[11] Relative to placebo, the evidence demonstrates a higher risk of drug-induced movement disorders with haloperidol, pimozide, and risperidone, a higher risk of weight gain with risperidone and aripiprazole, a higher risk of somnolence with risperidone, aripiprazole, and tiapride, a higher risk of QT prolongation with pimozide, and a higher risk of elevated prolactin with haloperidol, pimozide, and metoclopramide.[11] Systematic reviews of trials and cohort studies demonstrate a higher risk of drug-induced movement disorders (including tardive dyskinesa, drug-induced parkinsonism, akathisia, acute dystonia, and tardive dystonia), weight gain, adverse metabolic side effects, prolactin increase, and QT prolongation with both first- and second-generation antipsychotics across psychiatric and neurologic conditions.[11] The long-term use of metoclopramide is associated with tardive dyskinesia, resulting in a black box warning from the FDA.[11]

- *Physicians should prescribe topiramate for the treatment of tics when the benefits of treatment outweigh the risks (Level B recommendation).*[11]
  Topiramate is possibly more likely than placebo to reduce tic severity.[11] In patients with mild but troublesome tics who are not obtaining a satisfactory response or experience adverse effects from other treatments, topiramate may be a useful alternative. While generally well-tolerated at low doses (25–150 mg/day) it may cause adverse effects, including cognitive and language problems, somnolence, and weight loss, and may increase the risk of renal stones.[11]

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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.
The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Cochrane: Miscellaneous Treatments for Antipsychotic-Induced Tardive Dyskinesia
A 2018 Cochrane review updated previously published Cochrane reports with new evidence for therapies to treat TD.[1] Literature was searched through April 2017 for the efficacy of the many different types of medications used to treat TD; only one VAMT-2 inhibitor, valbenazine was included in the literature search.[1] Thirty-one RCTs of 24 interventions with 1278 participants met inclusion criteria; 22 of these trials provided new evidence for the 2018 update.[1] All participants were adults with chronic psychiatric disorders, (mostly schizophrenia) and antipsychotic-induced TD.[1] Studies were primarily of short duration (3 to 6 weeks) with small sample sizes (10 to 157 participants), and most studies (61%) were published prior to the year 2000.[1] Studies published after the year 2000 assessed melatonin, valbenazine, levetiracetam, and ginkgo biloba.[1] The Cochrane authors reported the overall risk of bias in these studies was unclear, mainly due to poor reporting of allocation concealment, generation of the sequence, and blinding.[1]

One study found moderate-quality evidence of a benefit for valbenazine in TD compared with placebo (RR 0.63, 95% CI 0.46 to 0.86, 1 RCT, n=92).[1] However, due to the small sample size, additional data from ongoing trials are needed to confirm these results.[1] Results for the remaining therapeutic interventions provided insufficient data due to low- to very low-quality of evidence in small studies.[1]

Efficacy and Tolerability of VMAT2 Inhibitors in the Treatment of Tic Disorders
A 2022 meta-analysis evaluated evidence for the efficacy of VMAT2 inhibitors in treating chronic tic disorders including Tourette syndrome.[2] Studies were included in the meta-analysis if they reported on a double-blinded RCT of VMAT2 inhibitors (valbenazine, deutetrabenazine, tetrabenazine) against placebo for the acute treatment (up to 12 weeks) of tic disorders in patients with Tourette syndrome as determined by formal diagnostic criteria.[2] No restrictions were made regarding age (children/adolescents or adults) or dosing design (fixed-dose or flexible-dose studies).[2] Literature was searched through October 2021 and 5 double blinded RCTs involving 8 comparisons of VMAT2 inhibitors against placebo met inclusion criteria.[2] The primary efficacy outcomes assessed change from baseline in tic symptom severity scores on the YGTSS.[2] Other outcomes in the systematic review included acceptability as measured by total study withdrawal and tolerability as measured by the number of study withdrawals due to adverse effects.[2]

Only one RCT was conducted in adults (age range, 18 to 64 years).[2] This study involved 124 participants with a mean age of 35 years. Of these, 80 were men (67%), and 107 self-identified as White (89%).[2] The study tested fixed doses of valbenazine against placebo for 8 weeks.[2] This study was rated at high risk of bias (RoB).[2] The other 4 RCTs were conducted in children/adolescents (age range, 6–17 years).[2] These pediatric studies involved 502 participants with a mean age of 11.9 years (2.6 year standard deviation); 81% (n=398) were male, and 87% (n=426) identified as White.[2] Two studies tested valbenazine and 2 studies evaluated deutetrabenazine against placebo in both fixed-dose and flexible-dose designs—one study of each dosing design for each of the two medications—for a median

duration of 10 weeks (range, 6–12 weeks).[2] Three of the 4 trials were rated as low RoB and the other one as high RoB.[2] Only 2 RCTs were published. Data for the other 3 RCTs was obtained from clinicaltrials.gov. No RCTs were identified that evaluated the safety and efficacy of tetrabenazine in Tourette syndrome.

Change in tic symptom severity, as measured by the YGTSS, did not differ between valbenazine or deutetrabenazine and placebo (n = 583; 5 RCTs; MD = −0.71; 95% CI, −1.93 to 0.50; p=0.24; I^2 = 0%; high-quality evidence).[2] Subgroup testing did not identify differences between children/adolescents and adults (p = 0.37) nor between valbenazine and deutetrabenazine (p = 0.42).[2] Participants taking valbenazine and deutetrabenazine were more likely to dropout than those on placebo (n = 626; OR = 1.90; 95% CI, 1.14 to 3.18; p=0.01; I^2 = 3.2%; low-quality evidence).[2] Participants taking VMAT2 inhibitors were more likely to drop out as a result of adverse effects than those on placebo (N = 626; OR = 2.67; 95% CI, 1.21 to 5.92; p=0.01; I^2 = 0%; moderate-quality evidence).[2] This analysis suggests that valbenazine and deutetrabenazine are not associated with a clinically meaningful effect in the treatment of Tourette syndrome.[2] This study also demonstrates increased total dropout rates with valbenazine or deutetrabenazine versus placebo.[2] However, this effect was largely driven by considerably higher dropout rates in valbenazine comparisons, which was administered at 80 mg daily in a fixed-dose regimen or adopted flexible titration up to 80 mg daily.[2] In addition, the safety analyses were limited due to relatively small number of events across all 5 trials.[2] This meta-analysis only evaluates up to 12 weeks of VMAT2 inhibitor treatment, so long-term efficacy and safety data are needed.[2]

After review, 6 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).[47-52]

New Guidelines:

High Quality Guidelines:

Tardive Dyskinesia

The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia

The APA published updated guidance for schizophrenia treatment in 2020.[3] The guidance was supported by an AHRQ systematic review published in 2017.[53] Most of the guideline is centered on pharmacotherapy and psychosocial interventions to manage schizophrenia. Management of adverse effects associated with antipsychotic medications is discussed in depth. APA recommends that patients who have moderate to severe or disabling TD associated with antipsychotic therapy be treated with a VMAT2 inhibitor (strong recommendation; moderate-quality evidence).[3] The guideline authors concluded that the available studies of valbenazine and deutetrabenazine are of good quality with good sample sizes.[3] However, the duration of the trials was relatively short, as little as 4–6 weeks in some studies. The long-term follow-up data are based only on open-label extension phases of these RCTs. Data on tetrabenazine have a higher RoB, smaller samples sizes, and inadequate blinding, yielding a low strength of research evidence.[3]

In general, deutetrabenazine or valbenazine are preferred over tetrabenazine because of the greater evidence-base supporting their use.[3] In addition, tetrabenazine has a shorter half-life and greater rates of associated depression when used in the treatment of patients with Huntington's disease. In initial studies of tetrabenazine in patients with Huntington's disease, significant rates of depression were noted as well as concerns about suicidal ideas and behaviors. However, in studies of deutetrabenazine and valbenazine in patients with TD, there were no apparent increases in depression or suicidal ideation either in the randomized portions of the clinical trials or in longer open-label extension periods.[3] However, depression or suicidal ideation could occur during treatment for TD, and clinicians will want to be alert to this possibility.[3] The harms of treatment with VMAT2 inhibitors include sedation associated with deutetrabenazine and valbenazine; and extrapyramidal effects, akathisia, insomnia, anxiety, nausea, and falls with associated with tetrabenazine.[3]

Department of Veterans Affairs and the Department of Defense: Management Schizophrenia

In 2023 the VA/DoD updated 2021 guidance for management of schizophrenia.[4] The clinical practice guideline was developed after a systematic review of recent evidence.[4] The guideline was revised to include a recommendation that suggests a trial of a VMAT 2 inhibitor for the treatment of tardive dyskinesia for individuals with schizophrenia and tardive dyskinesia (weak recommendation).[4] The Work Group's confidence in the quality of the evidence was low.[4] The body of evidence had some limitations, including a small sample size, risk of bias, and study imprecision and indirectness.[4] The benefits of improving AIMS scores in individuals with schizophrenia or schizoaffective disorder and TD outweighed the potential harms, which were minimal.[4] Patient values and preferences were similar because most patients who have distressing TD would likely want treatment with an agent that is generally well tolerated.[4]

Huntington's Disease

European Huntington's Disease Network Guidelines for the Treatment of Huntington's Disease

In 2019, the EHDN commissioned an international task force to provide global evidence-based recommendations for treatment of HD.[5] Drug treatment should be considered if chorea causes the patient distress or discomfort.[5] Monotherapy to treat chorea is preferred because combination therapy (tetrabenazine with a neuroleptic) increases the risk of adverse effects and may complicate the management of non-motor symptoms.[5] Two recommendations are included in the guidance for management of HC.

- Tetrabenazine is a first-line treatment for HC unless the patient suffers from poorly managed depression or suicidal ideation (Grade A recommendation: high-quality evidence).[5]
- Second generation neuroleptics (e.g., olanzapine, risperidone, pimozide, and aripiprazole) are first-line treatments for chorea when patients have associated personality and/or behavioral or psychotic disorders (Grade C recommendation: low-quality evidence).[5]

After review, 4 guidelines were excluded due to poor quality.[54-57]

New Formulations or Indications:

- The manufacturer of valbenazine (INGREZZA) added a 60 mg capsule to the available dosing formulations of valbenazine in April 2021.[12] This was added to the other 2 strengths: 40 mg and 80 mg. Depending on response and tolerability, a dose of 40 mg or 60 mg once daily may be considered in some patients.[12] In patients with moderate or severe hepatic impairment or known CYP2D6 poor metabolizers, the maximum recommended dose is 40 mg per day.[12]
- A new extended-release formulation of deutetrabenazine (AUSTEDO XR) received FDA approval February 2023.[16] This formulation is taken once daily with or without food, unlike the immediate-release formulation, which must be taken twice daily with food.[16] The extended-release tablets are available in 3 strengths: 6 mg, 12 mg, and 24 mg.[16] The approval for the extended-release formulation was based on clinical trials with the immediate-release tablets of deutetrabenazine.[16]
- In August 2023, the FDA approved an expanded indication for valbenazine (INGREZZA) to include chorea associated with HD.[12] A total of 125 adults with genetically confirmed HD were enrolled in a double-blind, placebo-controlled, phase 3 RCT (KINECT-HD) to evaluate the safety and efficacy of valbenazine in managing HC.[17] The primary endpoint was a least-squares mean (LSM) change in UHDRS-TMC score from baseline to week 12.[17] Least-squares mean changes in the UHDRS TMC score over 12 weeks were –4.6 for valbenazine and –1.4 for placebo (LSM mean difference = –3.2, 95% CI –4.4 to –2.0; p<0·0001).[17] The most commonly reported treatment-emergent adverse event was somnolence (ten [16%] with valbenazine, two [3%] with placebo).[17] No clinically important changes in vital signs, electrocardiograms, or laboratory tests were found.[17] No suicidal behaviour or worsening of suicidal ideation was reported in participants treated with valbenazine.[17]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Valbenazine	INGREZZA	7/2019	Warnings and Precautions	Parkinsonism: Cases of Parkinson-like symptoms, some of which were severe, have been reported in the post marketing period. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant Parkinson-like signs or symptoms.[12]

Randomized Controlled Trials:

A total of 24 citations were manually reviewed from the initial literature search. After further review, 22 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. The Full abstracts are included in **Appendix 2**.

Table 4. Description of Randomized Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Jankovic J., et al.[9] ARTISTS 1 Phase 2/3 DB, MC, PC, PG, RCT	1. Deutetrabenazine immediate release 3 mg PO BID titrated over 7 weeks up to 48 mg per day per weight-based dosing protocol and assessment of CYP2D6 impairment (n=59). Maintenance phase lasted 5 weeks. vs. 2. Placebo PO BID (n=60).	- Ages 6 to 16 yo - TS - Weight ≥20 kg - YGTSS-TTS score ≥ 20 points	Change in the YGTSS-TTS score from baseline to week 12	LSM change in YGTSS-TTS score at 12 weeks 1. -9.1 2. -8.4 Difference: -0.7 95% CI -4.1 to 2.8 P=0.69	-Medical history was comparable between the deutetrabenazine and placebo groups, except for the proportion of patients with psychiatric disorders (81% vs 67%), including ADHD (63% vs 52%). -Method of titrating matching placebo doses to maintain blinding not described. - Trial duration may have been too short to identify changes in tic severity associated with TS, as drug was titrated upward over 7 weeks with a 5-week maintenance period at the final dose.
Coffey, B., et al[8] ARTISTS 2 Phase 3, DB, MC, PC, PG, RCT	1. Low dose: Deutetrabenazine immediate release 36 mg/day titrated over 4 weeks to the target dose followed by a 4-week maintenance phase (n=54). vs. 2. High dose: Deutetrabenazine 48 mg/day titrated over 4 weeks to the	-Ages 6 to 16 yo -TS - Weight >20 kg -YGTSS-TTS score ≥ 20 points	Primary: Change in the YGTSS-TTS score from baseline to week 8 for high-dose deutetrabenazine compared with placebo	Primary: LSM change in YGTSS-TTS score at 8 weeks for high-dose deutetrabenazine 1. -7.8 3. -7.0 Difference: -0.8 95% CI -3.9 to 2.3 P=0.60	-Prior TS treatment was more common in the deutetrabenazine high-dose group (83%) and low-dose group (83%) than the placebo group (63%). -Trial duration may have been too short to identify changes in tic severity associated with TS.

	target dose followed by a 4-week maintenance phase (n=52). vs. 3. Matching placebo titrated according to protocol (n=52).		Secondary: Change in the YGTSS-TTS score from baseline to week 8 for low-dose deutetrabenazine compared with placebo	Secondary: LSM change in YGTSS-TTS score at 8 weeks for low-dose deutetrabenazine 2. -5.9 3. -7.0 Difference: 1.1 95% CI -1.9 to 4.2 P=0.47	-Majority of participants were non-Hispanic, White children, which limits generalizability to more diverse populations.
Abbreviations: BID = twice daily; CI = Confidence Interval; DB = double blind; LSM = least squares mean; MC = multi-center; PC = placebo controlled; PG = parallel group; PO = orally; RCT = randomized controlled trial; TEAEs = treatment emergent adverse events; TD = tardive dyskinesia; TS = Tourette syndrome; YGTSS-TTS = Yale Global Tic Severity Scale-Total Tic Score; yo = years old					

References:

1. Soares-Weiser K, Rathbone J, Ogawa Y, Shinohara K, Bergman H. Miscellaneous treatments for antipsychotic-induced tardive dyskinesia. *Cochrane Database Syst Rev.* 2018;3:CD000208.
2. Behling E, Farhat LC, Landeros-Weisenberger A, Bloch MH. Meta-Analysis: Efficacy and Tolerability of Vesicular Monoamine Transporter Type 2 Inhibitors in the Treatment of Tic Disorders. *Mov Disord.* 2022;37(4):684-693.
3. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. 2020. https://psychiatryonline.org/doi/epdf/10.1176/appi.books.9780890424841. Accessed July 27, 2023. In.
4. VA/DoD Clinical Practice Guideline. (2023). Management of First-Episode Psychosis and Schizophrenia Work Group. Washington, DC: U.S. Government Printing Office. https://www.healthquality.va.gov/guidelines/MH/scz/VADoDCPGSchizophreniaCPG_Final_508.pdf. Accessed August 9, 2023.
5. Bachoud-Lévi AC, Ferreira J, Massart R, et al. International Guidelines for the Treatment of Huntington's Disease. *Front Neurol.* 2019;10:710.
6. Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. *Neurology.* 1988;38(3):391-394.
7. Kenney CJ, Hunter CB, Mejia NI, Jankovic J. Tetrabenazine in the treatment of Tourette syndrome. *Journal of Pediatric Neurology.* 2007;5(1):9-13.
8. Coffey B, Jankovic J, Claassen DO, et al. Efficacy and Safety of Fixed-Dose Deutetrabenazine in Children and Adolescents for Tics Associated With Tourette Syndrome: A Randomized Clinical Trial. *JAMA network open.* 2021;4(10):e2129397.
9. Jankovic J, Coffey B, Claassen DO, et al. Safety and Efficacy of Flexible-Dose Deutetrabenazine in Children and Adolescents With Tourette Syndrome: A Randomized Clinical Trial. *JAMA network open.* 2021;4(10):e2128204.
10. Jankovic J. Treatment of tics associated with Tourette syndrome. *J Neural Transm (Vienna).* 2020;127(5):843-850.
11. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology.* 2019;92(19):896-906.
12. INGREZZA (valbenazine) oral capsules. Prescribing Information. Neurocrine Biosciences, Inc. San Diego, CA. Augst 2023.
13. AUSTEDO (deutetrabenazine) oral tablets. Prescribing Information. Teva Neuroscience, Inc.; Parsippany, NJ. May 2022.
14. XENAZINE (tetrabenazine) oral tablets. Prescribing Information. Lundbeck; Deerfield, IL. September 2017.

15. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed July 19, 2023.
16. AUSTEDO XR (deutetrabenazine extended-release) oral tablets. Prescribing Information. Teva Neuroscience, Inc.; Parsippany, NJ. February 2023.
17. Furr Stimming E, Claassen DO, Kayson E, et al. Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled trial. *The Lancet Neurology.* 2023;22(6):494-504.
18. Engen DE, Sentena K. Class Review with New Drug Evaluation: Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors. January 2018. https://www.orpdl.org/durm/meetings/meetingdocs/2018_01_25/archives/2018_01_25_VMAT2Inhibitors_ClassReview.pdf Accessed June 6, 2023.
19. Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor Other Hyperkinet Mov (N Y).* 2013;3.
20. Takeuchi H, Mori Y, Tsutsumi Y. Pathophysiology, prognosis and treatment of tardive dyskinesia. *Ther Adv Psychopharmacol.* 2022;12:20451253221117313.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.
22. Frei K, Truong DD, Fahn S, Jankovic J, Hauser RA. The nosology of tardive syndromes. *Journal of the Neurological Sciences.* 2018;389:10-16.
23. Bashir HH, Jankovic J. Treatment of Tardive Dyskinesia. *Neurol Clin.* 2020;38(2):379-396.
24. Cornett EM, Novitch M, Kaye AD, Kata V, Kaye AM. Medication-Induced Tardive Dyskinesia: A Review and Update. *Ochsner J.* 2017;17(2):162-174.
25. Solmi M, Pigato G, Kane JM, Correll CU. Clinical risk factors for the development of tardive dyskinesia. *J Neurol Sci.* 2018;389:21-27.
26. Gharabawi GM, Bossie CA, Lasser RA, Turkoz I, Rodriguez S, Chouinard G. Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia. *Schizophrenia research.* 2005;77(2-3):119-128.
27. Guy W. *ECDEU assessment manual for psychopharmacology.* US Department of Health, Education, and Welfare, Public Health Service …; 1976.
28. Citrome L. Tardive dyskinesia: placing vesicular monoamine transporter type 2 (VMAT2) inhibitors into clinical perspective. *Expert review of neurotherapeutics.* 2018;18(4):323-332.
29. Bergman H, Walker DM, Nikolakopoulou A, Soares-Weiser K, Adams CE. Systematic review of interventions for treating or preventing antipsychotic-induced tardive dyskinesia. *Health Technol Assess.* 2017;21(43):1-218.
30. Stacy M, Sajatovic M, Kane JM, et al. Abnormal involuntary movement scale in tardive dyskinesia: Minimal clinically important difference. *Mov Disord.* 2019;34(8):1203-1209.
31. Hauser RA, Barkay H, Wilhelm A, Wieman M, Savola JM, Gordon MF. Minimal clinically important change in Abnormal Involuntary Movement Scale score in tardive dyskinesia as assessed in pivotal trials of deutetrabenazine. *Parkinsonism & Related Disorders.* 2022;97:47-51.
32. Stoker TB, Mason SL, Greenland JC, Holden ST, Santini H, Barker RA. Huntington's disease: diagnosis and management. *Practical Neurology.* 2022;22(1):32-41.
33. Walker FO. Huntington's disease. *Lancet (London, England).* 2007;369(9557):218-228.

34. Coppen EM, Roos RA. Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease. *Drugs.* 2017;77(1):29-46.
35. Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. *Mov Disord.* 2012;27(9):1083-1091.
36. Khorassani F, Luther K, Talreja O. Valbenazine and deutetrabenazine: Vesicular monoamine transporter 2 inhibitors for tardive dyskinesia. *Am J Health-Syst Pharm.* 2020;77(3):167-174.
37. Group HS. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology.* 2006;66(3):366-372.
38. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. *Handb Clin Neurol.* 2017;144:209-225.
39. Armstrong MJ, Miyasaki JM. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology.* 2012;79(6):597-603.
40. Gibson JS, Claassen DO. State-of-the-art pharmacological approaches to reduce chorea in Huntington's disease. *Expert Opin Pharmacother.* 2021;22(8):1015-1024.
41. Institute for Clinical and Economic Review. Vesicular monoamine transporter 2 inhibitors for tardive dyskinesia: effectiveness and value. New England Comparative Effectiveness Public Advisory Council. November 21, 2017. http://icerorg.wpengine.com/wp-content/uploads/2020/10/NECEPAC_TD_FINAL_REPORT_122217.pdf Accessed May 22, 2023.
42. McGuire JF, Piacentini J, Storch EA, et al. A multicenter examination and strategic revisions of the Yale Global Tic Severity Scale. *Neurology.* 2018;90(19):e1711-e1719.
43. Chou CY, Agin-Liebes J, Kuo SH. Emerging therapies and recent advances for Tourette syndrome. *Heliyon.* 2023;9(1):e12874.
44. Haas M, Jakubovski E, Fremer C, et al. Yale Global Tic Severity Scale (YGTSS): Psychometric Quality of the Gold Standard for Tic Assessment Based on the Large-Scale EMTICS Study. *Front Psychiatry.* 2021;12:626459.
45. Ondo WG, Hanna PA, Jankovic J. Tetrabenazine treatment for tardive dyskinesia: assessment by randomized videotape protocol. *Am J Psychiatry.* 1999;156(8):1279-1281.
46. Watson MW, Skelton D, Jamali F. Treatment of tardive dyskinesia: preliminary report on use of tetrabenazine. *Can J Psychiatry.* 1988;33(1):11-13.
47. Caroff SN, Aggarwal S, Yonan C. Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic review. *Journal of Comparative Effectiveness Research.* 2018;7(2):135-148.
48. Solmi M, Pigato G, Kane JM, Correll CU. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug design, development & therapy.* 2018;12:1215-1238.
49. Aggarwal S, Serbin M, Yonan C. Indirect treatment comparison of valbenazine and deutetrabenazine efficacy and safety in tardive dyskinesia. *Journal of Comparative Effectiveness Research.* 2019;8(13):1077-1088.
50. Artukoglu BB, Li F, Szejko N, Bloch MH. Pharmacologic Treatment of Tardive Dyskinesia: A Meta-Analysis and Systematic Review. *J Clin Psychiatry.* 2020;81(4).
51. Citrome L. Deutetrabenazine for tardive dyskinesia: A systematic review of the efficacy and safety profile for this newly approved novel medication-What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract.* 2017;71(11).
52. Citrome L. Valbenazine for tardive dyskinesia: A systematic review of the efficacy and safety profile for this newly approved novel medication-What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract.* 2017;71(7).
53. McDonagh MS, Dana T, Selph S, Devine EB, Cantor A, Bougatsos C, Blazina I, Grusing S, Fu R, Kopelovich SL, Monroe-DeVita M, Haupt DW. Treatments for Schizophrenia in Adults: A Systematic Review. Comparative Effectiveness Review No. 198. (Prepared by the Pacific

Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 17(18)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality; October 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI: https://doi.org/10.23970/AHRQEPCCER198.
54. Caroff SN, Citrome L, Meyer J, et al. A Modified Delphi Consensus Study of the Screening, Diagnosis, and Treatment of Tardive Dyskinesia. *Journal of Clinical Psychiatry.* 2020;81(2):28.
55. Ricciardi L, Pringsheim T, Barnes TRE, et al. Treatment Recommendations for Tardive Dyskinesia. *Can J Psychiatry.* 2019;64(6):388-399.
56. Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;81(5):463-469.
57. Ferreira JJ, Rodrigues FB, Duarte GS, et al. An MDS Evidence-Based Review on Treatments for Huntington's Disease. *Mov Disord.* 2022;37(1):25-35.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
deutetrabenazine	AUSTEDO 12MG START TITR(WK1-4)	ORAL	TAB DS PK	N
deutetrabenazine	AUSTEDO TD TITRATN PK (WK 1-2)	ORAL	TAB DS PK	N
deutetrabenazine	AUSTEDO XR	ORAL	TAB ER 24H	N
deutetrabenazine	AUSTEDO	ORAL	TABLET	N
tetrabenazine	TETRABENAZINE	ORAL	TABLET	N
tetrabenazine	XENAZINE	ORAL	TABLET	N
valbenazine tosylate	INGREZZA INITIATION PACK	ORAL	CAP DS PK	N
valbenazine tosylate	INGREZZA	ORAL	CAPSULE	N

Appendix 2: Abstracts of Comparative Clinical Trials

Safety and Efficacy of Flexible-Dose Deutetrabenazine in Children and Adolescents With Tourette Syndrome: A Randomized Clinical Trial[9]

Objective: To examine whether deutetrabenazine is effective and safe for the treatment of Tourette syndrome in children and adolescents.

Design, setting, and participants: This phase 2/3, randomized, double-masked, placebo-controlled, parallel-group, dose-titration study included children and adolescents (aged 6-16 years) with Tourette syndrome with active tics causing distress or impairment (i.e., Yale Global Tic Severity Scale-Total Tic Score [YGTSS-TTS] ≥20). The trial was conducted over 12 weeks, with 1 week of follow-up from February 2018 to November 2019 at 36 centers in the United States, Canada, Denmark, Russia, Serbia, and Spain. Data analysis was conducted from January 31 to April 22, 2020.

Intervention: Patients were randomized (1:1) to receive deutetrabenazine or placebo, titrated during 7 weeks to an optimal level, followed by a 5-week maintenance period. The maximum total daily deutetrabenazine dose was 48 mg/d.

Main outcomes and measures: The primary efficacy end point was change from baseline to week 12 in YGTSS-TTS. Key secondary end points included changes in Tourette Syndrome-Clinical Global Impression, Tourette Syndrome-Patient Global Impression of Impact, and Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Activities of Daily Living subscale score. Safety was assessed based on treatment-emergent adverse events, vital signs, questionnaires, and laboratory parameters.

Results: A total of 119 participants were randomized to deutetrabenazine (59 participants; mean [SD] age, 11.5 [2.5] years; 53 [90%] boys; 49 [83%] White; 3 [5%] Black) and placebo (60 participants; mean [SD] age, 11.5 [2.6] years; 51 [85%] boys; 53 [88%] White; 3 [5%] Black). At week 12, the difference in YGTSS-TTS score was not significant between deutetrabenazine and placebo (least squares mean difference, -0.7; 95% CI, -4.1 to 2.8; P = .69; Cohen d, -0.07). There were no nominally significant differences between groups for key secondary end points. Treatment-emergent adverse events were reported for 38 patients (66%) and 33 patients (56%) receiving deutetrabenazine and placebo, respectively, and were generally mild or moderate.
Conclusions and relevance: In this study of deutetrabenazine in children and adolescents with Tourette syndrome, the primary efficacy end point was not met. No new safety signals were identified. These results may be informative for future studies of treatments for tics in Tourette syndrome.
Trial registration: ClinicalTrials.gov Identifier: NCT03452943.

Efficacy and Safety of Fixed-Dose Deutetrabenazine in Children and Adolescents for Tics Associated With Tourette Syndrome: A Randomized Clinical Trial.[8]
Importance: Tourette syndrome is a neurodevelopmental disorder characterized by childhood onset of motor and phonic tics, often accompanied by behavioral and psychiatric comorbidities. Deutetrabenazine is a vesicular monoamine transporter 2 inhibitor approved in the US for the treatment of chorea associated with Huntington disease and tardive dyskinesia.
Objective: To report results of the ARTISTS 2 (Alternatives for Reducing Tics in Tourette Syndrome 2) study examining deutetrabenazine for treatment of Tourette syndrome.
Design, setting, and participants: This phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study was conducted over 8 weeks with a 1-week follow-up (June 21, 2018, to December 9, 2019). Children and adolescents aged 6 to 16 years with a diagnosis of Tourette syndrome and active tics causing distress or impairment were enrolled in the study. Children were recruited from 52 sites in 10 countries. Data were analyzed from February 4 to April 22, 2020.
Interventions: Participants were randomized (1:1:1) to low-dose deutetrabenazine (up to 36 mg/d), high-dose deutetrabenazine (up to 48 mg/d), or a matching placebo, which were titrated over 4 weeks to the target dose followed by a 4-week maintenance period.
Main outcomes and measures: The primary efficacy end point was change from baseline to week 8 in the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) for high-dose deutetrabenazine. Key secondary end points included changes in YGTSS-TTS for low-dose deutetrabenazine, Tourette Syndrome Clinical Global Impression score, Tourette Syndrome Patient Global Impression of Impact score, and Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Activities of Daily Living subscale score. Safety assessments included incidence of treatment-emergent adverse events, laboratory parameters, vital signs, and questionnaires.
Results: The study included 158 children and adolescents (mean [SD] age, 11.7 [2.6] years). A total of 119 participants (75%) were boys; 7 (4%), Asian; 1 (1%), Black; 32 (20%), Hispanic; 4 (3%), Native American; 135 (85%), White; 2 (1%), multiracial; 9 (6%), other race; and 1 (0.6%), of unknown ethnic origin. Fifty-two participants were randomized to the high-dose deutetrabenazine group, 54 to the low-dose deutetrabenazine group, and 52 to the placebo group. Baseline characteristics for participants were similar between groups. Of the total 158 participants, 64 (41%) were aged 6 to 11 years, and 94 (59%) were aged 12 to 16 years at baseline. Mean time since Tourette syndrome diagnosis was 3.3 (2.8) years, and mean baseline YGTSS-TTS was 33.8 (6.6) points. At week 8, the difference in YGTSS-TTS was not significant between the high-dose deutetrabenazine and placebo groups (least-squares mean difference, -0.8 points; 95% CI, -3.9 to 2.3 points; P = .60; Cohen d, -0.11). There were no nominally significant differences between groups for key secondary end points. Treatment-emergent adverse events were reported for 34 participants (65%) treated with high-dose deutetrabenazine, 24 (44%) treated with low-dose deutetrabenazine, and 25 (49%) treated with placebo and were generally mild or moderate.
Conclusions and relevance: In this fixed-dose randomized clinical trial of deutetrabenazine in children and adolescents with Tourette syndrome, the primary efficacy end point was not met. No new safety signals were identified.

Trial registration: ClinicalTrials.gov Identifier: NCT03571256.

Appendix 3: Tardive Dyskinesia and Huntington's Disease Assessments

Table 1. Outcome Assessment Measurements for Tardive Dyskinesia and Chorea Symptoms[18]

Outcome	Description	Minimal Clinically Significant Change	Clinical Relevance
Tardive Dyskinesia			
Abnormal Involuntary Movement Scale **(AIMS)**	Validated 12-item scale with a total score ranging from 0-28 in the first 7 items. Higher scores indicate increased severity of TD symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from zero (no abnormalities) to four (severe movements).	Not defined	Interpretation of scores has not been well-established and may lack sensitivity due to limited range and non-specificity for movement frequency.
Huntington's disease			
Unified Huntington's disease Rating Scale Total Motor Score **(UHDRS-TMS)**	Scoring ranges from 0-106 points with higher scores indicating greater disability.	Not defined	Limited evidence suggests a 1-point increase, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children.
Unified Huntington's disease Rating Scale– total chorea movement subscore **(UHDRS-TCS)**	Subscore is based on frequency and severity of chorea in 7 areas of the body on a scale of 0-28, with a higher number indicating worse disease.	Not defined	Most studies show a difference of 2-4 points which represents a 7-14% change.
Tardive Dyskinesia and Huntington's Disease			
Patients' Global Impression of Change (**PGIC)** score	PGIC measures patient's perspective on overall improvement in movement dysfunction. This is a 1–7-point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Patient's perception of symptom improvement is critical in justifying use of therapy.
Clinical Global Impression of Change **(CGIC)**	CGIC is a clinician perspective of the severity of the patient's symptoms using a 1–7-point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Limitations of this assessment tool is reliance on provider recall to determine symptom improvement.
Clinical Global Impression – Tardive Dyskinesia **(CGI-TD)**	CGI-TD is a modified version of the CGIC utilizing the same Likert scale with a focus on tardive dyskinesia symptoms.	Not defined	Limitations of this assessment tool is reliance on provider recall to determine symptom improvement.
Abbreviations: HD = Huntington's disease; TD = tardive dyskinesia			

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to June Week 2 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to June 19, 2023

1	Tardive Dyskinesia/ or Dyskinesia, Drug-Induced/	4157
2	Chorea/ or Huntington Disease/	12178
3	exp Tourette Syndrome/	3241
4	exp Tetrabenazine/	624
5	valbenazine.mp.	104
6	Vesicular Monoamine Transport Proteins/ or deutetrabenazine.mp.	1241
7	1 or 2 or 3	19427
8	4 or 5 or 6	1567
9	7 and 8	250
10	limit 9 to (english language and humans and yr="2018 -Current")	122
11	limit 10 to (clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	24

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Goal(s):
- Promote safe use of VMAT2 inhibitors in adult patients.
- Promote use that is consistent with medical evidence.

Length of Authorization:
- Initial: Up to 2 months
- Renewal: Up to 12 months

Requires PA:
- All VMAT2 inhibitors

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the request for continuation of vesicular monoamine transporter 2 (VMAT2) inhibitor therapy previously approved by FFS criteria (patient has completed ~~2~~3-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the medication being prescribed by, or in consultation with, a neurologist or psychiatrist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for ~~tetrabenazine or tetrabenazine in~~ a patient 18 years or older with a diagnosis of chorea as a result of Huntington's disease?	**Yes:** Go to #5	**No:** Go to #7

Approval Criteria		
5. Does the patient have a baseline total maximal chorea score of 8 or higher as assessed by the Unified Huntington's disease Rating Scale–Total Chorea Movement subscore **(**UHDRS-TCS**)**?	**Yes:** Go to #~~6~~5 Document baseline score: _____	**No:** Pass to RPh. Deny; medical appropriateness
6. Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?	**Yes:** Approve for ~~2~~ 3 months.	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for deutetrabenazine or valbenazine in a patient 18 years or older with a diagnosis of moderate to severe tardive dyskinesia?	**Yes:** Approve for ~~2~~ 3 months. Document baseline modified AIMS* score: _____	**No:** Go to #8
8. Is the request for tetrabenazine in a patient with tics associated with Tourette syndrome?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient tried and failed an adequate trial of at least **2** of the following guideline directed medications[1]: a. Clonidine or guanfacine OR b. Topiramate OR c. One of the following antipsychotics: pimozide, aripiprazole or risperadone? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the guideline directed medications?	**Yes:** Approve for ~~2~~3 months Document baseline Yale Global Tic Severity Score (YGTSS) Total Tic Severity (range 0 to 50)_____	**No:** Pass to RPh. Deny; medical appropriateness
~~9.~~10. ~~Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?~~	~~**Yes:** Go to #15~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

Approval Criteria		
~~10.~~11. ~~Is the request for valbenazine in a patient 18 and older with a diagnosis of moderate to severe tardive dyskinesia?~~	~~**Yes:** Go to #14~~ ~~Document baseline modified AIMS* score: _____~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~10.Has the patient recently been evaluated and determined to not be at risk for a prolonged QT interval?~~	~~**Yes:** Approve for 2 months.~~ ~~Documented evidence of benefit required for renewal consideration (see renewal criteria).~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

* The dyskinesia score for the modified Abnormal Involuntary Movement Scale (AIMS) for numbers 1-7

1. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology.* 2019;92(19):896-906.

Renewal Criteria		
1. Is the request for a renewal of valbenazine or deutetrabenazine in a patient with tardive dyskinesia?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement by a reduction in AIMS dyskinesia score (items 1-7) by at least 50%?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for valbenazine, tetrabenazine or deutetrabenazine in a patient with chorea as a result of Huntington's disease?	**Yes:** Go to #4	**No**: Go to #6

Renewal Criteria		
4. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement in total maximal chorea score as assessed by the Unified Huntington's disease Rating Scale–Total Chorea Movement subscore **(**UHDRS-TCS**),** of at least 2 points from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has it been determined that the mental status of the patient is stable and there is no indication of uncontrolled depression or risk of violent or suicidal behavior?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for tetrabenazine in a patient with tics associated with Tourette syndrome?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient been taking tetrabenazine for >2 months and has there been documented evidence of reduced tic severity from baseline as assessed by the Yale Global Tic Severity Score (YGTSS) Total Tic Score (range 0-50) ?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 10/23 (DM); 1/2018(KS)
Implementation: TBD ; 3/1/18

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Drug Use Evaluation: Asthma Rescue Inhalers

Plain Language Summary:

- Clinical practice guidelines for the treatment of asthma have changed in the past few years. Inhaled medicines called short-acting beta agonists (SABA) alone are no longer recommended for most patients with asthma, and may actually make asthma control worse when used without other asthma medicines. An example of a short-acting beta agonist is albuterol.
- The purpose of this evaluation is to assess if short-acting beta agonist use has changed to match recommendations in the current clinical guidelines, and if overall use of short-acting beta agonist inhalers is appropriate in fee-for-service/open card Medicaid members.
- We found that many patients with asthma who are using short-acting beta agonists are not receiving additional medications for asthma. Most patients should be taking a medicine called an inhaled corticosteroid, such as budesonide. An inhaled corticosteroid paired with a different beta agonist (formoterol) decreases severe asthma attacks compared to only using short-acting beta agonist inhalers. Many patients have filled prescriptions for so many short-acting beta agonist inhalers that they may be at higher risk of bad health outcomes. These include hospitalization and death. Most of the patients who received a short-acting beta agonist inhalers did not have asthma or chronic obstructive pulmonary disease (COPD) in medical records. It is unclear if this is due to inaccurate medical records or other medical uses of this type of medicine.
- DURM recommends putting in place a quantity limit for short-acting beta agonist inhalers to prevent potentially harmful overuse in patients.
- DURM recommends notifying medical prescribers of asthma patients who appear to be receiving short-acting beta agonist inhalers when other therapy might be more beneficial. Other types of inhalers, which match current guideline recommendations are available to fee-for-service/open card Medicaid members.

Research Questions:

- What proportion of Fee-For-Service (FFS) members with claims for a SABA rescue inhaler also have claims for controller inhaler therapy?
- How many FFS members have multiple claims for SABA inhalers indicating potential overuse (overuse is defined as daily use of ≥3 canisters [200 count] in a year with extremely high use as 12 or more canisters in a year)?
- Do FFS members with SABA claims, indicating overuse or monotherapy, have more adverse outcomes (e.g., hospitalizations, emergency department visits, or asthma exacerbations) than those using SABA with controller medications and without excessive use of a controller?
- Are there subgroups of FFS members based on demographics (e.g., age, diagnoses, or symptom severity) who are more likely to overuse SABA in their asthma treatment regimen?

Conclusions:

- There were 459 patients with an asthma diagnosis identified as having a SABA claim. Controller therapy of some kind was identified in 41.4% (N=190) of those patients (**Table 3**).
- Potential SABA overuse was identified in 208 (45%) of the 459 patients with diagnosed asthma. Extremely high use was identified in 78 patients (17%) carrying an asthma diagnosis (**Table 2)**.
- Oral corticosteroid use appeared highest for members with claims for more than 5 inhalers (28.7%; N=62). The rate of emergency room visits was also highest in those with more than 5 inhalers compared to the other subgroups **(Table 5)**. Hospitalization rates were similar among subgroups, while deaths were almost twice as common in members receiving 2 to 5 inhalers (2.2%, N=17) or more than 5 inhalers (2.3%; N=5) compared to all members with SABA prescriptions (1.5%; N=28) and SABA monotherapy (1.2%; N=16). Given high rate of non-asthma diagnoses and differences in number of inhalers seen in subgroups with and without asthma or COPD, the outcome groups compared in **Table 5** are likely fundamentally different patient populations.
- The most common asthma subtype in patients with SABA claims was "unknown or unspecified" (47.9%, 220 of 459). Most patients identified were female assigned at birth (64.9%) and of Native American or Alaskan native (HNA) ancestry (48.7%). The HNA population is highly represented in fee-for-service/open card Medicaid compared to the general Medicaid population.
- Patients with neither a diagnosis of asthma or COPD represented most of the population identified as having a SABA claim (70.2%, 1311 of 1867). These patients were most likely to only have claims for 1 (52.6%, N=689) or 2 (20.8%, N=273) inhalers in the 6 month follow up period (**Table 2 and 6**), though 242 patients (18.5%) had claims for 3-5 inhalers and 107 patients (8.2%) had claims for 6 or more inhalers. A post-hoc analysis revealed many of these patients had cough (13.6%, N=178), nicotine dependence (12.7%, N=167), and abnormalities of breathing (11.6%, N=152). They likely received SABA for acute infections such as upper respiratory tract infections, viral illnesses, acute pharyngitis (**Table 6**).

Recommendations:

- Implement one-time targeted provider fax notification requesting SABA therapy reassessment for specific patients identified in this DUE:
    - All patients without either asthma or COPD diagnosis with more than 2 SABA inhalers in 6 months.
    - All patients with asthma who are 6 years or older identified as having SABA monotherapy.
    - All patients with mild persistent asthma, moderate persistent asthma, or severe persistent asthma with any SABA claim regardless of concomitant controller therapy.
    - All patients with asthma and claims for 2 or more SABA inhalers in 6 months regardless of concomitant controller therapy.
- Implement targeted ongoing RetroDUR with provider fax notification when 3 SABA inhalers are filled within 6 months. Exclude patients with COPD diagnosis.
- Consider implementation of quantity limit for more than 6 SABA claims in 6 months. Exclude patients with a COPD diagnosis.

Background

Asthma is a heterogenous, non-communicable disease, typically characterized by chronic airway inflammation. Typical respiratory symptoms include wheezing, shortness of breath, chest tightness, and cough.[1] Patients with this disease exhibit variable expiratory airflow limitation, which may become persistent.[2] Asthma severity varies is typically treated with inhaled beta-agonists and different strengths of inhaled corticosteroids (ICS).[1] Other therapies for asthma include oral leukotriene receptor antagonists (LTRA), inhaled muscarinic agents, and injectable biologic agents, which are reserved for patients with more severe and difficult to control asthma.[1] Oral corticosteroids are used in exacerbations and can be considered in those presenting with severe uncontrolled asthma.[1] Treatment regimens involve "reliever" therapy for immediate symptoms and "controller" therapy to prevent exacerbations and control symptoms.[1] Treatments progress

along a stepwise algorithm based on frequency and severity of symptoms.[1] The Global Initiative for Asthma (GINA) algorithms differ slightly between age groups.[1]

In 2019, GINA changed recommendations regarding use of inhaled SABA as evidence shows that patients treated with SABA-monotherapy had an increased risk of severe exacerbations and that ICS significantly reduces the risk.[2,3] Higher use of SABA (ie., Daily use or ≥3 canisters [200 count] in a year) is associated with higher risk for severe exacerbations while 12 or more canisters in a year is associated with much higher risk of death).[1] Guidelines for COPD differ.[4]

Step 1 treatment for adults and adolescents (12 years and older) recommend ICS containing controller treatment. These recommendations were clarified in 2021.[1,2] Current recommendations are for Track 1 (preferred) use of ICS-formoterol as the reliever medication.[1] Formoterol is a long-acting beta agonist (LABA) with rapid onset. Track 2 (alternative) recommendations include a SABA reliever with use of an ICS anytime SABA is taken either as a combination inhaler or separate inhalers (Step 1) or low dose maintenance ICS (Step 2).[1]

Treatment recommendations for children (6 to 11 years) differs as there is one track and Step 1 includes low-dose ICS as a controller, taken when SABA reliever is taken, with an alternative for daily lose dose ICS. Step 2 involves daily low dose ICS as the controller, though a low dose ICS taken when SABA reliever taken or a daily LTRA are alternatives as controllers. Children 5 years and younger in Step 1 are the only age group where SABA reliever without a separate controller are recommended. Daily ICS (preferred) or daily LTRA (alternative) or short courses of ICS (alternative) are the controller therapies for Step 2 in this age group.

Based on this guidance, SABA use without ICS is only preferred in ages 5 years and younger in Step 1.[1] Certain patients 5 years and younger and 6 to 11 years in Step 2 using daily LTRA as an alternative controller therapy may have SABA reliever use without ICS.[1] Those patients aged 12 years and older should preferentially receive ICS-formoterol rather than a SABA with separate ICS or SABA-ICS combination product, but all patients in this age range should have some form of ICS controller in these steps.[1]

Inhalers with SABA, ICS, LABA and their combinations are categorized in several different preferred drug list (PDL) classes. The LABA and ICS single agent classes have a prior authorization (PA) for non-preferred agents to ensure appropriate combination use with other single-agent inhalers. Combination LAMA-ICS. Inhalers only have preferred and non-preferred status. There are preferred options of SABA (albuterol) in inhaler and nebulizer form, salmeterol xinafoate (SEREVENT DISKUS), and multiple single agent ICS. Multiple LABA-ICS combinations are preferred, including two different ICS-formoterol options. Gross costs for SABA and ICS classes were approximately $110,000 in the first quarter of 2023. Combination LABA-ICS costs were $200,000 during the same time period while single agent LABA use was minimal compared to the other two. Drugs in these classes can additionally be used in patients with COPD.

Methods:

Oregon Health Plan (OHP) members were identified for inclusion based on paid FFS claims for a SABA inhaler (**Appendix 2, Table C, Inhaler formulations**). The evaluation window for SABA was from 7/1/21 to 6/30/22. The index event (IE) was defined as the first paid FFS claim for a SABA in the evaluation window. Demographics were evaluated at the time of the IE.

The following timeframes were used to evaluate outcomes and determine inclusion of members in the study:

- Baseline period: 6 months before the IE (exclusive of the IE)
- Follow-up period: 6 months after the IE (inclusive of the IE)

Members were categorized into groups by:

- Diagnoses present in medical claims in the 6 month baseline period. Diagnoses of interest included asthma and COPD (defined in **Appendix 2, Table J**).
- Presence or absence of an asthma controller medication in the 8 weeks before or after the IE. Asthma controller therapy is defined based on drugs in **Appendix 2 (Tables B, D, E, F, G, and I)**.

Inclusion Criteria:

1. At least one point-of-sale (POS) FFS paid claim for SABA inhaler during the evaluation window

Exclusion Criteria:

1. Individuals with benefit packages listed below. Certain benefit packages have limited or no drug benefits, and claims 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

2. Non-continuous Medicaid eligibility during the baseline period
3. Non-continuous FFS eligibility during the follow-up period
4. Members with third-party liability during the baseline or follow-up period

Outcomes evaluated in this analysis included:

- Emergency department visit, hospitalization, or prescription for oral corticosteroid in the follow-up period (6 months). Codes for oral corticosteroids are defined in **Appendix 2, table H**.
- Number of SABA inhalers dispensed in the 6 month follow-up period, where inhalers are defined based on package size for a given NDC. Each HFA inhaler contains 200 doses. According to GINA 2023 SABA use of 3 or more 200 dose canisters in a year, corresponding to average use more than daily (1.6 doses/day) and increases risk of asthma exacerbations, and 12 or more canisters in a year increases risk of death. Since this study evaluated a shorter follow up period, we defined overuse as more than 2 inhalers over 6 months.
- Proportion of members with prescribed asthma controller therapy in the 8 weeks before or after the IE (inclusive of the IE). The total 16 week period was chosen to identify and include any members who were filling maintenance controller medication for a 90 day supply.
- Subgroups based on diagnoses or asthma severity were analyzed to determine if these outcomes varied by group. For patients with medical claims denoting more than one different asthma severities, members were categorized based on the more severe diagnosis and most specific diagnosis. For example, members with diagnoses of both mild intermittent and mild persistent asthma would be categorized as mild persistent. Members with diagnoses of both moderate persistent and other/unspecified asthma would be categorized as moderate persistent.
- Post-hoc assessment of most common medical diagnoses likely associated with SABA claim.

Results:

Table 1 describes characteristics for patients prescribed SABA inhalers. Most patients were adult females assigned at birth of American Indian/Alaskan Native descent. Nearly 20% were children, and 3% were 5 years of age or younger. Asthma diagnosis was recorded in 24.6% of patients, while 75.4% of patients had no recorded diagnosis of asthma and only 5.2% of that group carried a COPD diagnosis.

Table 1: Demographics Data of FFS members with Short-Acting Beta-Agonist Pharmacy Claims

	1,867	%
Age groups based on GINA guidelines		
5 years and younger	56	3.0%
6 to 11 years	110	5.9%
12 to 17 years	206	11.0%
18 years and older	1,495	80.1%
Sex		
Female	1,211	64.9%
Male	656	35.1%
Race		
White	436	23.4%
American Indian/Alaskan Native (HNA)	909	48.7%
Hispanic	96	5.1%
Black	23	1.2%
Unknown	398	21.3%
Other	5	0.3%
Asthma Type		
Asthma	459	24.6%
Mild intermittent asthma	94	5.0%
Mild persistent asthma	41	2.2%
Moderate persistent asthma	87	4.7%
Severe persistent asthma	17	0.9%
Other and unspecified asthma	220	11.8%
No Asthma diagnosis	1,408	75.4%
COPD	97	5.2%

A total of 1,867 patients had at least 1 SABA claim in the follow-up period, 459 of these had a diagnosis of asthma and 125 a diagnosis of COPD (N=28 both asthma+COPD). Nearly half of patients with a SABA claim received only a single inhaler claim during the six month follow-up period. This varied by diagnosis and those with COPD were the most likely subgroup to fill claims for four or more inhalers and 24% received more than six SABA inhalers. Over half of patients with asthma filled 2 or more SABA inhalers in the 6 month time period, indicating possible daily use, while 17.0% (N=78) of patients with asthma filled 6 or more SABA inhalers in 6 months. Patients with neither asthma or COPD were most likely to only have a single SABA inhaler claim.

Table 2: Number of SABA inhalers filled by individual members in a 6 month follow-up period

	All members with a SABA claim		Asthma Diagnosis		COPD Diagnosis		Neither Diagnosis	
	1,867	%	459	%	125	%	1,311	%
Number of inhalers								
1	877	47.0%	164	35.7%	27	21.6%	689	52.6%
2	373	20.0%	87	19.0%	18	14.4%	273	20.8%
3	200	10.7%	63	13.7%	15	12.0%	125	9.5%
4	124	6.6%	40	8.7%	14	11.2%	73	5.6%
5	77	4.1%	27	5.9%	9	7.2%	44	3.4%
6	79	4.2%	31	6.8%	12	9.6%	40	3.1%
>6	137	7.3%	47	10.2%	30	24.0%	67	5.1%

Table 3 describes patients with SABA claims by diagnosis and concomitant medication therapy. SABA monotherapy was identified in 58.6% (N=269) of patients with asthma, 44% of patients with COPD (N=55), and 79.3% (N=1039) of patients without asthma or COPD.

Table 3: Concomitant Controller Drugs by Indication

	All members with a SABA claim		Asthma Diagnosis		COPD Diagnosis		Neither Diagnosis	
	1,867	%	459	%	125	%	1,311	%
SABA only (monotherapy)	1,353	72.5%	269	58.6%	55	44.0%	1,039	79.3%
SABA + controller	514	27.5%	190	41.4%	70	56.0%	272	20.7%
SABA + Leukotriene only	56	3.0%	18	3.9%	3	2.4%	36	2.7%
SABA + ICS/ICS combo product +/- additional controllers	452	24.2%	169	36.8%	63	50.4%	236	18.0%
SABA + anything else	110	5.9%	49	10.7%	22	17.6%	48	3.7%

Pediatric and adolescent patients with SABA claims were more likely to only have 1-2 inhalers in 6 months compared to more than 2 inhalers. Adults made up the vast majority of patients with more than 2 inhaler claims (88.7%; N=547) compared to younger ages, and patients with comorbid COPD were also more likely to have more than 2 inhalers (13.0%; N=80) compared to 1-2 inhalers (3.6%; N=45). Those with an asthma diagnosis were most commonly classified as "other or unspecified asthma" (N=220) compared to other specific asthma severities. Most patients with severe persistent and moderate persistent asthma were more likely to have more than 2 inhaler claims compared to 1-2 inhaler claims (2.6%, N=16 vs. 0.1%, N=1 for severe; 8.8%, N=54 vs. 2.6%, N=33 for moderate). There were 51 children 5 years and younger with SABA monotherapy, and 8 of those children had greater than 2 inhalers. Similarly, 78 children 6 to 11 years had SABA monotherapy and 10 of those children received greater than 2 inhalers. Most people with SABA monotherapy were 12 years or older and 339 of them received more than 2 inhalers in the 6 month follow up period.

Table 4: Short-Acting Beta-Agonist Overuse by Subgroup

	Patients by count of SABA Inhalers in 6 month follow-up period			
	1-2 Inhalers		>2 Inhalers	
	1,250	%	617	%
Age groups based on GINA guidelines				
5 years and younger	47	3.8%	9	1.5%
6 to 11 years	91	7.3%	19	3.1%
12 to 17 years	164	13.1%	42	6.8%
18 years and older	948	75.8%	547	88.7%
Asthma Severity				
Mild intermittent asthma	61	4.9%	33	5.3%
Mild persistent asthma	22	1.8%	19	3.1%
Moderate persistent asthma	33	2.6%	54	8.8%
Severe persistent asthma	1	0.1%	16	2.6%
Other and unspecified asthma	134	10.7%	86	13.9%
Comorbid COPD	45	3.6%	80	13.0%
SABA Monotherapy				
5 years and younger	43	3.4%	8	1.3%
6 to 11 years	68	5.4%	10	1.6%
12 years and older	885	70.8%	339	54.9%

Oral corticosteroid use appeared highest for members with claims for 2 to 5 inhalers (19.3%; N=149) and more than 5 inhalers (28.7%; N=62). The rate of emergency room visits was also highest in those with more than 5 inhalers compared to the other subgroups **(Table 5)**. Hospitalization rates were similar among subgroups, while deaths were almost twice as common in members receiving 2 to 5 inhalers (2.2%, N=17) or more than 5 inhalers (2.3%; N=5) compared to all members with SABA prescriptions (1.5%; N=28) and SABA monotherapy (1.2%; N=16).

Table 5: Short-Acting Beta-Agonist Overuse and Adverse Events in the follow-up period

	ALL members with SABA Rx		**Members with SABA monotherapy**		**Members with SABA claims indicating 2-5 inhalers in 6 months**		**Members with SABA claims indicating >5 inhalers in 6 months**	
	1,867	%	1,353	%	774	%	216	%
Members with claims for oral corticosteroids	343	18.4%	221	16.3%	149	19.3%	62	28.7%
Members with emergency room visits	604	32.4%	439	32.4%	257	33.2%	82	38.0%
Members with hospitalizations	115	6.2%	79	5.8%	54	7.0%	15	6.9%
Death	28	1.5%	16	1.2%	17	2.2%	5	2.3%

Table 6 represents a post-hoc analysis of the 1311 (70.2%) patients with SABA claims but without a diagnosis of asthma or COPD. Patients may have more than one or zero of the ICD 10 codes of interest. These patients were most likely to only have claims for 1 (52.6%, N=689) or 2 (20.8%, N=273) inhalers in the 6 month follow up period, though 242 patients (18.5%) had claims for 3-5 inhalers and 107 patients (8.2%) had claims for 6 or more inhalers. Cough (13.6%, N=178), nicotine dependence (12.7%, N=167), and abnormalities of breathing (11.6%, N=152) were these most common diagnoses listed in these patients. Various types of acute respiratory infections such as upper respiratory tract infections, acute pharyngitis, and viral illnesses were identified in this list.

Table 6: Top 50 Selected ICD Codes of Interest for Patient with neither a diagnosis for Asthma or COPD in six months prior to IE

Grouped by first 3 digits of ICD-10 code												
			Members with Neither Asthma or COPD Diagnosis									
			Any number of Inhalers		1 Inhaler		2 Inhalers		3-5 Inhalers		>=6 Inhalers	
	ICD	Description	1,311	%	689	%	273	%	242	%	107	%
	R05	Cough	178	13.6%	109	15.8%	41	15.0%	21	8.7%	7	6.5%
	F17	Nicotine dependence	167	12.7%	93	13.5%	24	8.8%	37	15.3%	13	12.1%
	R06	Abnormalities of breathing	152	11.6%	85	12.3%	27	9.9%	29	12.0%	11	10.3%
	U07	Emergency use of U07	108	8.2%	64	9.3%	19	7.0%	17	7.0%	8	7.5%
	J06	Acute upper resp infections of multiple and unsp sites	90	6.9%	57	8.3%	16	5.9%	16	6.6%	1	0.9%
	J02	Acute pharyngitis	85	6.5%	53	7.7%	18	6.6%	11	4.5%	3	2.8%
	R53	Malaise and fatigue	83	6.3%	47	6.8%	15	5.5%	17	7.0%	4	3.7%
	G47	Sleep disorders	75	5.7%	34	4.9%	11	4.0%	23	9.5%	7	6.5%
	R09	Oth symptoms and signs involving the circ and resp sys	75	5.7%	47	6.8%	14	5.1%	13	5.4%	1	0.9%
	J30	Vasomotor and allergic rhinitis	49	3.7%	24	3.5%	10	3.7%	11	4.5%	4	3.7%
	Z72	Problems related to lifestyle	43	3.3%	21	3.0%	4	1.5%	13	5.4%	5	4.7%
	J01	Acute sinusitis	36	2.7%	18	2.6%	6	2.2%	11	4.5%	1	0.9%
	R91	Abnormal findings on diagnostic imaging of lung	36	2.7%	20	2.9%	5	1.8%	5	2.1%	6	5.6%
	J98	Other respiratory disorders	28	2.1%	12	1.7%	6	2.2%	6	2.5%	4	3.7%
	J03	Acute tonsillitis	26	2.0%	17	2.5%	5	1.8%	3	1.2%	1	0.9%
	B34	Viral infection of unspecified site	25	1.9%	17	2.5%	7	2.6%	1	0.4%	0	0.0%
	J18	Pneumonia, unspecified organism	22	1.7%	13	1.9%	3	1.1%	6	2.5%	0	0.0%
	Z86	Personal history of certain other diseases	20	1.5%	9	1.3%	6	2.2%	5	2.1%	0	0.0%
	J96	Respiratory failure, not elsewhere classified	19	1.4%	9	1.3%	1	0.4%	7	2.9%	2	1.9%
	J34	Other and unspecified disorders of nose and nasal sinuses	15	1.1%	9	1.3%	2	0.7%	3	1.2%	1	0.9%
	J12	Viral pneumonia, not elsewhere classified	14	1.1%	10	1.5%		0.0%	2	0.8%	2	1.9%
	J32	Chronic sinusitis	14	1.1%	9	1.3%	2	0.7%	1	0.4%	2	1.9%
	J20	Acute bronchitis	13	1.0%	5	0.7%	3	1.1%	4	1.7%	1	0.9%
	J40	Bronchitis, not specified as acute or chronic	9	0.7%	5	0.7%	2	0.7%	1	0.4%	1	0.9%
	J43	Emphysema	8	0.6%	4	0.6%	1	0.4%	2	0.8%	1	0.9%
	J00	Acute nasopharyngitis [common cold]	6	0.5%	4	0.6%	1	0.4%	1	0.4%	0	0.0%

	J38	Diseases of vocal cords and larynx, not elsewhere classified	5	0.4%	3	0.4%		0.0%	2	0.8%	0	0.0%
	J81	Pulmonary edema	5	0.4%	3	0.4%	1	0.4%	0	0.0%	1	0.9%
	J84	Other interstitial pulmonary diseases	5	0.4%	3	0.4%	1	0.4%	0	0.0%	1	0.9%
	J31	Chronic rhinitis, nasopharyngitis and pharyngitis	5	0.4%	3	0.4%		0.0%	2	0.8%	0	0.0%
	J90	Pleural effusion, not elsewhere classified	4	0.3%	2	0.3%	1	0.4%	1	0.4%	0	0.0%
	J21	Acute bronchiolitis	3	0.2%	3	0.4%		0.0%	0	0.0%	0	0.0%
	J42	Unspecified chronic bronchitis	3	0.2%	1	0.1%	1	0.4%	1	0.4%	0	0.0%
	J80	Acute respiratory distress syndrome	3	0.2%	1	0.1%	1	0.4%	1	0.4%	0	0.0%
	J33	Nasal polyp	2	0.2%		0.0%		0.0%	1	0.4%	1	0.9%
	U09	Post COVID-19 condition	2	0.2%	2	0.3%		0.0%	0	0.0%	0	0.0%
	J93	Pneumothorax and air leak	2	0.2%	2	0.3%		0.0%	0	0.0%	0	0.0%
	J41	Simple and mucopurulent chronic bronchitis	2	0.2%	1	0.1%		0.0%	1	0.4%	0	0.0%
	J35	Chronic diseases of tonsils and adenoids	2	0.2%	1	0.1%		0.0%	1	0.4%	0	0.0%
	J15	Bacterial pneumonia, not elsewhere classified	2	0.2%	1	0.1%		0.0%	1	0.4%	0	0.0%
	J11	Influenza due to unidentified influenza virus	2	0.2%	2	0.3%		0.0%	0	0.0%	0	0.0%
	J05	Acute obstructive laryngitis [croup] and epiglottitis	2	0.2%		0.0%	1	0.4%	1	0.4%	0	0.0%
	J36	Peritonsillar abscess	2	0.2%	1	0.1%	1	0.4%	0	0.0%	0	0.0%
	J95	Intraop and postproc comp and disorders of resp sys, NEC	1	0.1%		0.0%		0.0%	1	0.4%	0	0.0%
	E84	Cystic fibrosis	1	0.1%		0.0%		0.0%	1	0.4%	0	0.0%
	J04	Acute laryngitis and tracheitis	1	0.1%		0.0%		0.0%	1	0.4%	0	0.0%
	J22	Unspecified acute lower respiratory infection	1	0.1%	1	0.1%		0.0%	0	0.0%	0	0.0%
	J37	Chronic laryngitis and laryngotracheitis	1	0.1%		0.0%		0.0%	1	0.4%	0	0.0%
	J39	Other diseases of upper respiratory tract	1	0.1%		0.0%	1	0.4%	0	0.0%	0	0.0%
	J47	Bronchiectasis	1	0.1%		0.0%		0.0%	0	0.0%	1	0.9%
	J69	Pneumonitis due to solids and liquids	1	0.1%		0.0%		0.0%	1	0.4%	0	0.0%
		Total:	**1,455**	**111.0%**	**825**	**119.7%**	**257**	**94.1%**	**283**	**116.9%**	**90**	**84.1%**

Limitations:

- This study evaluates a short point in time. Prescription claims data are subject to inherent limitations based on the design and may not accurately reflect true medication use. For albuterol, duplicate claims with the intent to store the medication at multiple locations (e.g. home and school) cannot be ascertained.
- Asthma has multiple diagnosis codes with varying severity and condition may wax and wane seasonally and in response to medication adherence.
- Those with more severe asthma may be more likely to have extra inhalers at multiple locations to ensure access, while also more likely to have adverse outcomes due to disease severity.
- Medical claims data and diagnosis codes may be incomplete. Post-hoc analysis of potential indications for SABA use in patients without asthma or COPD diagnoses must be interpreted with caution and is not all-inclusive.
- Inclusion criteria limited ability to follow patients for full year to describe high SABA use as defined by GINA.
- Inclusion limited SABA of interest to inhaler formulations; individuals relying on nebulizer formulations are not reflected.
- A significant portion of patients were excluded based on Medicare and TPL eligibility, and Medicaid eligibility requirements **(Table 7)**.
- Timing of evaluation window likely captured most first claims in fall. Seasonal differences such as wildfire smoke in fall and pollen in spring may affect claims.
- Given high rate of non-asthma diagnoses and differences in number of inhalers seen in subgroups with and without asthma or COPD, the outcome groups compared in **Table 5** are likely fundamentally different patient populations.

Table 7. Population of included patients

	Number of included patients
Members with FFS paid claims for a SABA	5,846
After exclusion of Medicare and TPL	3,222
After 6 month baseline Medicaid eligibility requirement	2,427
After 6 month follow-up FFS eligibility requirement	**1,867**

References:

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated May 2023. Available from: www.ginasthma.org. Accessed June 8, 2023.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: www.ginasthma.org. Accessed June 8, 2023.
3. Chipps BE, Murphy KR, Oppenheimer J. 2020 NAEPP Guidelines Update and GINA 2021-Asthma Care Differences, Overlap, and Challenges. *J Allergy Clin Immunol Pract.* 2022;10(1S):S19-S30.
4. Agusti A, Celli BR, Criner GJ, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am J Respir Crit Care Med.* 2023;207(7):819-837.

Short-Acting Beta Agonist Inhaler-Quantity Limit

Goal(s):
- Restrict use of short-acting beta agonist inhalers (SABA) inhalers to reduce overuse and risk of harmful outcomes as supported by medical literature for patients with asthma.

Length of Authorization:
- Up to 12 months

Requires PA:
- Any SABA claim for more than 6 claims in 6 months.
- Auto-PA patients with chronic obstructive pulmonary disease (COPD) and certain asthma controller medications.

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. Does the patient have a diagnosis of COPD?	**Yes**: Approve for 12 months	**No:** Go to #3
3. Does the patient have a diagnosis of asthma?	**Yes**: Go to #4	**No:** Go to #5
4. Does prescriber agree to add a controller therapy or discuss adherence with patient for prescribed controller? Inform prescriber of preferred agents in classes. Note: Inhaled corticosteroids are preferred controller for most patients with asthma. Combinations with long-acting beta agonists, inhaled muscarinics, leukotriene modifiers, or biologic agents may be appropriate for some patients with asthma or COPD.	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the request from a pulmonary or allergy specialist?	**Yes**: Approve for 12 months	**No:** Go to #6
6. Is the request for a single inhaler for an acute condition?	**Yes**: Approve single inhaler. Chronic use requires a specialist or diagnosis of asthma or COPD with concomitant use of a guideline directed controller medication.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T / DUR Review: *10/23 (SF)*
Implementation: *TBD*

Long-acting Beta-agonists (LABA)

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease?	**Yes:** Go to #5	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded
5. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Implementation: *3/1/18; 10/9/15; 8/12; 1/10*

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

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- All LAMA/LABA and LAMA/LABA/ICS products

Covered Alternatives:

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Go to #8	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Is the request for a LAMA/LABA combination product?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Go to #6
6. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.

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

P&T Review: *10/23 (SF);* *10/22 (KS), 10/21 (SF); 12/20 (KS), 10/20, 5/19; 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*

Implementation: *1/1/21; 3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Inhaled Corticosteroids (ICS)

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred ICS products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for treatment of asthma or reactive airway disease?	**Yes:** Go to #6	**No:** Go to #4
4. Is the request for treatment of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.

Approval Criteria		
5. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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P&T/DUR Review: *10/23 (SF); 10/22 (KS), 10/20 (KS), 5/19 (KS), 1/18; 9/16; 9/15*

Implementation: *3/1/18; 10/13/16; 10/9/15*

Appendix 2: Drug classes and ICD 10 coding

Table A. Anticholinergic Inhalers

HIC3	HSN	GSN	RouteDesc	FormDesc	Brand	Generic	PDL
B60	000057	021700	INHALATION	SOLUTION	IPRATROPIUM BROMIDE	ipratropium bromide	Y
B60	000057	021700	INHALATION	SOLUTION	IPRATROPIUM BROMIDE	ipratropium bromide	Y
B60	000057	059081	INHALATION	HFA AER AD	ATROVENT HFA	ipratropium bromide	Y
B60	000057	059081	INHALATION	HFA AER AD	ATROVENT HFA	ipratropium bromide	Y
B61	024024	050714	INHALATION	CAP W/DEV	SPIRIVA HANDIHALER	tiotropium bromide	Y
B61	024024	063164	INHALATION	MIST INHAL	SPIRIVA RESPIMAT	tiotropium bromide	Y
B61	024024	074813	INHALATION	MIST INHAL	SPIRIVA RESPIMAT	tiotropium bromide	Y
B61	039528	069855	INHALATION	AER POW BA	TUDORZA PRESSAIR	aclidinium bromide	N
B61	041115	072375	INHALATION	BLST W/DEV	INCRUSE ELLIPTA	umeclidinium bromide	Y
B61	044687	078007	INHALATION	VIAL-NEB	LONHALA MAGNAIR STARTER	glycopyrrol/nebulizer/accessor	N
B61	044691	078010	INHALATION	VIAL-NEB	LONHALA MAGNAIR REFILL	glycopyrrolate/neb.accessories	N
B61	045477	079272	INHALATION	VIAL-NEB	YUPELRI	revefenacin	N
B62	009040	048018	INHALATION	AMPUL-NEB	DUONEB	ipratropium/albuterol sulfate	Y
B62	009040	048018	INHALATION	AMPUL-NEB	IPRATROPIUM-ALBUTEROL	ipratropium/albuterol sulfate	Y

B62	009040	048018	INHALATION	AMPUL-NEB	IPRATROPIUM-ALBUTEROL	ipratropium/albuterol sulfate	Y
B62	009040	069371	INHALATION	MIST INHAL	COMBIVENT RESPIMAT	ipratropium/albuterol sulfate	Y

Table B. Long-Acting Beta Agonists

HIC3	HSN	GSN	RouteDesc	FormDesc	Brand	Generic	PDL
B6Y	007393	031417	INHALATION	BLST W/DEV	SEREVENT DISKUS	salmeterol xinafoate	Y
B6Y	010747	063016	INHALATION	VIAL-NEB	FORMOTEROL FUMARATE	formoterol fumarate	N
B6Y	010747	063016	INHALATION	VIAL-NEB	FORMOTEROL FUMARATE	formoterol fumarate	N
B6Y	010747	063016	INHALATION	VIAL-NEB	PERFOROMIST	formoterol fumarate	N
B6Y	034087	061579	INHALATION	VIAL-NEB	ARFORMOTEROL TARTRATE	arformoterol tartrate	N
B6Y	034087	061579	INHALATION	VIAL-NEB	BROVANA	arformoterol tartrate	N
B6Z	040969	072077	INHALATION	MIST INHAL	STRIVERDI RESPIMAT	olodaterol HCl	N

Table C. Short Acting Beta Agonists

HIC3	HSN	GSN	RouteDesc	FormDesc	Brand	Generic	PDL
B6W	002058	004964	INHALATION	SOLUTION	ALUPENT	metaproterenol sulfate	N
B6W	002058	016033	INHALATION	AER W/ADAP	ALUPENT	metaproterenol sulfate	N
B6W	002073	005039	INHALATION	VIAL-NEB	AIRET	albuterol sulfate	Y
B6W	002073	005039	INHALATION	VIAL-NEB	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	005039	INHALATION	VIAL-NEB	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	005040	INHALATION	SOLUTION	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	005040	INHALATION	SOLUTION	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	005040	INHALATION	SOLUTION	PROVENTIL	albuterol sulfate	Y
B6W	002073	005040	INHALATION	SOLUTION	VENTOLIN	albuterol sulfate	Y
B6W	002073	028090	INHALATION	HFA AER AD	ALBUTEROL SULFATE HFA	albuterol sulfate	Y
B6W	002073	028090	INHALATION	HFA AER AD	ALBUTEROL SULFATE HFA	albuterol sulfate	Y
B6W	002073	028090	INHALATION	HFA AER AD	PROAIR HFA	albuterol sulfate	Y
B6W	002073	028090	INHALATION	HFA AER AD	PROAIR HFA	albuterol sulfate	Y

B6W	002073	028090	INHALATION	HFA AER AD	PROVENTIL HFA	albuterol sulfate	Y
B6W	002073	028090	INHALATION	HFA AER AD	PROVENTIL HFA	albuterol sulfate	Y
B6W	002073	028090	INHALATION	HFA AER AD	VENTOLIN HFA	albuterol sulfate	Y
B6W	002073	028090	INHALATION	HFA AER AD	VENTOLIN HFA	albuterol sulfate	Y
B6W	002073	048698	INHALATION	VIAL-NEB	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	048699	INHALATION	VIAL-NEB	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	054687	INHALATION	VIAL-NEB	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	054687	INHALATION	VIAL-NEB	ALBUTEROL SULFATE	albuterol sulfate	Y
B6W	002073	073806	INHALATION	AER POW BA	PROAIR RESPICLICK	albuterol sulfate	N
B6W	002073	080260	INHALATION	AER PW BAS	PROAIR DIGIHALER	albuterol sulfate	N
B6W	002074	005037	INHALATION	AEROSOL	PROVENTIL	albuterol	N
B6W	002074	005037	INHALATION	AEROSOL	VENTOLIN	albuterol	N
B6W	002074	005038	INHALATION	AER REFILL	ALBUTEROL	albuterol	N
B6W	019858	041848	INHALATION	VIAL-NEB	LEVALBUTEROL HCL	levalbuterol HCl	N
B6W	019858	041848	INHALATION	VIAL-NEB	LEVALBUTEROL HCL	levalbuterol HCl	N
B6W	019858	041848	INHALATION	VIAL-NEB	XOPENEX	levalbuterol HCl	N
B6W	019858	041848	INHALATION	VIAL-NEB	XOPENEX	levalbuterol HCl	N
B6W	019858	041849	INHALATION	VIAL-NEB	LEVALBUTEROL HCL	levalbuterol HCl	N
B6W	019858	041849	INHALATION	VIAL-NEB	XOPENEX	levalbuterol HCl	N
B6W	019858	049871	INHALATION	VIAL-NEB	LEVALBUTEROL HCL	levalbuterol HCl	N
B6W	019858	049871	INHALATION	VIAL-NEB	XOPENEX	levalbuterol HCl	N
B6W	019858	057879	INHALATION	VIAL-NEB	LEVALBUTEROL CONCENTRATE	levalbuterol HCl	N
B6W	019858	057879	INHALATION	VIAL-NEB	XOPENEX CONCENTRATE	levalbuterol HCl	N
B6W	032814	058890	INHALATION	HFA AER AD	LEVALBUTEROL TARTRATE HFA	levalbuterol tartrate	N
B6W	032814	058890	INHALATION	HFA AER AD	LEVALBUTEROL TARTRATE HFA	levalbuterol tartrate	N
B6W	032814	058890	INHALATION	HFA AER AD	XOPENEX HFA	levalbuterol tartrate	N

Note: Only highlighted agents are inhaler formulations

Table D. Combination Inhalers: Long-acting muscarinic, Long Acting Beta Agonist, and/or Inhaled Corticosteroids

HIC3	HSN	GSN	RouteDesc	FormDesc	Brand	Generic	PDL

B62	040852	071883	INHALATION	BLST W/DEV	ANORO ELLIPTA	umeclidinium brm/vilanterol tr	Y
B62	041692	073344	INHALATION	AER POW BA	DUAKLIR PRESSAIR	aclidinium brom/formoterol fum	N
B62	042048	074131	INHALATION	MIST INHAL	STIOLTO RESPIMAT	tiotropium Br/olodaterol HCl	Y
B62	043352	075984	INHALATION	HFA AER AD	BEVESPI AEROSPHERE	glycopyrrolate/formoterol fum	N
B64	044508	077780	INHALATION	BLST W/DEV	TRELEGY ELLIPTA	fluticasone/umeclidin/vilanter	N
B64	044508	081555	INHALATION	BLST W/DEV	TRELEGY ELLIPTA	fluticasone/umeclidin/vilanter	N
B64	046753	081351	INHALATION	HFA AER AD	BREZTRI AEROSPHERE	budesonide/glycopyr/formoterol	N

Note: Only highlighted agents include inhaled corticosteroids (ICS)

Table E. Long Acting Beta Agonists and Inhaled Corticosteroid combinations

HIC3	HSN	GSN	RouteDesc	FormDesc	Brand	Generic	PDL
B63	019963	043366	INHALATION	BLST W/DEV	ADVAIR DISKUS	fluticasone propion/salmeterol	Y
B63	019963	043366	INHALATION	BLST W/DEV	ADVAIR DISKUS	fluticasone propion/salmeterol	Y
B63	019963	043366	INHALATION	BLST W/DEV	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	043366	INHALATION	BLST W/DEV	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	043366	INHALATION	BLST W/DEV	WIXELA INHUB	fluticasone propion/salmeterol	Y
B63	019963	043367	INHALATION	BLST W/DEV	ADVAIR DISKUS	fluticasone propion/salmeterol	Y
B63	019963	043367	INHALATION	BLST W/DEV	ADVAIR DISKUS	fluticasone propion/salmeterol	Y
B63	019963	043367	INHALATION	BLST W/DEV	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	043367	INHALATION	BLST W/DEV	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	043367	INHALATION	BLST W/DEV	WIXELA INHUB	fluticasone propion/salmeterol	Y
B63	019963	043368	INHALATION	BLST W/DEV	ADVAIR DISKUS	fluticasone propion/salmeterol	Y
B63	019963	043368	INHALATION	BLST W/DEV	ADVAIR DISKUS	fluticasone propion/salmeterol	Y
B63	019963	043368	INHALATION	BLST W/DEV	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	043368	INHALATION	BLST W/DEV	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	043368	INHALATION	BLST W/DEV	WIXELA INHUB	fluticasone propion/salmeterol	Y
B63	019963	061343	INHALATION	HFA AER AD	ADVAIR HFA	fluticasone propion/salmeterol	Y
B63	019963	061343	INHALATION	HFA AER AD	FLUTICASONE-SALMETEROL HFA	fluticasone propion/salmeterol	Y
B63	019963	061344	INHALATION	HFA AER AD	ADVAIR HFA	fluticasone propion/salmeterol	Y
B63	019963	061344	INHALATION	HFA AER AD	FLUTICASONE-SALMETEROL HFA	fluticasone propion/salmeterol	Y
B63	019963	061345	INHALATION	HFA AER AD	ADVAIR HFA	fluticasone propion/salmeterol	Y
B63	019963	061345	INHALATION	HFA AER AD	FLUTICASONE-SALMETEROL HFA	fluticasone propion/salmeterol	Y
B63	019963	077072	INHALATION	AER POW BA	AIRDUO RESPICLICK	fluticasone propion/salmeterol	Y

B63	019963	077072	INHALATION	AER POW BA	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	077072	INHALATION	AER POW BA	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	077073	INHALATION	AER POW BA	AIRDUO RESPICLICK	fluticasone propion/salmeterol	Y
B63	019963	077073	INHALATION	AER POW BA	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	077073	INHALATION	AER POW BA	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	077074	INHALATION	AER POW BA	AIRDUO RESPICLICK	fluticasone propion/salmeterol	Y
B63	019963	077074	INHALATION	AER POW BA	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	077074	INHALATION	AER POW BA	FLUTICASONE-SALMETEROL	fluticasone propion/salmeterol	Y
B63	019963	081399	INHALATION	AER PW BAS	AIRDUO DIGIHALER	fluticasone propion/salmeterol	N
B63	019963	081400	INHALATION	AER PW BAS	AIRDUO DIGIHALER	fluticasone propion/salmeterol	N
B63	019963	081401	INHALATION	AER PW BAS	AIRDUO DIGIHALER	fluticasone propion/salmeterol	N
B63	021993	062725	INHALATION	HFA AER AD	BUDESONIDE-FORMOTEROL FUMARATE	budesonide/formoterol fumarate	Y
B63	021993	062725	INHALATION	HFA AER AD	BUDESONIDE-FORMOTEROL FUMARATE	budesonide/formoterol fumarate	Y
B63	021993	062725	INHALATION	HFA AER AD	SYMBICORT	budesonide/formoterol fumarate	Y
B63	021993	062726	INHALATION	HFA AER AD	BUDESONIDE-FORMOTEROL FUMARATE	budesonide/formoterol fumarate	Y
B63	021993	062726	INHALATION	HFA AER AD	BUDESONIDE-FORMOTEROL FUMARATE	budesonide/formoterol fumarate	Y
B63	021993	062726	INHALATION	HFA AER AD	SYMBICORT	budesonide/formoterol fumarate	Y
B63	037050	066480	INHALATION	HFA AER AD	DULERA	mometasone/formoterol	Y
B63	037050	066481	INHALATION	HFA AER AD	DULERA	mometasone/formoterol	Y
B63	037050	067555	INHALATION	HFA AER AD	DULERA	mometasone/formoterol	Y
B63	040319	070972	INHALATION	BLST W/DEV	BREO ELLIPTA	fluticasone/vilanterol	N
B63	040319	070972	INHALATION	BLST W/DEV	FLUTICASONE-VILANTEROL	fluticasone/vilanterol	N
B63	040319	071815	INHALATION	BLST W/DEV	BREO ELLIPTA	fluticasone/vilanterol	N
B63	040319	071815	INHALATION	BLST W/DEV	FLUTICASONE-VILANTEROL	fluticasone/vilanterol	N

Table F. Inhaled Corticosteroids

HIC3	HSN	GSN	RouteDesc	FormDesc	Brand	Generic	PDL
B6M	000070	077643	INHALATION	HFA AEROBA	QVAR REDIHALER	beclomethasone dipropionate	N
B6M	000070	077644	INHALATION	HFA AEROBA	QVAR REDIHALER	beclomethasone dipropionate	N
B6M	000070	077644	INHALATION	HFA AEROBA	QVAR REDIHALER	beclomethasone dipropionate	N

B6M	000072	000213	INHALATION	AER W/ADAP	AEROBID	flunisolide	N
B6M	002891	000212	INHALATION	AER W/ADAP	AZMACORT	triamcinolone acetonide	N
B6M	003329	051649	INHALATION	AER POW BA	ASMANEX	mometasone furoate	Y
B6M	003329	059326	INHALATION	AER POW BA	ASMANEX	mometasone furoate	Y
B6M	003329	059326	INHALATION	AER POW BA	ASMANEX	mometasone furoate	Y
B6M	003329	059327	INHALATION	AER POW BA	ASMANEX	mometasone furoate	Y
B6M	003329	059328	INHALATION	AER POW BA	ASMANEX	mometasone furoate	Y
B6M	003329	064010	INHALATION	AER POW BA	ASMANEX	mometasone furoate	Y
B6M	003329	073197	INHALATION	HFA AER AD	ASMANEX HFA	mometasone furoate	N
B6M	003329	073198	INHALATION	HFA AER AD	ASMANEX HFA	mometasone furoate	N
B6M	003329	080669	INHALATION	HFA AER AD	ASMANEX HFA	mometasone furoate	N
B6M	006545	018165	INHALATION	AMPUL-NEB	BUDESONIDE	budesonide	N
B6M	006545	018165	INHALATION	AMPUL-NEB	PULMICORT	budesonide	N
B6M	006545	046525	INHALATION	AMPUL-NEB	BUDESONIDE	budesonide	N
B6M	006545	046525	INHALATION	AMPUL-NEB	PULMICORT	budesonide	N
B6M	006545	046525	INHALATION	AMPUL-NEB	PULMICORT	budesonide	N
B6M	006545	046526	INHALATION	AMPUL-NEB	BUDESONIDE	budesonide	N
B6M	006545	046526	INHALATION	AMPUL-NEB	PULMICORT	budesonide	N
B6M	006545	046526	INHALATION	AMPUL-NEB	PULMICORT	budesonide	N
B6M	006545	062240	INHALATION	AER POW BA	PULMICORT FLEXHALER	budesonide	Y
B6M	006545	062241	INHALATION	AER POW BA	PULMICORT FLEXHALER	budesonide	Y
B6M	006545	062241	INHALATION	AER POW BA	PULMICORT FLEXHALER	budesonide	Y
B6M	006607	017184	INHALATION	AER W/ADAP	AEROBID-M	flunisolide/menthol	N
B6M	007873	019317	INHALATION	BLST W/DEV	FLOVENT DISKUS	fluticasone propionate	Y
B6M	007873	019317	INHALATION	BLST W/DEV	FLOVENT DISKUS	fluticasone propionate	Y
B6M	007873	019318	INHALATION	BLST W/DEV	FLOVENT DISKUS	fluticasone propionate	Y
B6M	007873	019319	INHALATION	BLST W/DEV	FLOVENT DISKUS	fluticasone propionate	Y
B6M	007873	021251	INHALATION	AER W/ADAP	FLOVENT HFA	fluticasone propionate	Y

B6M	007873	021251	INHALATION	AER W/ADAP	FLOVENT HFA	fluticasone propionate	Y
B6M	007873	021251	INHALATION	AER W/ADAP	FLUTICASONE PROPIONATE HFA	fluticasone propionate	Y
B6M	007873	021251	INHALATION	AER W/ADAP	FLUTICASONE PROPIONATE HFA	fluticasone propionate	Y
B6M	007873	021253	INHALATION	AER W/ADAP	FLOVENT HFA	fluticasone propionate	Y
B6M	007873	021253	INHALATION	AER W/ADAP	FLOVENT HFA	fluticasone propionate	Y
B6M	007873	021253	INHALATION	AER W/ADAP	FLUTICASONE PROPIONATE HFA	fluticasone propionate	Y
B6M	007873	021253	INHALATION	AER W/ADAP	FLUTICASONE PROPIONATE HFA	fluticasone propionate	Y
B6M	007873	021483	INHALATION	AER W/ADAP	FLOVENT HFA	fluticasone propionate	Y
B6M	007873	021483	INHALATION	AER W/ADAP	FLOVENT HFA	fluticasone propionate	Y
B6M	007873	021483	INHALATION	AER W/ADAP	FLUTICASONE PROPIONATE HFA	fluticasone propionate	Y
B6M	007873	021483	INHALATION	AER W/ADAP	FLUTICASONE PROPIONATE HFA	fluticasone propionate	Y
B6M	007873	081476	INHALATION	AER PW BAS	ARMONAIR DIGIHALER	fluticasone propionate	N
B6M	007873	081478	INHALATION	AER PW BAS	ARMONAIR DIGIHALER	fluticasone propionate	N
B6M	007873	081485	INHALATION	AER PW BAS	ARMONAIR DIGIHALER	fluticasone propionate	N
B6M	032691	058671	INHALATION	HFA AER AD	ALVESCO	ciclesonide	N
B6M	032691	058672	INHALATION	HFA AER AD	ALVESCO	ciclesonide	N
B6M	034756	072722	INHALATION	BLST W/DEV	ARNUITY ELLIPTA	fluticasone furoate	N
B6M	034756	072723	INHALATION	BLST W/DEV	ARNUITY ELLIPTA	fluticasone furoate	N
B6M	034756	078449	INHALATION	BLST W/DEV	ARNUITY ELLIPTA	fluticasone furoate	N

Table G. Therapeutic Immune Modulators For Asthma and Atopic Dermatitis

HIC3	HSN	GSN	RouteDesc	FormDesc	Brand	Generic	PDL
V4D	044180	077263	SUBCUT	SYRINGE	DUPIXENT SYRINGE	dupilumab	N
V4D	044180	079179	SUBCUT	SYRINGE	DUPIXENT SYRINGE	dupilumab	N
V4D	044180	081231	SUBCUT	PEN INJCTR	DUPIXENT PEN	dupilumab	N
V4D	044180	081615	SUBCUT	PEN INJCTR	DUPIXENT PEN	dupilumab	N
V4D	044180	082769	SUBCUT	SYRINGE	DUPIXENT SYRINGE	dupilumab	N

V4F	047740	082944	SUBCUT	SYRINGE	TEZSPIRE	tezepelumab-ekko	N
V4F	047740	084017	SUBCUT	PEN INJCTR	TEZSPIRE	tezepelumab-ekko	N
V4G	047741	082945	SUBCUT	SYRINGE	ADBRY	tralokinumab-ldrm	N
Z20	042775	075111	SUBCUT	VIAL	NUCALA	mepolizumab	N
Z20	042775	079828	SUBCUT	SYRINGE	NUCALA	mepolizumab	N
Z20	042775	079829	SUBCUT	AUTO INJCT	NUCALA	mepolizumab	N
Z20	042775	083454	SUBCUT	SYRINGE	NUCALA	mepolizumab	N
Z20	043211	075753	INTRAVEN	VIAL	CINQAIR	reslizumab	N
Z23	044635	077921	SUBCUT	SYRINGE	FASENRA	benralizumab	N
Z23	044635	080268	SUBCUT	AUTO INJCT	FASENRA PEN	benralizumab	N
Z2L	025399	052758	SUBCUT	VIAL	XOLAIR	omalizumab	N
Z2L	025399	067907	SUBCUT	SYRINGE	XOLAIR	omalizumab	N
Z2L	025399	067908	SUBCUT	SYRINGE	XOLAIR	omalizumab	N
Z2Z	047767	082989	ORAL	TABLET	CIBINQO	abrocitinib	N
Z2Z	047767	082990	ORAL	TABLET	CIBINQO	abrocitinib	N
Z2Z	047767	082991	ORAL	TABLET	CIBINQO	abrocitinib	N

Table H. Oral Glucocorticoids

HIC3	HSN	GSN	Route	Form	Brand	Generic	PDL
P5A	002860	006685	ORAL	TABLET	CORTISONE ACETATE	cortisone acetate	Y
P5A	002867	006703	ORAL	TABLET	CORTEF	hydrocortisone	Y
P5A	002867	006703	ORAL	TABLET	HYDROCORTISONE	hydrocortisone	Y
P5A	002867	006704	ORAL	TABLET	CORTEF	hydrocortisone	Y
P5A	002867	006704	ORAL	TABLET	HYDROCORTISONE	hydrocortisone	Y
P5A	002867	006705	ORAL	TABLET	CORTEF	hydrocortisone	Y
P5A	002867	006705	ORAL	TABLET	HYDROCORTISONE	hydrocortisone	Y
P5A	002874	006719	ORAL	SOLUTION	PREDNISOLONE	prednisolone	Y
P5A	002877	006737	ORAL	TABLET	MEDROL	methylprednisolone	Y
P5A	002877	006737	ORAL	TABLET	METHYLPREDNISOLONE	methylprednisolone	Y
P5A	002877	006738	ORAL	TABLET	MEDROL	methylprednisolone	Y
P5A	002877	006739	ORAL	TABLET	MEDROL	methylprednisolone	Y
P5A	002877	006740	ORAL	TABLET	METHYLPREDNISOLONE	methylprednisolone	Y
P5A	002877	006741	ORAL	TABLET	MEDROL	methylprednisolone	Y
P5A	002877	006741	ORAL	TABLET	METHYLPREDNISOLONE	methylprednisolone	Y
P5A	002877	006742	ORAL	TABLET	MEDROL	methylprednisolone	Y
P5A	002877	006742	ORAL	TABLET	METHYLPREDNISOLONE	methylprednisolone	Y
P5A	002877	045311	ORAL	TAB DS PK	MEDROL	methylprednisolone	Y

P5A	002877	045311	ORAL	TAB DS PK	METHYLPREDNISOLONE	methylprednisolone	Y
P5A	002879	006745	ORAL	ORAL CONC	PREDNISONE INTENSOL	prednisone	Y
P5A	002879	006746	ORAL	SOLUTION	PREDNISONE	prednisone	Y
P5A	002879	006748	ORAL	TABLET	PREDNISONE	prednisone	Y
P5A	002879	006749	ORAL	TABLET	PREDNISONE	prednisone	Y
P5A	002879	006750	ORAL	TABLET	PREDNISONE	prednisone	Y
P5A	002879	006751	ORAL	TABLET	PREDNISONE	prednisone	Y
P5A	002879	006753	ORAL	TABLET	PREDNISONE	prednisone	Y
P5A	002879	006754	ORAL	TABLET	PREDNISONE	prednisone	Y
P5A	002879	045267	ORAL	TAB DS PK	PREDNISONE	prednisone	Y
P5A	002879	045268	ORAL	TAB DS PK	PREDNISONE	prednisone	Y
P5A	002879	069864	ORAL	TABLET DR	RAYOS	prednisone	Y
P5A	002879	069865	ORAL	TABLET DR	RAYOS	prednisone	Y
P5A	002879	069866	ORAL	TABLET DR	RAYOS	prednisone	Y
P5A	002889	006780	ORAL	ELIXIR	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006781	ORAL	SOLUTION	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006782	ORAL	DROPS	DEXAMETHASONE INTENSOL	dexamethasone	Y
P5A	002889	006784	ORAL	TABLET	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006785	ORAL	TABLET	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006786	ORAL	TABLET	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006787	ORAL	TABLET	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006788	ORAL	TABLET	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006789	ORAL	TABLET	DEXAMETHASONE	dexamethasone	Y
P5A	002889	006790	ORAL	TABLET	DEXAMETHASONE	dexamethasone	Y
P5A	002889	045306	ORAL	TAB DS PK	DEXAMETHASONE	dexamethasone	Y
P5A	002889	046463	ORAL	TAB DS PK	DEXAMETHASONE	dexamethasone	Y
P5A	002889	061392	ORAL	TAB DS PK	DEXAMETHASONE	dexamethasone	Y
P5A	002889	064893	ORAL	TAB DS PK	DEXAMETHASONE	dexamethasone	Y
P5A	002889	064893	ORAL	TAB DS PK	TAPERDEX	dexamethasone	Y

P5A	002889	077133	ORAL	TAB DS PK	TAPERDEX	dexamethasone	Y
P5A	002889	077745	ORAL	TAB DS PK	TAPERDEX	dexamethasone	Y
P5A	002867	079919	ORAL	CAP SPRINK	ALKINDI SPRINKLE	hydrocortisone	N
P5A	002867	079920	ORAL	CAP SPRINK	ALKINDI SPRINKLE	hydrocortisone	N
P5A	002867	079921	ORAL	CAP SPRINK	ALKINDI SPRINKLE	hydrocortisone	N
P5A	002867	079922	ORAL	CAP SPRINK	ALKINDI SPRINKLE	hydrocortisone	N
P5A	002871	038375	ORAL	SOLUTION	PEDIAPRED	prednisolone sodium phosphate	N
P5A	002871	038375	ORAL	SOLUTION	PREDNISOLONE SODIUM PHOSPHATE	prednisolone sodium phosphate	N
P5A	002871	041424	ORAL	SOLUTION	PREDNISOLONE SODIUM PHOSPHATE	prednisolone sodium phosphate	N
P5A	002871	047282	ORAL	SOLUTION	PREDNISOLONE SODIUM PHOSPHATE	prednisolone sodium phosphate	N
P5A	002871	060956	ORAL	TAB RAPDIS	PREDNISOLONE SODIUM PHOS ODT	prednisolone sodium phosphate	N
P5A	002871	060957	ORAL	TAB RAPDIS	PREDNISOLONE SODIUM PHOS ODT	prednisolone sodium phosphate	N
P5A	002871	060958	ORAL	TAB RAPDIS	PREDNISOLONE SODIUM PHOS ODT	prednisolone sodium phosphate	N
P5A	002871	063898	ORAL	SOLUTION	PREDNISOLONE SODIUM PHOSPHATE	prednisolone sodium phosphate	N
P5A	002871	064528	ORAL	SOLUTION	PREDNISOLONE SODIUM PHOSPHATE	prednisolone sodium phosphate	N
P5A	002874	006721	ORAL	TABLET	MILLIPRED	prednisolone	N
P5A	002874	006721	ORAL	TABLET	PREDNISOLONE	prednisolone	N
P5A	002889	080270	ORAL	TABLET	HEMADY	dexamethasone	N

Table I. Leukotriene Modifiers

HIC3	HSN	GSN	Route	Form	Brand	Generic	PDL
Z4B	016911	037003	ORAL	TAB CHEW	MONTELUKAST SODIUM	montelukast sodium	Y
Z4B	016911	037003	ORAL	TAB CHEW	SINGULAIR	montelukast sodium	Y

Z4B	016911	038451	ORAL	TABLET	MONTELUKAST SODIUM	montelukast sodium	Y
Z4B	016911	038451	ORAL	TABLET	SINGULAIR	montelukast sodium	Y
Z4B	016911	044803	ORAL	TAB CHEW	MONTELUKAST SODIUM	montelukast sodium	Y
Z4B	016911	044803	ORAL	TAB CHEW	SINGULAIR	montelukast sodium	Y
Z2X	037123	066612	ORAL	TABLET	DALIRESP	roflumilast	N
Z2X	037123	066612	ORAL	TABLET	ROFLUMILAST	roflumilast	N
Z2X	037123	078213	ORAL	TABLET	DALIRESP	roflumilast	N
Z2X	037123	078213	ORAL	TABLET	ROFLUMILAST	roflumilast	N
Z4B	011815	027962	ORAL	TABLET	ACCOLATE	zafirlukast	N
Z4B	011815	027962	ORAL	TABLET	ZAFIRLUKAST	zafirlukast	N
Z4B	011815	043557	ORAL	TABLET	ACCOLATE	zafirlukast	N
Z4B	011815	043557	ORAL	TABLET	ZAFIRLUKAST	zafirlukast	N
Z4B	016911	051512	ORAL	GRAN PACK	MONTELUKAST SODIUM	montelukast sodium	N
Z4B	016911	051512	ORAL	GRAN PACK	SINGULAIR	montelukast sodium	N
Z4E	012321	029803	ORAL	TABLET	ZYFLO	zileuton	N
Z4E	012321	063062	ORAL	TBMP 12HR	ZILEUTON ER	zileuton	N
Z2X	037123	078213	ORAL	TABLET	ROFLUMILAST	roflumilast	

Note: roflumilast is indicated only for COPD and was not included in the definition for leukotriene modifiers

Table J. ICD 10 codes of Interest

Diagnosis	ICD-10 Code-CM code
Asthma	J45.x
Asthma Types	
Mild intermittent asthma	J45.2x
Mild persistent asthma	J45.3x
Moderate persistent asthma	J45.4x
Severe persistent asthma	J45.5x
Other and unspecified asthma	J45.5x
Other asthma (includes exercised induced bronchospasm)	J45.9x
Comorbidities	
Chronic Obstructive Pulmonary Disease	J44.x

Table K. Package sizes for asthma inhalers

NameDrugGen	NameDrugBrand	QuanSizeDrugPkg	TextDrugStr	GSN
albuterol sulfate	ALBUTEROL SULFATE HFA	6.7	90 mcg	28090
albuterol sulfate	PROVENTIL HFA	6.7	90 mcg	28090
albuterol sulfate	ALBUTEROL SULFATE HFA	7	90 mcg	28090
albuterol sulfate	VENTOLIN HFA	8	90 mcg	28090
albuterol sulfate	ALBUTEROL SULFATE HFA	8.5	90 mcg	28090
albuterol sulfate	PROAIR HFA	8.5	90 mcg	28090
albuterol sulfate	ALBUTEROL SULFATE HFA	18	90 mcg	28090
albuterol sulfate	VENTOLIN HFA	18	90 mcg	28090

Table L. ICD-10 codes of interest for post-hoc assessment of patients without asthma or chronic obstructive pulmonary disease

Diagnosis	**ICD-10 Code-CM code**
Diseases of respiratory system	Jx
Provisional assignment of new disease of uncertain etiology or emergency use	U00-U85
Personal history of Covid-19	Z86.16
Viral infection of unspecified site	B34x
Sleep apnea	G473x
Tobacco use and nicotine dependence	Z72.0 and F17x
Cystic fibrosis	E.84.x
R codes: Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	
Cough	R05x
Abnormalities of breathing	R06x
Other symptoms of the circulatory/respiratory system	R09x
Malaise/fatigue	R53x
Abnormal findings in specimens from respiratory organs and thorax	R84x
Abnormal findings on diagnostic imaging of lung	R91x