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 6th, 2022 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Approval of Agenda	R. Citron (OSU)
	C. Conflict of Interest Declaration	R. Citron (OSU)
	D. Approval of Minutes	R. Citron (OSU)
	E. Department Update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)

A. TIMS DERP Summary
B. Colony Stimulating Factors Literature Scan
C. Antiepileptics Class Update and New Drug Evaluation
D. P&T Annual Report
   1. Public Comment

V. PREFERRED DRUG LIST NEW BUSINESS

1:40 PM	A. Multiple Sclerosis Drugs Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
1:55PM	B. HIV Literature Scan 1. Literature Scan 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
2:10 PM	C. GLP-1 Agonist and SGLT-2 Inhibitors Focused Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Mounjaro (tirzepatide) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)

2:35 PM	BREAK	
2:50 PM	D. Dupixent (dupilumab) Indication Update a. New Indication Review/Prior Authorization Criteria b. Public Comment c. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
	III. DUR NEW BUSINESS	
3:05 PM	E. ADHD Drugs Literature Scan 1. Literature Scan 2. Drug Use Evaluation/Prior Authorization Criteria 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	 D. Engen (OSU) S. Servid (OSU)
3:35 PM	B. Lumateperone Drug Utilization Review 1. Drug Utilization Evaluation 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	T. Williams (OSU)
3:50 PM	C. Annovera® (ethinyl estradiol/segesterone) yearly contraceptive ring quantity limit 1. Drug Utilization Evaluation 2. Prior Authorization/Quantity Limit 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
4:00 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, August 4th, 2022 1:00 - 5:00 PM

Via Zoom webinar

MEETING MINUTES

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

Members Present:; Stacy Ramirez, PharmD; Bill Origer, MD; Tim Langford, PharmD; Eddie Saito, PharmD; Russ Huffman, PMHNP; Mark Helm, MD; Cat Livingston, MD

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

Audience: **Arlene Mejia, Pierre Fabre USA**; **Allison Small, OHSU**; Brady Hurtgen, Horizon Therapeutics; Brandie Feger, Advanced Health; Chris Ferrin, Samaritan Health Plans; Evie Knisely, Novartis; Gloria Zepeda, P4 Pharmacy AllCare; Kaitlyn Molina, Samaritan Health Plan; Lisa Rawlins; Lori McDermott, Viking HCS; Marc Rueckert, Argenx; Mark Kantor, AllCare CCO; Matt Worthy, OHSU; Michael Foster, BMS; Michele Sabados, Alkermes; Nana Ama Kuffour, IHN; **Phil Wettestad, Novartis**; Saghi Maleki, Takeda Pharmaceuticals; Sarah Lott, Artia Solutions; Shirley Quach; Tina Andrews, Umpqua Health Alliance; Tom Telly, Supernus; Trish Olson; Andrea Willcuts, Idorsia; YJ Shukla, EOCCO Moda Health

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

I. CALL TO ORDER

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

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B. Conflict of Interest Declaration – no new conflicts of interest were declared
C. Approval of Agenda and June 2022 Minutes presented by Roger Citron
ACTION: Motion to approve, 2nd, Drs. Langford and Saito abstained, all in favor
D. Department Update provided by Andrew Gibler, PharmD

II. CONSENT AGENDA TOPICS

A. **CMS Annual Report**
B. **Review Standards and Methods for Evidence Assessment**
C. **P&T Operating Procedures**
D. **Quarterly Utilization Report**
- **Public Comment**

III. DUR ACTIVITIES

A. **ProDUR Report**: Lan Starkweather, PharmD
B. **RetroDUR Report**: Dave Engen, PharmD
C. **Oregon State Drug Review**: Kathy Sentena, PharmD
- **Second-Generation Antipsychotic Use in Children and Adolescents**
- **Updated 2021 Treatment Guidelines for Sexually Transmitted Infections**

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

IV. PREFERRED DRUG LIST NEW BUSINESS

A. **Estrogen Class Update**: Kathy Sentena, PharmD
Recommendations:
- No PDL changes recommended based on review of recently published evidence
- Evaluate costs in executive session

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

B. **PCSK9 Modulator Class Update with New Drug Evaluation**: Megan Herink, PharmD
Recommendations:
- Change the name of the class to "PCSK9 Modulators" and no PDL changes recommended based on review of recently published evidence
- Maintain inclisiran as non-preferred on the PDL
- Modify the PCSK9 Modulators PA criteria to limit inclisiran to its FDA indication and require trial of agents with evidence of CV risk reduction
- Evaluate costs in executive session

Public Comment: Phil Wettestad, Novartis

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

C. **Oral Thyroid Hormones Class Update:** Kathy Sentena, PharmD
Recommendations:
- Add class to the PDL and designate at least one formulation of levothyroxine preferred
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

D. **Oral Beta Blocker Class Update:** Deanna Moretz, PharmD
Recommendations:
- Designate acebutolol non-preferred and at least one formulation of extended-release propranolol and propranolol oral solution preferred on the PDL
- Evaluate costs in executive session
Public Comment: Phil Wettestad, Novartis; Arlene Mejia, Pierre Fabre Group; Alison Small, OHSU
ACTION: Motion to approve, 2nd, all in favor

E. **Nasal Allergy inhaler Class Update**: Deanna Moretz, PharmD
Recommendations:
- No PDL changes recommended based on review of recently published evidence
- Remove PA requirement for intranasal allergy products for children 20 years of age and younger who are eligible for EPSDT
- Evaluate costs in executive session
ACTION: The Committee amended the recommendation to limit to preferred agents and changed the wording from 20 and younger to "up to their 21st birthday"
Motion to approve, 2nd, all in favor

F. **Sedative Class Update and New Drug Evaluation:** Sarah Servid, PharmD
Recommendations:
- No PDL changes recommended based on review of recently published evidence
- Update the PA criteria to facilitate benzodiazepine tapers as described in recent guidance from the Mental Health Clinical Advisory Group (MHCAG)
- Evaluate costs in executive session
Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Bill Origer, MD; Tim Langford, PharmD; Eddie Saito, PharmD; Russ Huffman, PMHNP; Mark Helm, MD; Cat Livingston, MD

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

VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Estrogen Class Update**
Recommendation: Make: oral Prempro, Premarin, Premphase and Angeliq; topical Elestrin; and vaginal Femring, Estring, estradiol cream and Estrace preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. **PCSK9 Modulator Class Update with NDE**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

C. **Oral Thyroid Hormones Class Update:**
Recommendation: Make levothyroxine preferred and all other agents non-preferred and grandfather patients on non-preferred agents for 12 months
ACTION: Motion to approve, 2nd, majority in favor with one opposed

D. **Oral Beta Blocker Class Update**
Recommendation: Make propranolol SA 24 hour capsules, generic oral propranolol solution, and nadolol tabs preferred on the PDL and Hemangeol open access up to 6 months old
ACTION: Motion to approve, 2nd, all in favor

E. **Nasal Allergy Inhaler Class Update**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

F. **PCSK9 Modulator Class Update with NDE**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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

OHSU Drug Effectiveness Review Project Summary Reports – (1) Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis (March 2022) (2) Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis (April 2022)

Date of Review: Oct 2022

Date of Last Review: Oct 2021
Literature Search: 01/01/19-07/22/21 (RA/AS) and 05/01/19-08/25/22 (PsO/PsA)

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

Research Questions:
March 2022 Report:
1. What is the comparative effectiveness of targeted immune modulators (TIMs) to treat rheumatoid arthritis (RA) or ankylosing spondylitis (AS)?
2. What are the comparative harms of TIMs to treat RA or AS?
3. Do the included drugs differ in their effectiveness or harms for managing RA or AS based on age, race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease?

April 2022 Report:
1. What is the comparative effectiveness of targeted TIMs to treat plaque psoriasis (PsO) or psoriatic arthritis (PsA)?
2. What are the comparative harms of TIMs to treat PsO or PsA?
3. Do the included drugs differ in their effectiveness or harms for managing PsO or PsA based on age and race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease?

Conclusions:
Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis
- There is moderate certainty evidence that there is no difference in response (America College of Rheumatology [ACR]50) or remission (ACR70) of RA between certolizumab pegol, tocilizumab, and abatacept when used as first-line treatment.[1] As second-line treatment, abatacept is less effective than upadacitinib for achieving response in RA based on the Disease Activity Score-28 joints-C-reactive protein [DAS-28-CRP] mean change from baseline (-2.0 vs. -2.52 respectively; p<0.001; 95% Confidence Interval [CI] not reported [NR]) and RA remission (percent of patients achieving DAS-28-CRP <2.6, 13% vs. 30% respectively; p<0.001; 95% CI NR) at 24 weeks.[1] (High certainty of evidence [CoE] for response; moderate CoE for remission).[1]
- Three new randomized clinical trials (RCTs) provide data on the overall incidence of adverse effects (AEs) and serious adverse effects (SAEs) for TIMS when used to treat RA.[1] Moderate to very low CoE from RCTs indicate a lower incidence of overall AEs and SAEs with abatacept and certolizumab pegol compared with tocilizumab.[1] Overall AEs were less frequent for abatacept compared with tocilizumab (80% vs. 95%, respectively; RR 0.48; 95% CI, 0.31 to 0.74) at 24

weeks; however no differences in SAEs were reported at 24 weeks (RR 0.42; 95% CI, 0.14 to 1.29; low CoE for AEs; very low CoE for SAEs).[1] When certolizumab pegol was compared with tocilizumab, a lower incidence of overall AEs was reported at 24 weeks (83% vs. 95%, respectively; RR 0.87; 95% CI, 0.81 to 0.93); however, no differences in SAEs were reported at 24 weeks (RR 1.72; 95% CI, 0.79 to 3.76; moderate CoE for overall AEs; low CoE for SAEs).[1]

- Most observational studies have not found statistically significant differences in mortality, malignancies, cardiovascular events or heart failure between TIMs.[1] However, some studies suggest, based on moderate CoE, that infliximab may be associated with higher incidence of serious infections compared to other TIMs, and tocilizumab may be associated with higher incidence of gastrointestinal perforations compared to other TIMs, when used in the treatment of RA.
- New comparative evidence for the efficacy of TIMs in treatment of AS was sparse.[1] Only one RCT with high risk of bias that compared etanercept and infliximab was identified.[1] Although etanercept was less effective for clinical improvement compared to infliximab at 12 weeks, no statistically significant differences in response were observed at weeks 54 and 104 (very low CoE).[1]
- No new evidence was identified to evaluate comparative harms of TIMs when used to treat AS.[1]
- No studies were identified that addressed differences in effectiveness or harms of TIMs when used to manage RA or AS in specific populations based on age, gender, race, comorbidities, concomitant medications, or different disease stages.[1]

Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis

- New head-to-head RCTs were published for certolizumab pegol, etanercept, ixekizumab, guselkumab, secukinumab and risankizumab in the treatment of moderate-to-severe PsO.[2] No differences were found between ixekizumab and secukinumab for disease remission of PsO at 24 weeks (moderate CoE).[2] The following head-to-head comparisons found statistically significant results:
    - In one RCT, 200 mg and 400 mg doses of certolizumab pegol were compared with etanercept.[2] At 12 weeks, 61.3% of certolizumab 200 mg patients, 66.7% of certolizumab 400 mg patients and 53.3% of etanercept patients achieved a Psoriasis Area and Severity Index (PASI) 75 response. The PASI 75 response rate was higher for certolizumab pegol 400 mg versus etanercept (calculated RR 1.2; 95% CI, 0.04 to 1.5).[2] (Moderate CoE).[2]
    - At 12 weeks, ixekizumab achieved higher PASI 100 remission versus guselkumab (41% vs. 25%, respectively; calculated RR 1.7; 95% CI 1.4 to 2.0; high CoE).[2] However, no differences were noted between ixekizumab and guselkumab for disease remission at 24 weeks (PASI 100: 50% vs. 52%, respectively; calculated RR 0.96; 95% CI, 0.85 to 1.1; high CoE).
    - No difference in disease remission was observed between risankizumab and secukinumab at 16 weeks (PASI 90: 73.8% vs. 65.6%, respectively; absolute risk difference [ARD] 8.2%; 95% CI, -2.2 to 18.6). However at 52 weeks, risankizumab achieved higher PASI 90 remission than secukinumab (PASI 90: 86.6% vs. 57.1%, respectively; ARD 29.8; 95% CI, 20.8 to 38.8; moderate CoE).[2]
- Few differences in harms were found between certolizumab pegol, etanercept, ixekizumab, guselkumab, secukinumab, and risankizumab when used to treat PsO based on low and moderate CoE.[2] No differences in AEs, SAEs, or withdrawals due to AEs were observed between these agents in recently published RCTs.[2] A higher risk of injection-site reactions was observed for ixekizumab compared with guselkumab (RR, 3.4; 95% CI 2.1 to 5.6) over 24 weeks (moderate CoE).[2]
- Most of the new cohort studies evaluated patients receiving TIMs for either PsO or PsA.[2] Only one cohort study evaluated TIMs used to treat PsO and no cohort studies just evaluated PsA. When used to managed PsO or PsA, one cohort study found a lower risk of hospitalization for serious infections for ustekinumab compared with adalimumab (HR 0.62; 95% CI 0.56 to 0.76) and infliximab (HR 2.3; 95% CI 1.9 to 2.8) with no difference with certolizumab pegol (HR 1.09; 95% CI, 0.68 to 1.75; very low CoE).[2] Another cohort study reported similar results; fewer serious infections with ustekinumab (HR 0.59; 95% CI 0.39 to 0.90) compared with TNF inhibitors in patients treated for PsO or PsA (very low CoE).[2] A French cohort study observed that compared with etanercept, the risk for serious infection was increased with adalimumab (HR 1.22; 95% CI, 1.07 to 1.38) and infliximab (HR 1.79; 95% CI, 1.49 to 2.16) and decreased for ustekinumab (HR 0.79; 95% CI, 0.67 to 0.94; very low CoE for all comparisons) when these TIMs were used to treat PsO.[2]

- In patients with PsA, the efficacy of ixekizumab, secukinumab, and upadacitinib were all superior to adalimumab for improving skin disease based on moderate CoE, but only higher doses of upadacitinib (30 mg) were superior for improving arthritis symptoms.[2]
- Few differences in harms were found between TIMs when used to treat PsA based on low to moderate CoE; however, upadacitinib had more AEs compared with adalimumab over 24 weeks (RR 1.1; 95% CI, 1.02 to 1.20; moderate CoE).[2]
- Subgroup analyses found notable differences for a comparison for PsO and a comparison for PsA:[2]
    - Guselkumab vs. secukinumab for PsO*:* guselkumab was superior to secukinumab overall and in all subgroups evaluated based on age, weight, body mass index (BMI), severity of disease, body area affected and prior medication use.[2]
    - Ixekizumab vs. adalimumab for PsA*:* ixekizumab was more effective than adalimumab for individuals with and without concomitant use of methotrexate (MTX), but this difference was not statistically significant in concomitant users of MTX.[2]

Targeted Immune Modulators Expanded Indications

- Risankizumab received expanded approval by the U.S. Food and Drug Administration (FDA) for treatment of moderately to severely active Crohn's disease.[3]
- Baricitinib received expanded approval for inpatient treatment of coronavirus disease-2019 (COVID-19) and outpatient treatment of alopecia areata.[4] Alopecia areata is not funded by the Oregon Health Plan (OHP).[5]
- Ustekinumab received expanded approval for the treatment of children aged 6 years and older with active PsA.[6]

Recommendations:

- After clinical review, no changes to the Preferred Drug List (PDL) are recommended.
- Modify prior authorization (PA) criteria to reflect updated indications for risankizumab, baricitinib, and ustekinumab.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- The TIMs for autoimmune conditions were last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the October 2021 meeting. After clinical review, no changes to the PDL were recommended. After review of costs in executive session, secukinumab was made preferred on the PDL. Prior authorization (PA) criteria were modified to reflect expanded ages and indications for FDA-approvals that occurred in 2021. The PA criteria were recently updated after the June 2022 meeting to reflect FDA approvals in the first 6 months of 2022.
- Currently, adalimumab, etanercept, and secukinumab are preferred medications on the PDL (see **Appendix 1** for PDL status of all TIMS for autoimmune conditions). All preferred and nonpreferred TIMs require PA to ensure appropriate utilization. A 3-month trial and failure of adalimumab or etanercept is required for management of AS, RA, PsO or PsA before advancing to another TIM. Current clinical PA criteria are outlined in **Appendix 3.** In the second quarter of 2022, 51% of pharmacy claims for TIMs for autoimmune conditions were for the preferred agents adalimumab, etanercept and secukinumab. For the non-preferred agents, 9% of claims were for apremilast, 9% were for tocilizumab, and 5% each were for certolizumab pegol, ustekinumab, guselkumab, tofacitinib, and anakinra. About 1-2% of claims were for abatacept, risankizumab, and canakinumab. In the first quarter of 2022, there were 56 claims for physician administered TIMs (reflects decreased utilization from 71 claims in the first quarter of 2021). The most frequent claims for physician administered drugs were for infliximab, golimumab, tocilizumab, rituximab, and vedolizumab.

Methods:

The March 2022 drug class report on TIMs for RA and AS[1] and the April 2022 drug class report on TIMs for PsO and PsA[2] by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) were 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 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.

Background:
Targeted immune modulators include biologic disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs. Biologic DMARDs are large, complex, proteins that must be administered parentally. The biologic DMARDs include tumor necrosis factor (TNF) inhibitors (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), IL antagonists (e.g., anakinra, sarilumab, tocilizumab, ustekinumab, secukinumab, brodalumab, ixekizumab, secukinumab guselkumab, risankizumab and tildrakizumab), and lymphocyte antagonists (e.g., rituximab and abatacept). FDA-approved biosimilars are available for adalimumab, etanercept, infliximab, and rituximab.[7] Targeted synthetic DMARDs are small chemical molecules that can be taken orally. The Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, and upadacitinib), and the phosphodiesterase (PDE)-4 inhibitor (apremilast) are classified as targeted synthetic DMARDs. **Table 1** summarizes the TIMs indicated for management of AS, RA, PsA, and PsO discussed in this report.

Table 1. FDA-Approved Targeted Immune Modulators for Selected Auto-Immune Diseases[8,9]

Drug – Route of Administration	Molecular Target	Approved Indication(s)
Biologic DMARDs		
Adalimumab (HUMIRA) - SC	TNF	AS, RA, PsA, PsO
Certolizumab Pegol (CIMZIA) - SC		AS, RA PsA, PsO,
Etanercept (ENBREL) - SC		AS, RA, PsA, PsO
Golimumab - (SIMPONI and SIMPONI ARIA) – SC or IV		AS, RA, PsA
Infliximab (REMICADE) - IV		AS, RA, PsA, PsO
Anakinra (KINERET) - SC	IL-1	RA
Sarilumab (KEVZARA) - SC	IL-6	RA
Tocilizumab (ACTEMRA) – IV or SC		RA
Ustekinumab (STELARA) – IV or SC	IL-12 and IL-23	PsA, PsO
Brodalumab (SILIQ) - SC	IL-17	PsO
Ixekizumab (TALTZ) - SC		AS, PsA, PsO
Secukinumab (COSYNTEX) - SC		AS, PsA, PsO
Guselkumab (TREMFYA) - SC	IL-23	PsA, PsO
Risankizumab (SKYRIZI) - SC		PsO
Tildrakizumab (ILUMYA) - SC		PsO
Abatacept (ORENCIA) - IV or SC	T-lymphocyte	RA, PsA

Rituximab (RITUXAN) - IV	B-lymphocyte	RA
Targeted Synthetic DMARDs		
Baricitinib (OLUMIANT) - PO	JAK 1,2	RA
Tofacitinib (XELJANZ)- PO	JAK 1,2,3	RA, PsA
Upadacitinib (RINVOQ) - PO	JAK 1	RA, PsA
Apremilast (OTEZLA) - PO	PDE4	PsA, PsO
Abbreviations: AS=ankylosing spondylitis; FDA=Food and Drug Administration; IL=interleukin; IV=intravenous; JAK=Janus Kinase; PDE=phosphodiesterase; PO=oral; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SC=subcutaneous; TNF=tumor necrosis factor		

Rheumatoid Arthritis and Ankylosing Spondylitis

The hallmarks of RA are inflammation of the synovial tissues with progressive erosion of bone leading to malalignment of the joint and, in most cases, disability.[10] Tumor necrosis factor plays a central role in the pathophysiology of RA.[10] The 2019 European League against Rheumatism (EULAR) recommendations suggest RA treatment begin with a conventional synthetic DMARD such as methotrexate (MTX) as soon as diagnosis of RA is established.[11] Other conventional synthetic DMARDs recommended to treat RA include sulfasalazine and leflunomide.[11] Biologic DMARDs or targeted synthetic DMARDs are recommended for patients with a suboptimal response or intolerance to conventional synthetic DMARDs.[11] Monotherapy with biologic DMARDs or targeted synthetic DMARDs or combination therapy that includes MTX can be initiated as second-line therapy, depending on the patient's response to previous therapy and any pertinent comorbidities.[11] Primary endpoints used in RA clinical trials are American College of Rheumatology (ACR) response, EULAR response, the Health Assessment Questionnaire Disability Index (HAQ-DI), and the DAS-28. Outcomes used to assess RA in clinical trials are summarized in **Appendix 2**.

Ankylosing spondylitis is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine.[12] Diagnosis is based on radiologic confirmation of sacroiliitis and the presence of at least one clinical symptom: low back pain for at least 3 months, limited lumbar spine motion, or decreased chest expansion.[13] All TNF inhibitors are proven to provide sustained improvement in patient functioning and reduced disease activity as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDI) and Functional Index (BASFI) scores.[14] More details for these 2 outcomes are presented in **Appendix 2.** Two IL-antagonists, secukinumab and ixekizumab, have also demonstrated efficacy in treating AS.[15] However, ACR/ Spondylitis Association of America (SAA) guidance recommends a TNF inhibitor as the first TIM for use after nonsteroidal anti-inflammatory drug (NSAID) therapy over secukinumab or ixekizumab.[15] Co-administration of low-dose MTX with a TNF inhibitor is not recommended for AS management.[15]

Plaque Psoriasis and Psoriatic Arthritis

Plaque psoriasis is a chronic, immune-mediated inflammatory disorder of the skin, scalp and nails that affects about 2 to 3% of the population.[16] The development of the disease is driven by multiple pathways of immune mediators, including TNF, IL-23 and IL-17 cytokines.[17] Psoriasis ranges from mild to severe disease. The severity of PsO is classified based on the percentage of body surface area (BSA) involved. Moderate PsO affects 5 to 10% of BSA; severe PsO affects more than 10% of BSA. Mild PsO (less than 5% of BSA) is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[18] Per 2017 NICE guidance, first-line agents for PsO include: topical medications including corticosteroids, vitamin D analogs (e.g., calcipotriene), retinoids (e.g., tazarotene) or calcineurin inhibitors (e.g., tacrolimus or pimecrolimus).[19] Biologics including TNF inhibitors, IL-12/23 antagonists, IL-23 antagonists, or IL-17 antagonists, may be added for patients with moderate-to-severe PsO not controlled by other therapies.[19]

Psoriatic arthritis is a disease with heterogeneous manifestations in patients who have manifest or latent psoriasis.[20] Symptoms included pain and stiffness in the affected joint, swelling, and loss of range of motion.[2] Psoriatic arthritis comprises both musculoskeletal as well as non-musculoskeletal manifestations; the latter

particularly include the skin and the nails, but also potentially the gut (inflammatory bowel disease) or the eyes (uveitis).[20] First-line treatment for PsA includes NSAIDs, although in most cases conventional synthetic DMARDs (MTX, sulfasalazine or leflunomide) are necessary.[20]

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the PASI, the static Physician's Global Assessment scale (sPGA), or the Psoriasis Symptom Inventory (PSI). There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[21] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, an improvement of 100%, indicating complete disease clearance, is considered more clinically significant.[22] Additional outcomes used to assess PsO and PsA in clinical trials are summarized in **Appendix 2.**

Summary Findings:

Targeted Immune Modulators for Rheumatoid Arthritis or Ankylosing Spondylitis

The DERP authors identified comparative RCTs with at least 12 weeks duration and cohort studies with a minimum sample size of 10,000 patients to evaluate the effectiveness and harms of TIM agents FDA-approved for the treatment of RA and AS.[1] Outcomes of interest included measures of clinical improvement (ACR20, ACR50), disease remission (ACR70), quality of life (HAQ-DI), AEs, and SAEs.[1] Descriptions of the clinical outcomes used in the RA trials are presented in **Appendix 2**. Literature was searched through July 22, 2021.[1] Nine new studies were identified for the 2022 update; one RCT in patients with AS, and 8 RCTs in patients with RA.[1] Fifty-one studies were carried forward from the previous report for a total of 60 studies.[1] Of the 60 eligible studies, 35 were RCTs and 25 were cohort studies.[1] Among the 35 RCTs, 8 RCTs were rated as high risk of bias, 3 RCTs as low risk of bias, and the others were rated as moderate risk of bias, primarily due to extensive manufacturer involvement in study design, execution, and reporting.[1] Manufacturers sponsored nearly all the RCTs.[1] Among the 25 cohort studies, one study had high risk of bias, 3 studies were at low risk of bias and the rest were evaluated as having moderate risk of bias.[1]

A. Comparative Effectiveness of TIMs as First-Line Rheumatoid Arthritis Treatments

Fifteen head-to-head comparisons provided evidence for the effectiveness of TIMs used as first-line RA treatments (i.e., no prior treatment with TIMs).[1] Two studies evaluated combination TIM treatment with TIM monotherapy.[1] All RCTs enrolled subjects with moderate-to-severe RA despite treatment with DMARDs.[1]

New Evidence:

- ***Abatacept vs. Certolizumab Pegol (n = 407); Abatacept vs. Tocilizumab (n = 392); and Certolizumab Pegol vs. Tocilizumab (n = 391):*** a single low risk-of-bias RCT was identified.[1] The Nordic Rheumatic Diseases Strategy Trials and Registries (NORD-STAR) was a multicenter, pragmatic, open-label, observer-blinded, phase 4 trial conducted at 29 sites in Denmark, Finland, Iceland, the Netherlands, and Sweden in 812 adults.[23] The NORD-STAR study compared abatacept 125 mg subcutaneously (SC) once weekly (n = 204) versus certolizumab 200 mg every 2 weeks SC (after 400 mg loading dosing x 3 doses; n = 203) versus tocilizumab 8 mg/kg every 4 weeks intravenously (IV) or 162 mg SC once weekly (n = 188) versus conventional treatment (either MTX plus oral prednisolone or oral sulfasalazine combined with hydroxychloroquine and intra-articular corticosteroids).[23] Methotrexate was given as background therapy to all patients who received a TIM.[23] Participants were treatment-naïve, with early RA (less than 2 years).[23] The primary outcome was Clinical Disease Activity Index (CDAI) less than or equal to 2.8 at 24 weeks for conventional treatment compared to the selected TIMs.[23] Secondary outcomes at 24 weeks included DAS-28 remission and EULAR response. The following results were reported by DERP authors:
    - ***Abatacept vs. Certolizumab Pegol:*** No difference in EULAR response (84.9% vs. 86.7%; p-value not reported [NR]) or remission (CDAI <2.8; 56.3% vs. 52.6%; p-value NR) at 24 weeks (moderate CoE for response and remission).[1]

- ***Abatacept vs. Tocilizumab:*** No difference in EULAR response (84.9% vs. 82.2%; p-value NR) or remission (CDAI <2.8; 56.3% vs. 48.7%, p-value NR) at 24 weeks (moderate CoE for response and remission).[1]
- ***Certolizumab Pegol vs. Tocilizumab:*** No difference in EULAR response (84.9% vs. 82%; p-value NR) or remission (CDAI <2.8; 53% vs. 49%, p-value NR) at 24 weeks (moderate CoE for response and remission).[1]

- ***Anakinra vs. TNF-Inhibitors (adalimumab, etanercept, infliximab, golimumab, or certolizumab pegol); (n = 39):*** One new, high risk-of-bias, open-label RCT was identified. The trial enrolled 39 patients with type 2 diabetes mellitus who had moderate-to-severe RA and an inadequate response to MTX.[1] Patients received weekly anakinra SC injections (n = 22) or TNF-inhibitors at unreported doses (n = 17).[1] The primary outcome was the change in percent glycated hemoglobin (Hb1c) levels.[1] No significant differences in the secondary outcomes of EULAR response (95% vs. 63%; odds ratio [OR] 1.47; 95% CI, 0.95 to 2.26) or EULAR remission (50% vs. 25%; OR 1.93; 95% CI, 0.73 to 5.10) at 24 weeks were reported (very low CoE for response and remission).[1]

Previously Reported Evidence:
No new RCTs were identified for the head-to-head comparisons listed below,[1] previous conclusions are included for context. No differences were identified for over half of the head-to-head comparisons.

- ***Abatacept vs. Adalimumab (1 RCT; n = 646):*** No differences were found in response (ACR50; 46% vs. 46%), remission (ACR70; 29% vs. 26%; p-value NR), or improvement in functional capacity (HAQ-DI; -0.60 vs.-0.58; p-value NR) at 48 weeks.[1] (Low CoE for response, functional improvement, and remission).[1]
- ***Abatacept vs. Infliximab (1 RCT; n = 431):*** No differences were found in response (ACR50; 40% vs. 37%; p-value NR) or remission (ACR70; 21% vs. 24%; p-value NR) at 24 weeks.[1] (Low CoE for response and remission).[1]
- ***Adalimumab vs. Baricitinib (1 RCT; n = 1,305):*** Adalimumab was less effective than baricitinib for achieving response (ACR20, 61% vs. 70%; p=0.01; 95% CI NR) and improvement in functional capacity (HAQ-DI ≥ 0.22, 58% vs. 68%; p<0.01; 95% CI NR) at 52 weeks.[1] No difference in remission was found (Simplified Disease Activity Index [SDAI] < 3.3; 7% vs. 8%; p-value NR).[1] (High CoE for response and functional capacity; low CoE for remission).[1]
- ***Adalimumab vs. Certolizumab Pegol (1 RCT; n = 915):*** No difference in response was found (ACR20; 71% vs. 69%; p=0.47) at 12 weeks (high CoE).[1]
- ***Adalimumab vs. Etanercept (1 RCT; n = 64);*** No differences in disease activity (DAS-28; -2.12 vs. -2.84; p-value NR) or improvement in functional capacity (HAQ-DI; 0.69 vs. 0.68; p-value NR) at 24 weeks was found (very low CoE for both outcomes).[1]
- ***Adalimumab vs. Sarilumab (1 RCT; n = 369):*** Adalimumab was less effective than sarilumab for achieving response (ACR 50, 30% vs. 46%; p=0.002; 95% CI NR), remission (CDAI, 3% vs. 7%; p=0.047; 95% CI NR), improvement in functional capacity (HAQ-DI, -0.43 vs. -0.61; p<0.005; 95% CI NR), and quality of life (Short Form 36-item Health Survey [SF-36], 6.09 vs. 8.75; p<0.001; 95% CI NR) at 24 weeks.[1] (Moderate CoE for response, functional improvement, and quality of life; low CoE for remission).[1]
- ***Adalimumab vs. Tocilizumab (1 RCT; n = 326):*** Adalimumab was less effective than tocilizumab for achieving response (ACR50, 28% vs. 47%; p<0.001; 95% CI NR) and remission (ACR70, 18% vs. 33%; p=0.002; 95% CI NR) at 24 weeks.[1] No difference in quality of life was found (SF-36; 7.6 vs. 9.2; p=0.16) at 24 weeks.[1] Tocilizumab was used at higher doses than are FDA-approved.[1] (Low CoE for all 3 measures).[1]
- ***Adalimumab vs. Tofacitinib (1 RCT; n = 1,146):*** No differences in response (ACR50, 44% vs. 46%; p-value NR), remission (ACR70, 28% vs. 31%; p-value NR), or improvement in functional capacity (HAQ-DI; -0.54 vs -0.58%; p-value NR) were found at 24 weeks.[1] (High CoE for response, remission, and functional improvement).[1]

- ***Adalimumab vs. Upadacitinib (1 RCT; n = 1,629):*** Adalimumab was less effective than upadacitinib for achieving response (ACR50, 29% vs. 45%; p<0.001; 95% CI NR), remission (DAS-28-CRP<2.6; 18% vs. 29%; p<0.001; 95% CI NR), and improvement in functional capacity (HAQ-DI, -0.49 vs. -0.60; p<0.01; 95% CI NR) at 12 weeks.[1] (High CoE for response, remission, and functional improvement).[1]
- ***Etanercept vs. Infliximab (1 RCT; n = 32):*** Etanercept achieved higher response than infliximab (ACR20, 74% vs. 60%; p-value NR) and more improved functional capacity (HAQ-DI, -32.30 vs. -21.60; p-value NR) at 54 weeks.[1] (Very low CoE for clinical improvement and functional capacity).[1]
- ***Etanercept vs. Tocilizumab (1 RCT; n = 64):*** No differences in clinical improvement (DAS-28; -2.84 vs. -2.10; p-value NR) or improvement in functional capacity (HAQ-DI 0.68 vs. 0.70; p-value NR) was found at 24 weeks.[1] (Very low CoE for clinical improvement and functional capacity).[1]
- ***Combination Therapies (2 RCTs; total n = 365):*** No additional benefits (response, remission) from the combination of etanercept with abatacept or anakinra was identified compared with etanercept monotherapy.[1] (Moderate CoE for response and remission).[1]

B. Comparative Effectiveness of TIMs as Second-Line Rheumatoid Arthritis Treatments

Six head-to-head comparisons provided evidence of TIM agents as second-line treatment for RA (i.e., at least one inadequate response to a TIM).[1] Two studies evaluated TIM combination treatment with TIM monotherapy.[1]

New Evidence:

- ***Abatacept vs. Upadacitinib:*** One multinational , double-blinded, non-inferiority, low risk-of-bias RCT (n = 613) was identified.[1] Abatacept 500 to 1,000 mg IV once a month was compared with oral upadacitinib 15 mg once daily over 24 weeks in patients with active RA and moderate-to-high disease activity with an inadequate response to a TNF-inhibitor.[1] Abatacept was less effective than upadacitinib for achieving response (DAS-28 C-reactive protein [CRP] mean change from baseline, -2.0 vs. -2.52 respectively; p<0.001; 95% CI NR) and remission (DAS-28-CRP <2.6, 13% vs. 30% respectively; p<0.001; 95% CI NR) at 24 weeks.[1] (High CoE for response; moderate CoE for remission).[1]

- ***Rituximab vs. Tocilizumab:*** One open-label, noninferiority, high risk-of-bias RCT (n = 164) was identified.[1] Rituximab 1,000 mg IV every 2 weeks was compared with tocilizumab 8 mg/kg IV once monthly in patients with RA, despite treatment with a TNF inhibitor.[1] All patients continued MTX while enrolled in the study. No difference in clinical improvement (CDAI 50% improvement; 45.2% vs. 55.7%; OR, 0.81; 95% CI 0.59 to 1.10) at 16 weeks was observed between rituximab and tocilizumab (very low CoE).[1]

Previously Reported Evidence:

No new RCTs were identified for the head-to-head comparisons listed below,[1] previous conclusions are included for context. No significant differences were identified for most of the head-to-head comparisons.

- ***Abatacept vs. TNF-Inhibitors (adalimumab, etanercept, infliximab, golimumab, or certolizumab pegol; 2 RCTs; n = 93 and 176):*** No difference in clinical improvement (DAS-28; 3.8 vs. 3.5; p-value NR) at 52 weeks (low CoE).[1]
- ***Abatacept vs. Rituximab (2 RCTs; n = 93 and 122):*** No difference in clinical improvement (DAS-28; 3.8 vs. 3.4; p-value NR) at 52 weeks (low CoE).[1]
- ***Abatacept vs. Tocilizumab (1 RCT; n = 132):*** No significant differences in clinical improvement (DAS-28; 2.8 vs. 2.5; p=0.06) or functional improvement (HAQ-DI; 1.01 vs. 0.89; p=0.56) at 24 weeks.[1] (Low CoE for both outcomes).[1]
- ***TNF-Inhibitors (adalimumab, etanercept, infliximab, or certolizumab pegol) vs. Other TIMs (abatacept, rituximab, tocilizumab); (1 RCT; n = 300):*** Non-TNF-inhibitors were more effective than TNF-inhibitors for achieving EULAR response (69% vs. 52%; OR 2.06; 95% CI, 1.27 to 3.37) and remission (DAS-28 <2.6; 27% vs. 14%; p<0.01; 95% CI NR) at 52 weeks.[1] (Low CoE for response and remission).[1]

- ***Combination Therapy (rituximab plus adalimumab or etanercept; 1 RCT, n = 54):*** Combination treatment was more effective than monotherapy for achieving response (ACR50, 12% vs. 6%; p-value NR) and remission (DAS-28 <2.6, 18% vs. 6%; p-value NR) at 24 weeks.[1] (Low COE for response and remission).[1]
- ***Combination Therapy (abatacept added to existing TIM therapy; 1 RCT, n = 167):*** No difference in functional capacity (HAQ-DI; 0.33 vs. 0.22; p-value NR) at 52 weeks (low CoE).[1]

C. Comparative Harms of TIMs When Used to Manage Rheumatoid Arthritis

Three new RCTs provided data on the overall incidence of AEs, discontinuation due to AEs, and SAEs. Seventeen head-to-head comparisons and 4 comparisons of TIM combination treatment with TIM monotherapy provided evidence for comparative harms between TIMs.[1] Overall, few differences in AE incidence, discontinuation due to AEs, or SAEs were observed in head-to-head comparisons of TIMs.[1] Twenty-five cohort studies also provided data.[1]

New Evidence (RCTs):

- ***Abatacept vs. Certolizumab pegol (1 RCT; n = 812):*** No differences between groups for overall AEs (risk ratio [RR], 0.97; 95% CI 0.88 to 1.06) or SAEs (RR, 0.58; 95% CI 0.27 to 1.24) were observed at 24 weeks.[1] (Moderate CoE for AEs; low CoE for SAEs).[1]
- ***Abatacept vs. Tocilizumab (1 RCT, n = 132; first line treatment):*** lower incidence of overall AEs for abatacept was observed versus tocilizumab (80% vs. 95%; RR 0.48 95% CI, 0.31 to 0.74) at 24 weeks.[1] No difference in SAEs (RR, 0.42; 95% CI 0.14 to 1.29) at 24 weeks was observed.[1] (Low CoE for overall AEs; very low CoE for SAEs).[1]
- ***Certolizumab Pegol vs. Tocilizumab (1 RCT, n = 812):*** lower incidence of overall AEs for certolizumab pegol was observed versus tocilizumab (83% vs. 95%; RR 0.87; 95% CI, 0.81 to 0.93) at 24 weeks.[1] No difference in SAEs (RR, 1.72; 95% CI 0.79 to 3.76) was observed at 24 weeks.[1] (Moderate CoE for overall AEs; low CoE for SAEs).[1]

Previously Reported Evidence (RCTs):

No new RCTs were identified for the head-to-head comparisons listed below,[1] previous conclusions are included for context.

- ***Abatacept vs. Adalimumab (1 RCT; n = 646*)**: No difference between groups for overall AEs (RR 1.02; 95% CI, 0.98 to 1.05) or SAEs (RR, 1.10; 95% CI, 0.69 to 1.77) was observed at 48 weeks (low CoE for AEs; very low CoE for SAEs).[1] At 96 weeks, the incidence of discontinuation due to AEs was lower for abatacept versus adalimumab (RR 0.40; 95% CI, 0.21 to 0.76; low CoE).[1]
- ***Abatacept vs. Infliximab (1 RCT, n = 321):*** fewer SAEs with abatacept were observe versus infliximab (5% vs. 12%; RR 0.45; 95% CI, 0.20 to 0.99) at 24 weeks.[1] No difference in overall AEs (RR 0.97; 95% CI, 0.88 to 1.07) was found at 24 weeks.[1] (Low CoE for SAEs; moderate CoE for overall AEs).[1]
- ***Abatacept vs. Tocilizumab (1 RCT, n = 812; second-line treatment):*** lower incidence of overall AEs for abatacept versus tocilizumab (28% vs. 60%; RR 0.84; 95% CI, 0.78 to 0.92) at 24 weeks.[1] No difference in SAEs (RR, 1.00; 95% CI 0.42 to 2.41) was observed at 24 weeks.[1] (Low CoE for overall AEs; very low CoE for SAEs).[1]
- ***Adalimumab vs. Baricitinib (1 RCT, n = 817):*** fewer SAEs with adalimumab were observed versus baricitinib (4% vs. 8%; RR 0.50; 95% CI, 0.27 to 0.93) at 52 weeks.[1] No difference in overall AEs (RR 0.97; 95% CI, 0.90 to 1.05) was observed at 52 weeks.[1] (Low CoE for SAEs; high CoE for overall AEs).[1]
- ***Adalimumab vs. Certolizumab pegol (1 RCT; n = 915):*** No difference between groups for overall AEs (RR 0.98; 95% CI, 0.91 to 1.05) or SAEs (RR 0.85; 95% CI, 0.61 to 1.19) was observed at 12 weeks.[1] (High CoE for AEs; low CoE for SAEs.)
- ***Tocilizumab vs. Sarilumab (1 RCT, n = 202):*** No differences in overall AEs (RR 0.94; 95% CI, 0.75 to 1.18) or SAEs (RR 1.17; 95% CI, 0.31 to 4.32) were observed at 24 weeks.[1] (Low CoE for overall AEs; very low CoE for SAEs).[1]
- ***Combination Therapies vs. Monotherapy (3 RCTs):***

- ***Anakinra plus Etanercept vs. Etanercept monotherapy (1 RCT; n = 244):*** No differences in SAEs (RR 1.98; 95% CI, 0.37 to 10.48) or overall AEs (RR 1.06; 95% CI, 0.97 to 1.15) observed over 24 weeks (moderate CoE).[1]
- ***Abatacept plus other TIMs vs. TIM monotherapy (1 RCT, n = 167):*** No differences in SAEs (RR 1.79; 95% CI, 0.85 to 3.75) or AEs (RR 1.07; 95% CI 0.97 to 1.18) observed when abatacept plus other TIMs (adalimumab, anakinra, etanercept, or infliximab) were compared with other TIMs alone over 52 weeks (low CoE).[1]
- ***Rituximab plus Adalimumab or Etanercept vs. Adalimumab or Etanercept Monotherapy (1 RCT, n = 54):*** No difference in overall AEs (94% vs. 83%; RR, 1.13; 95% CI 0.90 to 1.41) observed for combination rituximab with TNF-inhibitor (adalimumab or etanercept) compared with adalimumab monotherapy or etanercept monotherapy (low CoE).[1] SAEs were not estimable due to no events in 1 or both groups.[1]

Data from Cohort Studies

- ***Mortality:*** One retrospective cohort study (n = 20,922) found no difference in all-cause mortality for tocilizumab compared with abatacept (adjusted hazard ratio [HR] 0.99; 95% CI 0.62 to 1.60).[1]
- ***Serious Infections:*** Ten observational studies provided data on the comparative risk of serious infections associated with TIMs when used to treat RA.[1] Definitions of serious infections included deaths, hospitalizations, and use of IV antibiotics associated with infections.[1]
    - One comparative study evaluated abatacept, rituximab, tocilizumab, tofacitinib and TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab).[1] Infliximab was associated with the highest incidence of serious infections.[1]
    - The largest cohort study (n = 130,000) from 3 U.S. databases compared tofacitinib, TNF inhibitors, abatacept and tocilizumab.[1] Risk of serious infections was higher for tofacitinib versus etanercept (HR 1.41; 95% CI, 1.15 to 1.73).[1] No differences were identified between tofacitinib and other TNF inhibitors (adalimumab, certolizumab pegol golimumab, and infliximab) or tocilizumab and abatacept.[1]
    - Another observational study (n = 49,000) reported no differences in serious infections for tocilizumab compared with TNF inhibitors (HR 1.05; 95% CI, 0.95 to 1.16).[1] A higher risk of serious infections was noted with tocilizumab versus abatacept (HR 1.40; 95% CI, 1.20 to 1.63).[1]
    - A British cohort study (n = 19,000) reported the incidence of serious infections was higher with tocilizumab compared with etanercept (HR 1.22; 95% CI, 1.02 to 1.47), but lower when etanercept was compared with certolizumab pegol (HR 0.75; 95% CI, 0.58 to 0.97).[1] No differences were identified when etanercept was compared with infliximab, adalimumab, or rituximab.[1]
- ***Tuberculosis:*** Three retrospective studies reported on the comparative risk of tuberculosis in patients taking TIMs.[1] The evidence was collected from British and Swedish registries.[1]
    - The British registry (n = 10,000) provided data on patients treated with adalimumab, etanercept, or infliximab.[1] A comparative analysis showed increased risk of tuberculosis with adalimumab compared with etanercept (adjusted incidence rate ratio [RR] 4.2; 95% CI, 1.4 to 12.4).[1]
    - Another study based on British registry data found lower incidence of tuberculosis for patients receiving rituximab (12 events per 100,000 patient years) compared with those treated with TNF inhibitors (65 events per 100,000 patient years; HR 0.16; 95% CI, 0.04 to 0.67).[1]
    - Data from Swedish registries (n = 10,800) compared the risk of tuberculosis for abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab.[1] The crude incidence rates for tuberculosis per 100,000 person-years were numerically highest for infliximab (67.2; 95% CI, 29.0 to 132.4), followed by adalimumab (52.4; 95% CI, 19.2

to 114.1), rituximab (29.0; 95% CI, 0.7 to 161.7), and etanercept (15.7; 95% CI, 3.2 to 46.0).[1] No cases of tuberculosis were reported in patients treated with abatacept, anakinra, certolizumab pegol, golimumab, and tocilizumab.[1] Adjusted hazard ratios did not detect any statistically significant differences in the risk for tuberculosis among any of the treatments.

- ***Opportunistic Infections:*** Three cohort studies provided data on opportunistic infections.[1]
    - An American study included patients with different autoimmune diseases treated with TNF inhibitors. An analysis of 24,384 patients treated for RA indicated a higher incidence of nonviral opportunistic infections for infliximab than etanercept (HR 2.9; 95% CI, 1.5 to 5.4).[1] In the same study, no differences were reported between adalimumab and etanercept (HR 1.8; 95% CI, 0.8 to 4.0).[1]
    - Another study (n = 69,000) reported no differences for TNF inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab) compared with tocilizumab (HR 0.52; 95% CI, 0.17 to 1.65) or rituximab (HR 0.96; 95% CI, 0.62 to 1.50).[1] In general, the number of opportunistic infections was low (134 per 100,000 patient-years).[1] The most common infections were from herpes (n = 54), *Pneumocystis jirovecii* (n = 15), and *Legionella* (n = 11).[1]
- ***Varicella Zoster:*** Five observational studies provided evidence on the comparative risk of varicella zoster virus infections (herpes zoster, chicken pox, or shingles).[1]
    - Three cohort studies found the numerically highest risk for herpes zoster in patients treated with tofacitinib.[1] The largest of these studies (n = 130,000) analyzed data from 3 U.S. databases.[1] A higher risk of herpes zoster was found for tofacitinib versus other TIMs: adalimumab (aHR 1.99; 95% CI, 1.63 to 2.43); certolizumab pegol (aHR 2.24; 95% CI, 1.68 to 2.99); etanercept (aHR 2.12; 95% CI, 1.73 to 2.58); golimumab (aHR, 1.84; 95% CI 1.35 to 2.50); infliximab (aHR 1.94; 95% CI, 1.51 to 2.50); tocilizumab (aHR 2.14; 95% CI, 1.53 to 2.99); or abatacept (aHR 1.94; 95% CI, 1.53 to 2.44).[1]
    - Another study (n = 58,000) assessed the risk for herpes zoster and herpes simplex in patients treated with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib.[1] Abatacept was used as the reference drug for all comparisons.[1] Compared with abatacept, risk for herpes infection was higher for tofacitinib (HR 1.40; 95% CI, 1.09 to 1.81).[1] Risks of all other drugs did not differ from the risk associated with abatacept.[1] Only 74 patients treated with tofacitinib had a herpes zoster or herpes simplex infection.[1]
    - A smaller study (n = 10,019) observed higher risk of herpes zoster with tofacitinib (HR 2.16; 95% CI, 1.09 to 4.28), tocilizumab (HR 1.98; 95% CI, 1.06 to 3.68), and rituximab (HR 1.82; 95% CI, 1.02 to 3.24) compared with abatacept.[1] The overall number of events was low.[1]
- ***Malignancies***: One large observational study pooled data from 3 U.S. databases and no found no significant difference or the risk of malignancy for tocilizumab compared with abatacept.[1]
- ***Nonmelanoma and Melanoma Skin Cancer:*** One publication reported on the incidence of nonmelanoma skin cancers for patients receiving adalimumab, etanercept, or infliximab.[1] The risk of basal cell carcinoma did not differ between these drugs.[1]
- ***Cardiovascular Events and Congestive Heart Failure:*** Three studies reported on the comparative risks of cardiovascular events:[1]
    - The largest study (n = 47,000) used data from Medicare patients with RA.[1] The retrospective study assessed the risk of cardiovascular events in patients treated with abatacept compared with adalimumab, certolizumab pegol, etanercept infliximab, rituximab, tocilizumab, and golimumab. Etanercept (HR 1.33; 95% CI, 1.01 to 1.76) and infliximab (HR 1.30; 95% CI 1.03 to 1.64) were associated with higher risks of myocardial infarction compared with abatacept (moderate CoE).[1]

- In another analysis, no differences were found between tocilizumab and abatacept (HR 0.82; 95% CI, 0.55 to 1.22) for the incidence of composite cardiovascular endpoint of hospitalization due to myocardial infarction or stroke.[1] The number of events in this study was low (tocilizumab n=32; abatacept n=112).[1]
- One retrospective study with high risk of bias did not detect differences in incident heart failure between etanercept and infliximab.[1]

- ***Gastrointestinal Perforations:*** Two retrospective cohort studies examined the comparative risk for gastrointestinal perforations.[1] Both studies showed a higher incidence of lower gastrointestinal perforation in patients using tocilizumab compared with any TNF inhibitor (HR 2.51; 95% CI, 1.31 to 4.80; RR 4.0; 95% CI, 1.1 to 14.1).[1] However, one study did not find differences between the drugs in any perforation within the entire gastrointestinal tract.[1] Only 16 to 23 cases of lower gastrointestinal perforations occurred in this study.[1]
- ***Venous Thromboembolism:*** One cohort study (n = 87,653) provided data on the incidence of venous thromboembolism (VTE), a composite of pulmonary embolism or deep venous thrombosis).[1] Overall, 365 cases of VTE were diagnosed in 80,879 patients treated with a TNF-inhibitor (incidence rate 0.48 per 100 person-years) and 29 in 6,744 patients receiving the JAK inhibitor tofacitinib (incidence rate 0.55 per 100 person-years).[1] In propensity score weighted analysis, no difference was found for the incidence of VTE for tofacitinib versus any TNF inhibitor.

  Data from long-term extension trials resulted in an FDA advisory warning for the use of tofacitinib at a higher dose (10 mg twice daily) due to an increased risk of VTE.[24] In September 2021, the FDA issued a drug safety communication warning providers and patients about the increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors (i.e., tofacitinib, upadacitinib, baricitinib) used to treat RA, PsA, and ulcerative colitis.[25]

D. Comparative Effectiveness of TIMS for Ankylosing Spondylitis Treatments

One new open-label, high risk of bias, head-to-head comparison of etanercept versus infliximab (n = 50) was identified for the treatment of AS.[1] Enrolled participants had not responded to NSAIDs and were naïve to treatment with DMARDs or TIMs.[1] Etanercept 50 mg once weekly was compared to infliximab 5 mg/kg at weeks 0, 2, 6, and every 6 weeks over 102 weeks.[1] After 12 weeks, fewer participants on etanercept than on infliximab achieved ASAS 40 response (43% vs. 55%; p-value NR). Etanercept was less effective for clinical improvement compared with infliximab (BASDAI, 5.9 vs. 4.8; p<0.005; 95% CI NR) at 12 weeks (very low CoE).[1] Overall AEs or SAEs were not reported.[1]

E. Comparative Harms of TIMS for Ankylosing Spondylitis Treatment

In the previous DERP report, one high risk of bias RCT was identified that reported on general tolerability of TIMs when used to treat AS in 50 patients over 102 weeks.[1] The study had no discontinuations due to AEs, but overall AEs and SAEs were not reported.[1] No eligible cohort studies or RCTs were identified to evaluate comparative harms of TIMs when used for AS treatment.[1]

F. Differences In Effectiveness or Harms by Subgroup Analysis

No studies were identified to address the research question focused on differences in effectiveness or harms by subgroup analysis based on specific demographic characteristics in patients with RA or AS (age, race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease).[1]

<u>Targeted Immune Modulators for Plaque Psoriasis or Psoriatic Arthritis</u>

The DERP authors identified comparative RCTs with at least a 12 week duration and cohort studies with a minimum sample size of 1,000 subjects to evaluate the effectiveness and harms of TIMs FDA-approved for the treatment of PsO and PsA.[2] Literature for the DERP report was searched through August 25, 2021.[2] Eighteen new studies were identified and 33 studies were carried forward from the previous DERP report focused on TIMs for management of PsO and PsA.[2] Of the included studies, 40 were RCTs and 11 were cohort studies.[2] Forty-two studies evaluated TIMs for treatment of PsO and 9 studies focused on TIMs for PsA.[2] Three RCTs and 2 cohort studies were rated as high risk of bias; the rest of the studies were evaluated as moderate risk of bias, primarily because of extensive manufacturer involvement in study design, execution, and reporting.[2] Outcomes of interest included measures of clinical improvement and disease remission (PASI, PGA, ACR), quality of life (DLQI,HAQ), AEs and SAEs.[2] Outcomes of interest are described in more detail in **Appendix 2**. When the statistical analysis was not reported by the original authors, the DERP team calculated risk ratios and associated confidence intervals based on data provided in the study.[2]

A. Comparative Effectiveness of TIMs for Plaque Psoriasis

Eighteen head-to-head comparisons were conducted in patients with PsO.[2] Most of the studies enrolled patients with a history of at least 6 months of moderate-to-severe PsO.[2] Four new RCTs and 5 new cohort studies were identified for this updated DERP report.[2] One RCT comparing etanercept with infliximab was rated as high risk of bias due to insufficient blinding and switching of treatments.[2] The DERP authors rated the rest of the RCTs as moderate risk of bias.[2]

New Evidence

- ***Certolizumab pegol vs. Etanercept (1 RCT; n = 502 without placebo arm):*** Higher dose of certolizumab pegol (400 mg) was more effective than etanercept for clinical improvement (PASI 75: 66.7% vs. 53.3%; calculated RR 1.2; 95% CI, 1.04 to 1.5).[2] No differences between lower dose of certolizumab (200 mg) and etanercept for clinical improvement (PASI 75: 61.3% vs. 53.3%; statistics NR because primary comparison was vs. placebo).[2] (Moderate CoE for both outcomes).[2]
- ***Ixekizumab vs. Guselkumab (1 RCT; n = 1,027):*** Ixekizumab was more effective than guselkumab for disease remission (PASI 100: 41% vs. 25%; calculated RR 1.7; 95% CI, 1.4 to 2.0; high CoE) at 12 weeks.[2] No differences were noted between ixekizumab and guselkumab for disease remission at 24 weeks (PASI 100: 50% vs. 52%; calculated RR 0.96; 95% CI, 0.85 to 1.1; high CoE).[2]
- ***Ixekizumab vs. Secukinumab (1 RCT; n = 54):*** No differences were noted between ixekizumab and secukinumab for disease remission at 24 weeks (PGA 0 or 1: 85.7% vs. 84.6%; calculated RR 1.01; 95% CI, 0.81 to 1.3; moderate CoE).[2]
- ***Risankizumab vs. Secukinumab (1 RCT, n = 327):*** No difference in disease remission at 16 weeks (PASI 90: 73.8% vs. 65.6%; ARD, 8.2%; 95% CI -2.2 to 18.6). At 52 weeks, risankizumab was more effective that secukinumab (PASI 90: 86.6% vs. 57.1%; ARD, 29.8; 95% CI 20.8 to 38.8; moderate CoE).[2]

Previously Reported Evidence

No new RCTs were identified for the head-to-head comparisons listed below,[2] previous conclusions are included for context. Orange text indicates the intervention was significantly less effective than the comparison and blue text indicates the intervention was significantly more effective than the comparison.[2]

- ***Apremilast vs. Etanercept (1 RCT; n = 250):*** Apremilast 30 mg twice daily was compared with etanercept 50 mg once weekly. The etanercept dose is the standard labeled dose in Europe, but it is less than the recommended FDA dose (twice weekly for 3 months, followed by 50mg once a week).[2] No difference in clinical improvement (PASI 75: 40% vs. 48%; p=0.26) at 16 weeks was observed (low CoE).[2]
- ***Brodalumab vs. Ustekinumab (2 RCTs; n = 1,831 and n = 1881):*** Two large RCTs (AMAGINE-2 and AMAGINE-3) contributed data for this head-to-head comparison.[2] Brodalumab was more effective for achieving disease remission compared with ustekinumab (PASI 100: 44% vs. 22%; p<0.001; 95% CI NR [AMAGINE-2 results] and 37% vs. 19%; p<0.001; 95% CI NR [AMAGINE-3 results]) at 12 weeks (high CoE).[2]

- ***Etanercept vs. Infliximab (1 RCT; n = 50):*** Etanercept was less effective than infliximab for achieving clinical improvement (PASI 75: 35% vs. 72%; p=0.01; 95% CI NR) at 24 weeks (very low CoE).[2]
- ***Etanercept vs. Ixekizumab (2 RCTs; n = 1,224 and n = 1,346):*** Etanercept was less effective than ixekizumab for achieving clinical improvement (PASI 75: absolute risk differences [ARDs], 34% to 47%) and for improving quality of life (proportion of subjects achieving DLQI 0 or 1: ARDs, 20% to 30%) at 12 weeks.[2] (High CoE for both outcomes).[2]
- ***Etanercept vs. Secukinumab (1 RCT; n = 1,306):*** Etanercept was less effective than secukinumab for achieving clinical improvement (PASI 75: 44% [etanercept] vs. 77% [secukinumab 300 mg] vs. 67% [secukinumab 150 mg]; p<0.001 for both secukinumab doses vs. etanercept; 95% CI NR) at 12 weeks (high CoE).[2] Etanercept was less effective than secukinumab for improving quality of life (mean change DLQI : -7.9 [etanercept] vs. -10.4 [secukinumab 300 mg] vs. -9.7 [secukinumab 150 mg]); p-value NR at 12 weeks (moderate CoE).[2] Etanercept was less effective than secukinumab for maintaining disease remission at 52 weeks (PASI 75 : 73% [etanercept] vs. 84%; p<0.001 [secukinumab 300 mg]; vs. 82%; p<0.009 [secukinumab 150 mg]; high CoE).[2]
- ***Etanercept vs. Ustekinumab (1 RCT; n = 903):*** Etanercept was less effective than ustekinumab for achieving clinical improvement (PASI 75: 57% [etanercept] vs. 74%; p=0.01 [ustekinumab 90 mg] vs. 68%; p<0.001 [ustekinumab 45 mg]) at 12 weeks; moderate CoE).[2]
- ***Guselkumab vs. Adalimumab (3 RCTs; n = 251; n = 663; n = 744):*** Guselkumab was more effective than adalimumab for disease remission (PGA 0 or 1: ARD range, 16% to 28%; high CoE) and improving quality of life at 16 weeks (DLQI 0 or 1: ARD range 13 to 15%; moderate CoE).[2]
- ***Guselkumab vs. Secukinumab (1 RCT; n = 1,048):*** Guselkumab was more effective than secukinumab for disease remission (PASI 90: 84% vs. 70%; p<0.001; 95% CI NR) at 48 weeks (moderate CoE).[2] Guselkumab was noninferior to secukinumab for a clinical improvement at a combined endpoint that included 12 and 48 weeks (PASI 75: 85% vs. 80% p<0.001 for noninferiority; p=0.06 for superiority; CoE NR).
- ***Ixekizumab vs. Ustekinumab (1 RCT; n = 302):*** Ixekizumab was more effective than ustekinumab for disease remission at 12 weeks (PASI 90: 73% vs. 42%; p<0.001; 95% CI NR) and at 52 weeks (PASI 90: 77% vs. 59%; moderate CoE for both time intervals).[2] Ixekizumab was more effective than ustekinumab for improving quality of life at 12 weeks (DLQI 0 or 1: 61% vs. 45%; p=0.01) and at 52 weeks (DLQI 0 or 1: 71% vs. 57%; p-value NR; moderate CoE for both time intervals).[2]
- ***Risankizumab vs. Adalimumab (1 RCT; n = 605):*** Risankizumab was more effective than adalimumab for disease remission (PASI 90: 72% vs. 47%; p-value NR) and quality of life (DLQI 0 or 1: 66% vs. 49%; p<0.001) at 16 weeks.[2] (Moderate CoE for both outcomes).[2]
- ***Risankizumab vs. Ustekinumab (3 RCTs; n = 166; n = 506; n = 393):*** Risankizumab was more effective than ustekinumab for disease remission (PASI 90: ARD range 28% to 37%) and improving quality of life (DLQI 0 or 1: ARD range 19% to 23%) at 12 to 16 weeks.[2] (Moderate CoE for both outcomes).[2]
- ***Secukinumab vs. Ustekinumab (2 RCTs; n = 676 and n = 1,102):*** Secukinumab was more effective than ustekinumab for disease remission at 16 weeks (PASI 90: ARDs 21% to 22%) and 52 weeks (PASI 90: ARDs 14% to 13%) at 16 weeks.[2] (High CoE for both time frames).[2]
- ***Tildrakizumab vs. Etanercept (1 RCT; n = 934):*** Tildrakizumab was more effective than etanercept for clinical improvement at 12 weeks (PASI 75: 66%; p<0.001 [tildrakizumab 200 mg] vs. 61%; p=0.001 [tildrakizumab 100 mg] vs. 48% [etanercept]).[2] (High CoE).[2]

B. Comparative Harms of TIMs When Used To Manage Plaque Psoriasis

All the RCTs that evaluated efficacy also reported on harms of TIM agents; few differences in harms for TIMs were reported in head-to-head comparisons.[2] Five cohort studies were new to the updated DERP report.[2] One new cohort study was rated as high risk of bias, the rest were evaluated as moderate risk of text indicates the intervention was more harmful than the comparison and blue text indicates the intervention was significantly less harmful.[2]

New Evidence (RCTs)

- ***Certolizumab 200 mg and 400 mg vs. Etanercept (1 RCT; n= 502 without placebo arm):*** No significant differences in AEs between etanercept and certolizumab pegol (200 mg: RR 1.02; 95% CI, 0.81 to 1.3 and 400 mg: RR 1.06; 95% CI, 0.85 to 1.3) SAEs (200 mg: RR 1.02; 95% CI, 0.06 to 16.1 and 400 mg: RR 4.0; 95% CI, 0.45 to 35.6), or withdrawals due to AEs (200 mg: RR 0.25; 95% CI, 0.03 to 2.3 and 400 mg: RR 0.25; 95% CI, 0.03 to 2.2) over 12 weeks (moderate CoE for all reported harms at both doses).[2]
- ***Ixekizuamb vs. Guselkumab (1 RCT; n = 1,027):*** Higher risk of injection-site reactions for ixekizumab than guselkumab (RR 3.4; 95% CI, 2.1 to 5.6) over 24 weeks. No significant differences in AEs (RR 1.1; 95% CI, 0.99 to 1.2), SAEs (RR 1.1; 95% CI, 0.6 to 2.1), or withdrawals due to AEs (RR 1.8; 95% CI, 0.8 to 4.3) over 24 weeks (moderate CoE for all harms).[2]
- ***Ixekizumab vs. Secukinumab (1 RCT; n = 54):*** No significant differences in AEs (RR 1.04; 95% CI, 0.71 to 1.5), SAEs (none reported), or withdrawals due to AEs (none reported) over 24 weeks (moderate CoE).[2]
- ***Risankizumab vs. Secukinumab (1 RCT; n = 327):*** No significant differences in AEs (RR 1.002; 95% CI, 0.87 to 1.2), SAEs (RR 1.5; 95% CI, 0.54 to 4.1), or withdrawals due to AEs (RR 0.98; 95% CI, 0.06 to 15.07) over 52 weeks (moderate CoE).[2]

Previously Reported Evidence (RCTs)

This section describes findings where at least one statistically significant difference was observed in AEs, SAEs, or specific serious harms.[2]

- ***Apremilast vs. Etanercept (1 RCT; n = 250):*** Higher incidence of AEs apremilast compared with etanercept (71% vs. 53%; calculated RR 1.3; 95% CI, 1.05 to 1.7; low CoE) over 16 weeks.[2] No difference in SAEs (RR 1.5; 95% CI, 0.26 to 0.87) over 16 weeks (very low CoE).[2]
- ***Etanercept vs. Secukinumab (1 RCT; n = 1,306):*** Higher risk of injection-site reactions for etanercept than secukinumab 300 mg dose (11% vs. 1%: RR 14.9; 95% CI, 6.7 to 33.2) over 52 weeks.[2] No significant differences in AEs, SAEs, or withdrawals due to AEs (moderate CoE for all harms).[2]
- ***Etanercept vs. Tofacitinib (1 RCT; n = 1,106):*** Higher incidence of withdrawal due to AEs for etanercept than tofacitinib 5 mg twice daily (3% vs. 1%; RR 3.6; 95% CI, 1.01 to 12.8) over 12 weeks.[2] No significant differences in overall AEs or SAEs for either tofacitinib 5 mg or 10 mg twice daily moderate CoE for all harms).[2]
- ***Guselkumab vs. Adalimumab (3 RCTs; n = 251, n = 663, and n=744):*** Lower incidence of injection-site reactions with guselkumab compared to adalimumab over 16 weeks reported in 2 RCTs (RR 0.7; 95% CI, 0.01 to 0.33 and RR 0.38; 95% CI, 0.19 to 0.74; moderate CoE).[2] No significant differences in AEs, SAEs, or withdrawals due to AEs (moderate CoE for all harms).[2]
- ***Risankizumab vs. Ustekinumab (3 RCTs; n = 166, n = 506, n = 393):*** One RCT reported no significant differences in AEs or SAEs.[2] Two RCTs reported some differences, but not across all time periods evaluated.[2] In one RCT, fewer AEs were observed for risankizumab compared with ustekinumab over 17 to 52 weeks (RR 0.75; 95% CI, 0.11 to 0.77; low CoE).[2] In another RCT, fewer SAEs were observed with risankizumab compared with ustekinumab over 0 to 16 weeks (RR 0.29; 95% CI, 0.11 to 0.66; low CoE).[2]
- ***Tildrakizumab vs. Etanercept (1 RCT):*** Fewer overall AEs for tildrakizumab versus etanercept during weeks 13 to 28 (RR 0.80; 95% CI, 0.68 to 0.93); fewer AEs for the 100 mg tildrakizumab dose, but not the 200 mg dose during weeks 0 to 12 (moderate CoE).[2] No difference in incidence of SAEs during either time period (low CoE).[2]

Data from Cohort Studies

Most of the recent cohort studies evaluated patients receiving TIMs for either PsO or PsA. Only one cohort study evaluated TIMs used to treat PsO and no observational studies focused just on PsA.

- One cohort study (n = 123,383) reported a significantly lower risk of hospitalization for serious infection for ustekinumab compared with adalimumab and infliximab with no difference compared with certolizumab pegol (very low CoE) when used to manage PsO and PsA.[2] Additional data from this study is summarized below.
    - ***Certolizumab pegol vs. Ustekinumab:*** No differences in the incidence of serious infection (HR 1.09; 95% CI, 0.68 to 1.75; very low CoE).[2]
    - ***Infliximab vs. Ustekinumab:*** Higher incidence of serious infection with infliximab (HR 2.3; 95% CI 1.9 to 2.8; very low CoE).[2]
    - ***Ixekizumab vs. Infliximab:*** Lower incidence of serious infection with ixekizumab compared with infliximab (HR 0.46; 95% CI, 0.27 to 0.77; very low CoE).[2]
    - ***Secukinumab vs. Adalimumab:*** Lower incidence of serious infection with secukinumab compared with adalimumab (HR 0.77; 95% CI, 0.62 to 0.96; very low CoE).[2]
    - ***Secukinumab vs. Infliximab:*** Lower incidence of serious infection with secukinumab compared with infliximab (HR 0.53; 95% CI 0.41 to 0.68; very low CoE).[2]
    - ***Ustekinumab vs. Adalimumab:*** Fewer serious infections with ustekinumab compared with adalimumab (HR 0.70; 95% CI, 0.49 to 1.00; very low CoE).[2]
- In another cohort study (n = 11,560), fewer serious infections with ustekinumab (HR 0.59; 95% CI 0.39 to 0.90; very low CoE) compared with TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) in patients treated for PsO and PsA.[2]
- A French cohort study (n = 44,239) observed that compared with etanercept, the risk for serious infection was increased with adalimumab (HR 1.22; 95% CI, 1.07 to 1.38) and infliximab (HR 1.79; 95% CI, 1.49 to 2.16) and decreased for ustekinumab (HR 0.79; 95% CI, 0.67 to 0.94; very low CoE for all comparisons) when these TIMs were used to treat PsO.[2] In the same study, no statistically significant differences were observed on the outcome of serious infections for etanercept compared with apremilast, brodalumab, certolizumab pegol, guselkumab, ixekizumab, and secukinumab (very low CoE).[2] Additional data from this study is summarized below.
    - ***Certolizumab pegol vs. Ustekinumab:*** Higher incidence of serious infection for certolizumab pegol compared with ustekinumab (HR 1.45; 95% CI, 1.03 to 2.04).[2]
    - ***Apremilast vs. Infliximab:*** Lower incidence of serious infection for apremilast compared with infliximab (HR 0.46; 95% CI, 0.34 to 0.63; very low CoE).[2]
    - ***Certolizumab pegol vs. Infliximab:*** Lower incidence of serious infection for certolizumab pegol compared with infliximab (HR 0.64; 95% CI, 0.46 to 0.91; very low CoE).[2]
    - ***Infliximab vs. Adalimumab:*** Higher incidence of serious infection for infliximab compared with adalimumab (HR 1.47; 95% CI 1.24 to 1.74; very low CoE).[2]
- A prospective, multi-center, Spanish cohort study (n = 3,171) focused on the incidence of hepatic AEs.[2] Compared with TNF inhibitors, a higher incidence of nonalcoholic fatty liver disease was observed for users of ixekizumab or secukinumab (adjusted incidence rate ratio [IRR] 4.16; 95% CI, 1.36 to 12.70) and no difference for users of interleukin (IL)-23 antagonists (guselkumab, risankizumab; low CoE).[2] Overall, no statistically significant differences were reported in liver test abnormalities or overall hepatic AEs for IL-17 antagonists and IL-23 antagonists compared with TNF inhibitors (very low CoE).[2]

C. Comparative Effectiveness of TIMs for Psoriatic Arthritis

Six head-to-head comparisons provided data for the effectiveness of TIMs in PsA.[2] Three RCTs provided new evidence.[2] All studies enrolled patients with active PsA.[2] Two RCTs were rated as high risk of bias for various critical methodological flaws, the rest of the studies had moderate risk of bias because of extensive manufacturer involvement in study design, execution and reporting.[2]

New Evidence

- ***Ixekizumab vs. Adalimumab (1 RCT, n = 566):*** The primary outcome for this RCT was simultaneous ACR50 and PASI 100 at 24 weeks. The proportion of participants achieving clinical improvement was greater in the ixekizumab group compared with the adalimumab group (36% vs. 28%; RR 1.3; 95% CI, 1.01 to 1.60; moderate CoE).[2]
- ***Secukinumab vs. Adalimumab (1 RCT; n = 853):*** No difference in arthritis clinical improvement at 52 weeks (ACR 20: calculated RR 1.1; 95% CI, 0.98 to 1.20).[2] Larger clinical improvement in skin disease with secukinumab compared with adalimumab (PASI 90: calculated RR 1.5; 95% CI, 1.3 to 1.7; moderate CoE for both outcomes).[2]
- ***Upadacitinib vs. Adalimumab (1 RCT; n = 1,281):*** At 12 weeks, a larger proportion of participants showed arthritis improvement with upadacitinib 30 mg compared with adalimumab (ACR 20: 78.5% vs. 65%; calculated RR 1.2; 95% CI, 1.1 to 1.3), but no differences were observed between adalimumab versus upadacitinib 15 mg (moderate CoE).[2]

Previously Reported Evidence

- ***Adalimumab vs. Etanercept or Infliximab (1 RCT; n = 100):*** No difference in ACR20 response at 1 year (adalimumab: 70%; etanercept: 72%; infliximab: 75%; p-value NR; very low CoE).[2]
- ***Adalimumab vs. Tofacitinib 10 mg and 5 mg (1 RCT; n = 422):*** No differences between adalimumab and tofacitinib 10 mg or tofacitinib 5 mg in ACR20 response at 1 year (adalimumab: 60%; tofacitinib 10 mg: 70%; tofacitinib 5 mg: 68%; p-value NR; low CoE).[2]
- ***Ixekizumab vs. Adalimumab (1 RCT; n = 417):*** No difference between adalimumab compared with ixekizumab administered every 2 or 4 weeks in ACR20 response at 24 weeks (adalimumab: 57%; ixekizumab every 2 weeks: 62%; ixekizumab every 4 weeks: 58%; p value NR; low CoE).[2]
- ***Ustekinumab vs. TNF inhibitors (specific TNF inhibitors not reported; 1 RCT; n = 47):*** At 24 weeks, a higher proportion of participants achieved enthesitis remission with ustekinumab compared with TNF inhibitors (Spondyloarthritis Research Consortium of Canada Enthesitis Index [SPARCC EI]: 74% vs 42%; p=0.02; 95% CI NR) and skin disease remission (PASI 100: 50% vs. 29%; p=0.04; 95% CI NR), but not arthritis remission (tender joint count: 54% vs. 46%; p=0.78; swollen joint count: 59% vs. 46%; p=0.38; very low CoE for all outcomes).[2]

D. Comparative Harms of TIMs When Used to Manage Psoriatic Arthritis

All of the RCTs included for efficacy assessment also reported harms observed with TIMs when used to treat PsA.[2] Few differences in harms were observed (very low to moderate CoE) for overall AEs and SAEs.[2] No new cohort studies were identified that just focused on harms of TIMs when used to manage PsA.[2]

New Evidence

- ***Ixekizumab vs. Adalimumab (1 RCT, n = 566):*** Fewer SAEs, but more injection site reactions with ixekizumab versus adalimumab.[2] No statistically significant differences in overall AEs, or withdrawals due to AEs were observed (moderate CoE for all harms).[2]
- ***Secukinumab vs. Adalimumab (1 RCT; n = 853):*** Less withdrawals due to AE reported with secukinumab compared with adalimumab (4% vs. 7%; RR 0.53; 95% CI, 0.30 to 0.94) over 52 weeks. Injection site reactions were also less frequent with secukinumab vs. adalimumab (4% vs. 11%; RR 0.36; 95% CI, 0.21 to 0.62).[2] No statistically significant differences in overall AEs and SAEs were observed (moderate CoE for all harms).[2]

- ***Upadacitinib vs. Adalimumab (1 RCT; n = 1,281):*** More AEs observed with upadacitinib versus adalimumab over 24 weeks (RR 1.1; 95% CI, 1.02 to 1.20; moderate CoE); no difference in SAEs was reported (RR 1.6; 95% CI, 0.9 to 3.0; low CoE).[2]

Previously Reported Evidence

- ***Adalimumab vs. Etanercept or Infliximab (1 RCT; n = 100):*** Fewer AEs were observed with adalimumab versus etanercept (RR 0.38; 95% CI, 0.17 to 0.84); fewer AEs were observed with adalimumab versus infliximab (RR 0.23; 95% CI, 0.11 to 0.49); and more AEs were observed with infliximab versus etanercept over 12 months (RR 1.6; 95% CI, 1.1 to 2.4; very low CoE for all comparisons).[2]
- ***Adalimumab vs. Tofacitinib 10 mg and 5 mg (1 RCT; n = 422):*** No statistically significant differences in AEs, SAEs, or withdrawals due to AEs over 12 months (moderate CoE for all harms).[2]
- ***Ixekizumab vs. Adalimumab (1 RCT; n = 417):*** Injection site reactions were more frequently reported with ixekizumab versus adalimumab (13.9% vs. 2%; RR 0.14; 95% CI, 0.03 to 0.59) over 24 weeks. No statistically significant differences in overall AEs, SAEs, or withdrawals due to AEs (moderate CoE for all harms).[2]

E. Differences In Effectiveness or Harms by Subgroup Analysis

Relevant subgroup analyses were available for 3 comparisons for PsO and 1 comparison for PsA.[2]

- ***Brodalumab vs. Ustekinumab for PsO:*** No differences in comparative efficacy or safety in post hoc subgroup analysis of patients with BMI less than 30 kg/m^2 versus those with BMI 30 kg/m^2 and greater.[2]
- ***Guselkumab vs. Secukinumab for PsO:*** Guselkumab was superior to secukinumab overall and in all subgroups evaluated based on age, weight, BMI, severity of disease, body area affected and prior medication use.[2]
- ***Tildrakizumab vs. Etanercept for PsO:*** No differences in comparative efficacy for participants with metabolic syndrome compared with those without metabolic syndrome.[2]
- ***Ixekizumab vs. Adalimumab for PsA:*** Ixekizuamb was more effective than adalimumab for individuals with and without concomitant use of MTX, although the difference was not statistically significant in concomitant users.[2]

New Indications:

May 2022: Baricitinib (OLUMIANT) received FDA approval for treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).[4] The recommended dose for COVID-19 is 4 mg orally once daily for up to 14 days.[4] Inpatient treatment is not subject to prior authorization.

June 2022: Baricitinib received expanded FDA-approval for the treatment of adult patients with severe alopecia areata.[4] Alopecia areata is a chronic autoimmune disorder characterized by rapid onset of hair loss, typically on the scalp, eyebrows, and eyelashes.[26] Disorders of the hair and nails are not funded by the Health Evidence Review Commission on line 587.[5]

June 2022: Risankizumab (SKYRIZI) received expanded FDA-approval for treatment of moderately to severely active Crohn's disease in adults.[3] Risankizumab is also approved for treatment of moderate-to-severe PsO and active PsA in adults.[3] For PsO and PsA, risankizumab is initiated at 150 mg SC every 4 weeks for 2 doses, followed by 150 mg SC every 12 weeks thereafter.[3] The risankizumab dosing for Crohn's disease is higher than the recommended dose for psoriasis. For CD, the risankizumab induction dose is 600 mg via IV infusion every 4 weeks for 3 doses. The recommended maintenance dose is 360 mg SC at week 12 after induction is completed, followed by 360 mg SC every 8 weeks thereafter.[3]

Drug induced hepatotoxicity during induction therapy for Crohn's disease with risankizumab has been reported.[3] Therefore, the manufacturer recommends obtaining liver enzymes and bilirubin prior to starting risankizumab and during induction dosing, up to 12 weeks of treatment.[3] During maintenance dosing liver enzymes should monitored according to routine patient management.[3] Other AEs reported during induction dosing for CD included: upper respiratory infections, headache and arthralgia.[3] During maintenance dosing additional AEs included: injection site reactions, abdominal pain, anemia, pyrexia, back pain, and urinary tract infections.[3]

August 2022: Ustekinumab (STELARA) received expanded approval for treatment of children aged 6 years and older with active PsA.[6] Due to the limited availability of pediatric patients with PsA for clinical trials, researchers used an extrapolation strategy based on previous pharmacokinetic, efficacy and safety observations from a closely adjacent population of children with moderate-to-severe PsO who also had active PsA, as well as adults with moderate-to-severe PsO or active PsA.[6] The safety and effectiveness of ustekinumab have not been established in pediatric patients less than 6 years old.[6]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
adalimumab	HUMIRA PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA PEN PSOR-UVEITS-ADOL HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN PEDIATRIC UC	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN PSOR-UV-ADOL HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA	SUBCUT	SYRINGEKIT	Y
adalimumab	HUMIRA(CF)	SUBCUT	SYRINGEKIT	Y
adalimumab	HUMIRA(CF) PEDIATRIC CROHN'S	SUBCUT	SYRINGEKIT	Y
etanercept	ENBREL MINI	SUBCUT	CARTRIDGE	Y
etanercept	ENBREL SURECLICK	SUBCUT	PEN INJCTR	Y
etanercept	ENBREL	SUBCUT	SYRINGE	Y
etanercept	ENBREL	SUBCUT	VIAL	Y
secukinumab	COSENTYX PEN	SUBCUT	PEN INJCTR	Y
secukinumab	COSENTYX PEN (2 PENS)	SUBCUT	PEN INJCTR	Y
secukinumab	COSENTYX (2 SYRINGES)	SUBCUT	SYRINGE	Y
secukinumab	COSENTYX SYRINGE	SUBCUT	SYRINGE	Y
abatacept	ORENCIA CLICKJECT	SUBCUT	AUTO INJCT	N
abatacept	ORENCIA	SUBCUT	SYRINGE	N
abatacept/maltose	ORENCIA	INTRAVEN	VIAL	N
anakinra	KINERET	SUBCUT	SYRINGE	N
apremilast	OTEZLA	ORAL	TAB DS PK	N
apremilast	OTEZLA	ORAL	TABLET	N
baricitinib	OLUMIANT	ORAL	TABLET	N
brodalumab	SILIQ	SUBCUT	SYRINGE	N
canakinumab/PF	ILARIS	SUBCUT	VIAL	N
certolizumab pegol	CIMZIA	SUBCUT	KIT	N
certolizumab pegol	CIMZIA	SUBCUT	SYRINGEKIT	N
golimumab	SIMPONI ARIA	INTRAVEN	VIAL	N
golimumab	SIMPONI	SUBCUT	PEN INJCTR	N
golimumab	SIMPONI	SUBCUT	SYRINGE	N
guselkumab	TREMFYA	SUBCUT	AUTO INJCT	N
guselkumab	TREMFYA	SUBCUT	SYRINGE	N
infliximab	INFLIXIMAB	INTRAVEN	VIAL	N
infliximab	REMICADE	INTRAVEN	VIAL	N
infliximab-abda	RENFLEXIS	INTRAVEN	VIAL	N
infliximab-axxq	AVSOLA	INTRAVEN	VIAL	N

infliximab-dyyb	INFLECTRA	INTRAVEN	VIAL	N
ixekizumab	TALTZ AUTOINJECTOR	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (2 PACK)	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (3 PACK)	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ SYRINGE	SUBCUT	SYRINGE	N
natalizumab	TYSABRI	INTRAVEN	VIAL	N
risankizumab-rzaa	SKYRIZI PEN	SUBCUT	PEN INJCTR	N
risankizumab-rzaa	SKYRIZI	SUBCUT	SYRINGE	N
risankizumab-rzaa	SKYRIZI (2 SYRINGES) KIT	SUBCUT	SYRINGEKIT	N
rituximab	RITUXAN	INTRAVEN	VIAL	N
rituximab-abbs	TRUXIMA	INTRAVEN	VIAL	N
rituximab-arrx	RIABNI	INTRAVEN	VIAL	N
rituximab-pvvr	RUXIENCE	INTRAVEN	VIAL	N
sarilumab	KEVZARA	SUBCUT	PEN INJCTR	N
sarilumab	KEVZARA	SUBCUT	SYRINGE	N
tildrakizumab-asmn	ILUMYA	SUBCUT	SYRINGE	N
tocilizumab	ACTEMRA	INTRAVEN	VIAL	N
tocilizumab	ACTEMRA ACTPEN	SUBCUT	PEN INJCTR	N
tocilizumab	ACTEMRA	SUBCUT	SYRINGE	N
tofacitinib citrate	XELJANZ	ORAL	SOLUTION	N
tofacitinib citrate	XELJANZ XR	ORAL	TAB ER 24H	N
tofacitinib citrate	XELJANZ	ORAL	TABLET	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
ustekinumab	STELARA	INTRAVEN	VIAL	N
ustekinumab	STELARA	SUBCUT	SYRINGE	N
ustekinumab	STELARA	SUBCUT	VIAL	N
vedolizumab	ENTYVIO	INTRAVEN	VIAL	N

Appendix 2: Selected Outcomes Used for Assessment of Disease Progression in Clinical Trials[27,28]

Ankylosing Spondylitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Level of symptoms: 1. Fatigue 2. Pain in hips, back and neck 3. Pain in joints other than hips, back or neck 4. Discomfort in areas tender to touch or pressure Mean measurements of: 5. Intensity of morning stiffness 6. Duration of morning stiffness (0 to 2 hours scored on a 0-10 scale)	VAS scale 0-10: 0 is no symptoms, 10 is very severe BASADI score calculation: 1.Add scores for first 4 questions 2. Add one half of the sum of question 5 and 6 3. Divide the result by 5 A BASDI score ≥ 4 (on a scale of 0-10) indicates active disease that warrants consideration of therapy
BASDI 50	- ≥ 50% improvement in BASDAI	
Bath Ankylosing Spondylitis Functional Index (BASFI)	Severity of 10 functional abilities: 1. Putting on socks 2. Bend from the waist to pick up a pen from the floor 3. Reaching up to a high shelf 4. Getting up from an armless chair 5. Getting up off the floor 6. Standing unsupported 7. Climbing 12-15 steps unaided 8. Looking over shoulder 9. Doing physically demanding activities 10. Doing a full day's activities	VAS scale 0-10: easy (0) to impossible (10) BASFI score calculation: Total all 10 items and divide by 10 for final score Reported as change in score from baseline
Assessment of Spondyloarthritis International Society (ASAS) Response	Combines measures of symptoms and disability in 4 disease measures: 1. Spinal inflammation (BASDI questions 5 and 6) 2. Spinal pain 3. Patient global assessment of spondylitis 4. Functional impairment (BASFI score)	Scale of 0-10: 0 is no symptoms, 10 is very severe
ASAS 20	- Improvement of ≥ 20% and ≥ 1 unit in ≥ 3 of disease measures above - No worsening of ≥ 20% and ≥ 1 unit in remaining unimproved measure	Assessment of response to therapy by percent in symptom improvement
ASAS 40	- Improvement of ≥ 40% and ≥ 2 units in ≥ 3 of disease measures above	
ASAS Partial Remission	- No worsening at all in remaining measure	Value of ≤ 2 in each of the 4 domains

	• Reflects low disease activity	
Ankylosing Spondylitis Disease Activity Score (ASDAS)	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement
Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score (DAS)-28	Clinical assessment of disease activity in combination with an acute phase reactant level 1. Assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. General health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2- with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst)
CDAI (Clinical Disease Activity Index)	A clinical composite index composed of the sum of: • Swollen joint count (0-28) • Tender joint count (0-28) • Patient's global score of disease activity (0-10) • Investigator's global score (0-10)	0 to 76, lower scores are better CDAI remission ≤ 2.8

American College of Rheumatology (ACR)
 	
ACR 20
 	
ACR 50
 	
ACR 70
	Definition of improvement in RA symptoms
	
	• 20% improvement in tender and swollen joint counts
	• 20% improvement in 3 of 5 remaining ACR core set measures
	  ○ patient global assessment (VAS score)
	  ○ physician global assessment (VAS score)
	  ○ self-reported physical disability (HAQ score)
	  ○ an acute phase reactant (ESR or CRP)
	  ○ patient pain assessment (VAS score)
	
	• 50% improvement in tender and swollen joint counts
	• 50% improvement in 3 of 5 remaining ACR core set measures
	
	• 70% improvement in tender and swollen joint counts
	• 70% improvement in 3 of 5 remaining ACR core set measures
		
		20% improvement
		
		50% improvement
		
		70% improvement

European League Against Rheumatism (EULAR)	• A good response is defined as reaching a DAS of 2.4 or a DAS28 of 3.2 (low disease activity) in combination with an improvement > 1.2 in DAS or DAS28. • A nonresponse is defined as an improvement of 0.6 and also as an improvement of 1.2 with a DAS > 3.7 or other DAS28 > 5.1 (high disease activity).	Lower is better
Simplified Disease Activity Index (SDAI)	A sum of 5 outcome parameters • Tender and swollen joint count • Patient and physician global assessment of disease activity and level of C-reactive protein) used to monitor activity	0 to 86, lower is better
Short Form 36 (SF-36)	Measure of general level of well-being, consists of 8 domains reflecting 8 dimensions of life: • Physical functioning • Physical role • Bodily pain • General health • Vitality • Social functioning • Emotional role • Mental health	0 to 100, higher is better
Plaque Psoriasis and Psoriatic Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**

Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1
Psoriasis Area and Severity Index (PASI) PASI 75 PASI 90	Measure of overall psoriasis severity and coverage on head, upper extremities, trunk and lower extremities • Erythema • Induration • Scaling 75% Improvement in PASI score 90% Improvement in PASI score – clear or almost clear skin	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments

Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little, 2 a lot, and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effect on patient's life 6 – 10 moderate effect on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life
Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale		

Targeted Immune Modulators for Autoimmune Conditions

Goal(s):

- Restrict use of targeted immune modulators to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Table 1. Approved and Funded Indications for Targeted Immune Modulators

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo			aGVHD ≥ 2 yo
Adalimumab (HUMIRA) and biosimilars	≥18 y	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥5 yo (Humira) ≥18 yo (biosimilars)		Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo			NOMID DIRA
Apremilast (OTEZLA)				≥18 yo	≥18 yo				Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo			COVID ≥ 18 yo (hospitalized) Severe alopecia areata is unfunded; coverage may be considered

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
									under comorbidity rule
Brodalumab (SILIQ)				≥18 yo					
Canakinumab (ILARIS)			≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo Stills Disease
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo			Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥4 yo (biosimilars)	≥18 yo	≥18 yo			
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo		≥2 yo active polyarticular course		≥2 yo	≥18 yo	≥18 yo (Simponi)		
Guselkumab (TREMFYA)				≥18 yo	≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab (TALTZ)	≥ 18 yo			≥6 yo	≥18 yo				Nr-axSpA ≥ 18 yo
Risankizumab-rzaa (SKYRIZI)		≥18 yo		≥18 yo	≥ 18 yo				
Rituximab (RITUXAN) and biosimilars						≥18 yo			CLL ≥18 yo DLBCL≥6 mo BL≥6 mo BLL≥6 mo B-AL≥6 mo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yo Pemphigus Vulgaris ≥18 yo (Rituxan only)
Sarilumab (KEVZARA)						≥18 yo			
Secukinumab (COSENTYX)	≥18 yo			≥6 yo	≥2 yo				ERA ≥ 4 yo Nr-AxSpA ≥18 yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Tildrakizumab-asmn (ILUMYA)				≥18 yo					
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo			CRS ≥2 yo GCA ≥18 yo SSc-ILD ≥18 yo
Tofacitinib (XELJANZ)	≥18 yo		≥2 yo active polyarticular course		≥18 yo	≥18 yo	≥18 yo		
Upadacitinib (RINVOQ)	≥18 yo				≥18 yo	≥18 yo	≥18 yo	≥ 12 yo	
Ustekinumab (STELARA)		≥ 18 yo		≥6 yo	≥6 yo		≥18 yo		
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo		

Abbreviations: aGVHD = acute Graft Versus Host Disease; BD = Behcet's Disease; BL = Burkitt Lymphoma; BLL = Burkitt-like Lymphoma; B-AL = mature B-cell acute leukemia; CLL = Chronic Lymphocytic Leukemia; COVID = Covid-19 infection; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; DLBCL = Diffuse Large B-Cell Lymphoma; ERA = Enthesitis-Related Arthritis; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; mo = months old; MPA = Microscopic Polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; Nr-axSpA = Non-Radiographic Axial Spondyloarthritis; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

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

Approval Criteria		
3. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?* *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to # 4	**No:** Pass to RPh. Deny; medical appropriateness. If patient meets all other criteria, pharmacist may approve once for up to 3 months to allow time for screening for ongoing therapy to avoid interruptions in care.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives. Go to #6	**No:** Go to # 6
6. Is the request for a FDA-approved medication with a corresponding diagnosis listed in the "Other" column of table 1?	**Yes:** Approve for length of treatment.	**No:** Go to # 7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to # 8	**No:** Go to # 9

Approval Criteria		
8. Is this a request for a preferred agent OR if the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® branded product or an Enbrel® branded product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to # 10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; OR • Hand, foot, face, or mucous membrane involvement?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); AND • At least one other topical agent: calcipotriene, tazarotene, anthralin; AND • Phototherapy; AND • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; AND • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for a drug FDA-approved for atopic dermatitis as defined in Table 1? Note: only *severe* atopic dermatitis is funded by the OHP.	**Yes:** Go to # 13	**No**: Go to #15
13. Is the atopic dermatitis severe in nature, which has resulted in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; <u>or</u> • Hand and, foot, face, or mucous membrane involvement?	**Yes:** Go to # 14	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
14. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide), AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole), AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
15. Is the diagnosis rheumatoid arthritis, juvenile idiopathic arthritis, or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 16	**No:** Go to # 19

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

Approval Criteria		
20. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90-day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198.	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness**.**
21. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 22	**No:** Go to # 24
22. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Go to #23	**No:** Pass to RPh. Deny; medical appropriateness.
23. Is the request for risankizumab?	**Yes:** Go to #24	**No:** Go to # 25
24. Have baseline liver enzymes and bilirubin been obtained?	**Yes:** Go to #25 Document Labs and Date Obtained: LFTs: _____ Bilirubin: _____ _____	**No:** Pass to RPh. Deny; medical appropriateness

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

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

Renewal Criteria		
3. Have the patient's symptoms improved with upadacitinib therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started, OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started, OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 5	**No:** Go to # 6
5. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: • a reduction of 25% or more in the total abscess and inflammatory nodule count, AND • no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Implementation: *TBD; 7/1/22; 1/1/22; 1/1/2021; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*

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 Literature Scan: Colony Stimulating Factors

Date of Review: October 2022

Date of Last Review: June 2021
Literature Search: 01/01/2021 – 06/09/2022

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

Conclusions:
- Two new biosimilar products were approved by the Food and Drug Administration (FDA) since the last review.
- Guidelines from the National Cancer Care Network (NCCN) continue to recommend granulocyte colony stimulating factor (G-CSF) products for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[1]

Recommendations:
- No PDL changes recommended based on the clinical evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- Evidence for this class was last evaluated in June 2021. There are no class specific prior authorization criteria beyond preferred and non-preferred status. 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.
- Previous evidence summaries concluded no compelling differences in efficacy or harms between G-CSF products.[2] G-CSF products are recommended for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[2] Evidence is generally of moderate quality for these indications.
- The number of patients with claims (pharmacy or medical) for G-CSF products is relatively small in the fee-for-service only population and most products 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.

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 literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched

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

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

New Systematic Reviews:
No new high quality systematic reviews were identified.

After review, 11 systematic reviews were excluded due to poor quality,[3-10] wrong study design of included trials (e.g., observational),[11] comparator (e.g., no control, comparison which was not FDA-approved),[12,13] or outcome studied (e.g., non-clinical).

New Guidelines:
No new guidelines were identified.

Guidelines from the National Cancer Care Network on the use of hematopoietic growth factors were revised in December 2021 (version 1.2022).[1] However, major recommendations regarding use of colony stimulating factors remain unchanged since the prior review.[2] Guidelines note that any FDA-approved biosimilar is an appropriate substitute for the originator. Guidelines continue to recommend prophylactic use of G-CGF in patients with high risk for febrile neutropenia (>20%) and to consider use in patients with intermediate risk (10-20%) based on individual factors.[1]

New Formulations:
Releuko® (filgrastim-ayow), a new biosimilar for filgrastim, was FDA approved in March 2022 for prophylaxis and treatment of neutropenia.[14]

Fylnetra® (pegfilgrastim-pbbk), a new biosimilar for pegfilgrastim, was FDA approved in May 2022 for prevention of febrile neutropenia in patients with non-myeloid malignancies receiving cancer treatment.[15]

Approval of these products was based on data demonstrating that they were highly similar to the reference product. Neither of these products have FDA-approval for mobilization of progenitor cells for stem cell transplant.

New FDA Safety Alerts:
None identified.

References:

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2. 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. .
3. Mahtani R, Crawford J, Flannery SM, Lawrence T, Schenfeld J, Gawade PL. Prophylactic pegfilgrastim to prevent febrile neutropenia among patients receiving biweekly (Q2W) chemotherapy regimens: a systematic review of efficacy, effectiveness and safety. *BMC cancer.* 2021;21(1):621.
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5. Li H, Wang G, Wen X, Zhou L. Systematic review and meta-analysis of clinical efficacy of drug therapy for acute myelogenous leukemia. *Annals of palliative medicine.* 2021;10(7):7884-7893.
6. Hoshina H, Takei H. Granulocyte-colony stimulating factor-associated aortitis in cancer: A systematic literature review. *Cancer treatment and research communications.* 2021;29:100454.
7. Lapidari P, Vaz-Luis I, Di Meglio A. Side effects of using granulocyte-colony stimulating factors as prophylaxis of febrile neutropenia in cancer patients: A systematic review. *Critical reviews in oncology/hematology.* 2021;157:103193.
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9. Shi P, Zhang J, Wu M, et al. The effects of granulocyte-colony stimulating factor on chronic liver disease: a meta-analysis. *Journal of infection in developing countries.* 2022;16(3):537-546.
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11. Muzzana M, Pedrazzoli P, Lasagna A. G-CSF and G-CSF-related vasculitis: a systematic review of the literature and intriguing future research perspectives. *Future oncology (London, England).* 2021;17(33):4619-4634.
12. Diaz-Navarro R, Urrutia G, Cleland JG, et al. Stem cell therapy for dilated cardiomyopathy. *The Cochrane database of systematic reviews.* 2021;7:CD013433.
13. Wang L, Xiang H, Yan Y, et al. Comparison of the efficiency, safety, and survival outcomes in two stem cell mobilization regimens with cyclophosphamide plus G-CSF or G-CSF alone in multiple myeloma: a meta-analysis. *Annals of hematology.* 2021;100(2):563-573.
14. Releuko (filgrastim-ayow) injection for subcutaneous or intravenous use [package labeling]. Piscataway, NJ: Kashiv BioSciences, LLC; February 2022.
15. Fylnetra (pegfilgrastim-pbbk) injection for subcutaneous use [package labeling]. Piscataway, NJ: Kashiv BioSciences, LLC; May 2022.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
filgrastim	NEUPOGEN	SYRINGE	IJ	Y
filgrastim	NEUPOGEN	VIAL	IJ	Y
pegfilgrastim-apgf	NYVEPRIA	SYRINGE	SQ	Y
sargramostim	LEUKINE	VIAL	IJ	Y
tbo-filgrastim	GRANIX	SYRINGE	SQ	Y
tbo-filgrastim	GRANIX	VIAL	SQ	Y
filgrastim-aafi	NIVESTYM	SYRINGE	SQ	N
filgrastim-aafi	NIVESTYM	VIAL	IJ	N
filgrastim-ayow	RELEUKO	SYRINGE	SQ	N
filgrastim-ayow	RELEUKO	VIAL	IJ	N
filgrastim-sndz	ZARXIO	SYRINGE	IJ	N
pegfilgrastim	NEULASTA ONPRO	SYR W/ INJ	SQ	N
pegfilgrastim	NEULASTA	SYRINGE	SQ	N
pegfilgrastim-bmez	ZIEXTENZO	SYRINGE	SQ	N
pegfilgrastim-cbqv	UDENYCA	SYRINGE	SQ	N
pegfilgrastim-jmdb	FULPHILA	SYRINGE	SQ	N

Appendix 2: New Comparative Clinical Trials

A total of 111 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).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to June 09, 2022

1	exp Filgrastim/	2229
2	exp Granulocyte Colony-Stimulating Factor/	16466
3	pegfilgrastim.mp.	993
4	sargramostim.mp.	240
5	tbo-filgrastim.mp.	27
6	pegfilgrastim-apgf.mp.	3
7	filgrastim-aafi.mp.	1
8	filgrastim-ayow.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	0
9	filgrastim-sndz.mp.	38
10	pegfilgrastim-bmez.mp.	1
11	pegfilgrastim-cbqv.mp.	8
12	pegfilgrastim-imdb.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	0
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	16878
14	limit 13 to (english language and humans)	12968
15	limit 14 to yr="2021 -Current"	443
16	limit 15 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	111

Appendix 4: Key Inclusion Criteria

Population	Patients with FDA-approved indications for drugs in **Appendix 1** (e.g, neutropenia, mobilization of progenitor cells for stem cell transplant)
Intervention	Drugs in **Appendix 1**
Comparator	See **Appendix 1**
Outcomes	Febrile neutropenia, symptoms, morbidity, mortality, serious adverse events
Timing	Any study duration
Setting	Inpatient or outpatient therapy

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 with New Drug Evaluation: Antiepileptics (non-injectable)

Date of Review: October 2022

Date of Last Review: Oct 2021
Dates of Literature Search: 07/30/2021 - 07/31/2022

Generic Name: ganaxolone

Brand Name (Manufacturer): Ztalmy® (Marinus)
Dossier Received: yes

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

Plain Language Summary: Is there any new evidence that would change the current policy for medicines to treat seizures?

- National Institute for Health and Care Excellence (NICE) recommend many different medicines to treat seizures.
  - Guidelines from NICE recommend medicines based on the type of seizure and the person's specific situation.
  - Most recommendations include use of one medicine at a time. But if seizures are not controlled, then more than one medicine may be prescribed by a provider.
- Ganaxolone is a new medicine the Food and Drug Administration (FDA) approved to treat a rare type of seizures, called cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD). One small study lasting 17 weeks showed that adding this medicine decreased the number of seizures by 27% compared to patients who did not take ganaxolone. People were included in the study if:
  - they were at least 2 years old, and
  - had already tried taking other medicines for seizures, and
  - continue taking their current doses of other medicines for seizures while taking ganaxolone.
- Medicaid Open Card will pay for medicines that are most often used as the first seizure treatment when prescribed by a provider. Providers must explain to the Oregon Health Authority why someone needs other medicines for seizures. This process is called prior authorization.
- The Drug Use Research Management program does not recommend any changes to this policy.

Purpose for Class Update:
To define place in therapy for the new antiepileptic drug (AED), ganaxolone, recently approved with orphan drug status by the Food and Drug Administration (FDA) for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. In addition, new comparative evidence for antiepileptic agents used in management of seizures will be reviewed.[1,2]

Author: Sara Fletcher, PharmD, MPH, BCPS

Research Questions:

1. Is there new comparative evidence that AEDs differ in efficacy or harms for management of seizures?
2. What is the effectiveness of ganaxolone in reducing seizures in people with CDD?
3. What are the comparative harms of ganaxolone in people with CDD?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which ganaxolone may be beneficial or cause more harm?

Conclusions:

- Since the last AED update, one high-quality guideline has been published. National Institute for Health and Care Excellence (NICE) issued guidelines for treatment of epilepsy in children, young people, and adults.[3] Recommendations **(table 1)** align with current preferred drug list (PDL) and prior authorization (PA) polices.
- There is low quality evidence that ganaxolone reduces the percentage of seizures during a 28-day period as add-on therapy compared to placebo in patients with CDD experiencing at least 16 major motor seizures per 28 days, who are taking up to 4 other AEDs, and have failed appropriate trials of at least 2 AEDs (median change: ganaxolone -30.7%, interquartile range [IQR] -49.5 to -1.9%; placebo -6.9%, IQR -24.1% to 39.7 %; difference -27.1%, 95% confidence interval [CI] -47.9 to -9.6).[4,5] Evidence derives from results of a single, small, fair quality trial with concerns for unclear risk of bias and inconsistency.
- There is insufficient evidence evaluating efficacy and safety for the use of ganaxolone for seizure disorders other than CDD and in adults with drug-resistant partial-onset seizures.
- The most common treatment emergent adverse event (TEAE) was sedation (ganaxolone 36% vs. placebo 16%), which may be additive with other sedating medications. Most serious TEAEs were unlikely to be related to ganaxolone and there were no deaths and few discontinuations due to TEAE (ganaxolone 4% vs. placebo 8%).[5]
- There is insufficient safety and efficacy data on ganaxolone with long-term use and in those under 2 years old. The racial and ethnic make-up of this study is not representative of the general or Medicaid population, it is unclear if this is due to disease epidemiology or reduced access to testing and diagnosis of this rare disease.

Recommendations:

- Recommend ganaxolone be non-preferred to restrict to FDA approved indication.
- Recommend change class name to “Outpatient Antiepileptics” and include new autoinjector formulation of midazolam as non-preferred.
- No other change to PDL recommended based on clinical information.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

- Current PDL placement for agents listed in **Appendix 1**.
- Certain agents in this class fall within medication carve-out for mental health medications and may have a “preferred” or “voluntary non-preferred” status.
- Current PA policies for cannabidiol, clobazam, fenfluramine, pregabalin, stiripentol, and topiramate are available in **Appendix 5**.
- Class was most recently reviewed in Oct 2021 with inclusion of 5 high-quality systematic reviews and no new guidelines. No changes were made to PA or PDL.

Background:

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) results from gene mutations on the short arm of the X-chromosome and was previously thought to be an early onset variant of Rett Syndrome.[6] These mutations are typically *de novo* and present in an estimated 1 in 40,000 to 60,000 live births. Genetic testing for the disorder is becoming more common.[2] Females with CDD are 4-fold more common than males; it is hypothesized that a CDKL5 mutation is often lethal in male fetuses.[6] Seizures are often the first symptom of CDD, and 90% experience their first seizure in the first 3 months of life, and 96.9% in the first 6 months.[6] An estimated 8-16% of females with early-onset epilepsy have a CDKL5 mutation, as well as 28% of females and 5.4% of males with early infantile epileptic encephalopathy.[6]

Seizures in patients with CDD are often refractory. Other symptoms include hypotonia, psychomotor developmental disorders, intellectual disability, and cortical vision disorders.[6] Patients with mild cases are less common, though these patients can walk, use simple sentences, and may be able to control seizures with drug therapy.[6] Severe forms are often unresponsive to drug therapy and may have microcephaly as well as other severe complications.[6] Roughly 66% of females and 35% of males can sit unsupported, and 25% of females can stand. Almost all patients have normal head circumference at birth, but 44.4% may fall below the 3rd percentile as early as 2 years.[6] Patients with CDD may experience difference seizure types and drug therapy is targeted to type.[2,6] Drug resistance is common. Patients may also be diagnosed with Lennox Gastaut syndrome or West syndrome based on seizure semiology.[2] There were no previously approved AEDs for CDD, though levetiracetam, topiramate, clobazam, and phenobarbital were the most frequently prescribed off-label.[2] Cannabis derivatives, including cannabidiol (EPIDIOLEX), have also been used based off-label in a small number of individuals, though high-quality efficacy data are lacking and 29% experienced seizure worsening.[2]

Expert opinion is often used to define minimum clinically important difference (MCID) thresholds for seizure reduction in epilepsy. There are variations among experts and in type of seizure disorder. NICE discussed a 30% reduction in seizure frequency as the minimum to continue treatment in Dravet syndrome, while a 50% reduction would be a clearer indication of benefit.[7] The FDA noted that a 50% reduction in frequency responder analysis did not align with median seizure frequency change primary endpoint in the medication under review for CDD, and that a 25% responder rate supports the biologic effect of seizures in CDD. [2]

There were fewer than 5 patients identified in the Fee-for-Service population with CDD.

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.

Systematic Reviews:
After review, 83 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).

A systematic review and meta-analysis was
New Guidelines:
High Quality Guidelines:

NICE[3]
In April 2022, National Institute for Health and Care Excellence provided guidance for epilepsies in children, young people, and adults. Recommendations for first and second line monotherapy and add-on treatment are summarized in **table 1**. Updated recommendations from a July 2022 technical appraisal report are also included.[7] Certain AED agents may exacerbate specific seizure types, and recommendations may change for patients experiencing multiple seizure types.[3] General recommendations include use of monotherapy whenever possible, and when monotherapy is unsuccessful, to carefully cross taper to attempt monotherapy with another AED.[3] Attempt add-on therapy if monotherapy is unsuccessful.[3] Treatment for epilepsy should be individualized.[3] Non-pharmacologic therapies (e.g. ketogenic diet) are included in NICE guidance though omitted as beyond the scope of this class update.

Table 1. Treatment recommendations[3]

Seizure Type	Treatment Recommendation	Population (if applicable)
Generalized Tonic-Clonic	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: lamotrigine or levetiracetam	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Add-on treatment (first-line): Clobazam, lamotrigine, levetiracetam, perampanel, sodium valproate*, topiramate.	NA
	Add-on treatment (second-line): brivaracetam, lacosamide, phenobarbital, primidone, zonisamide	
Focal Seizures with or without evolution to bilateral tonic-clonic seizures	First line monotherapy: lamotrigine or levetiracetam	NA
	Second line monotherapy: carbamazepine, oxcarbazepine, zonisamide	
	Third line monotherapy: lacosamide	
	Add-on treatment: carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, zonisamide.	
Absence seizures	First line monotherapy: ethosuximide	NA
	Second line monotherapy or add on: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children

	Second line monotherapy or add on: lamotrigine or levetiracetam	NA
Myoclonic seizures	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: levetiracetam	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Second line monotherapy or add on: levetiracetam	NA
Tonic or atonic seizures	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: lamotrigine	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Second line monotherapy or add on: lamotrigine	NA
Idiopathic generalized epilepsies	First line monotherapy: sodium valproate	• Boys and men • Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children • Women who are unable to have children
	First line monotherapy: lamotrigine or levetiracetam	• Women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children).
	Second line monotherapy or add on: lamotrigine or levetiracetam	NA
Dravet Syndrome[7]	First line monotherapy: sodium valproate	• Use with caution in women and girls, but recommended first-line due to disease severity and lack of other effective first line treatments.
	First line add-on: stiripentol and clobazam	• Triple therapy • Stiripentol may be used alone as first add on, or as second add-on if clobazam already added to sodium valproate.[7]
	Second line add-on: consider cannabidiol in combination with clobazam	• Consider only for people age 2 years and over.
	Second line add-on: fenfluramine[7]	NA
Lennox-Gastaut Syndrome	First line monotherapy: sodium valproate	• Use with caution in women and girls, but recommended first-line due to disease severity and lack of other effective first line treatments.
	Second line monotherapy or add on: lamotrigine	NA
Infantile Spasms Syndrome	First line combination: high dose prednisolone and vigabatrin	• If not due to tuberous sclerosis, and child not at high risk of steroid-related side effects. Consider vigabatrin alone.

	Second line monotherapy or add-on: levetiracetam, nitrazepam (not available in United States), sodium valproate, topiramate, non-pharmacologic therapies.	NA
Self-limited Epilepsy with Centrotemporal Spikes	First line monotherapy: lamotrigine or levetiracetam	• If unsuccessful, try the other of these options.
	Second line monotherapy: carbamazepine, oxcarbazepine, zonisamide	NA
Epilepsy with myoclonic-atonic seizures (Doose Syndrome)	First line monotherapy: levetiracetam or sodium valproate	• If unsuccessful, try the other of these options.
	Second line monotherapy or add on: consider non-pharmacologic therapy	NA
Status epilepticus (community settings)	If patient has individualized emergency management plan, administer medication according to plan	NA
	First line in community settings: Give benzodiazepine (buccal midazolam [formulation available in United Kingdom] or rectal diazepam) immediately	• If seizure does not stop within 5 to 10 minutes, call emergency services and give second dose if available.
*Except in women and girls able to have children NA = not applicable		

After review, 2 guidelines were excluded for quality and topic focus, and 1[8] was excluded because recommendations were included in later publication by the same organization.

New Formulations or Indications:
Zonisamide (ZONISADE) was approved in July 2022 as a new 100 mg/5mL suspension formulation for the treatment of partial-onset seizures in adults and pediatric patients 16 years and older.[9] Zonisamide received initial U.S. approval in 2000[9] and is also available generically as 25 mg, 50 mg, and 100 mg capsules.

Midazolam autoinjector for intramuscular use was approved in August 2022 for treatment of status epilepticus in adults. Approval was based on an active control, double-blind, double-dummy trial (N=893) of 10 mg intramuscular midazolam (using a different autoinjector) to 4 mg intravenous lorazepam administered by paramedics, with the endpoint of termination of convulsive seizure activity prior to arrival at emergency department (midazolam 73.4% vs. lorazepam 63.4%; p=0.002). Additionally, approval was based on pharmacokinetic comparison of this midazolam autoinjector to midazolam vial in healthy adults. It carries same black box warnings of other benzodiazepines for risks of concomitant use with opioids; abuse, misuse, and addiction; and dependence and withdrawal reactions. Continuous monitoring of respiratory and cardiac function is recommended.[10]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[11]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ethosuximide	Zarontin	10/2021	Warnings and Precautions	Addition of drug-induced immune thrombocytopenia
Topiramate	Multiple	1/2022	Warnings and Precautions	Addition of decrease in bone mineral density and negative effects on growth (height and weight)

Randomized Controlled Trials:
A total of 222 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). An additional 41 citations (trials and systematic reviews) were excluded for a publication date prior to July 30, 2021 (search end date from previous literature scan presented in Oct 2021).

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:
Ganaxolone (ZTALMY) is a neuroactive steroid gamma-aminobutyric acid A ($GABA_A$) receptor positive modulator which received FDA approval in March 2022 for treatment of CDD in patients 2 years and older.[1] It has a controlled substance classification of schedule V from the Drug Enforcement Agency (DEA).

Ganaxolone was evaluated in a single, double-blind, randomized, placebo-controlled, multicenter trial enrolling patients aged 2 to 21 years with a pathogenic or possibly pathogenic CDKL5 variant and at least 16 major motor seizures during both 4-week periods within a historical 8-week period and were taking up to 4 concomitant AEDs at stable doses for 1 month.[5] Major motor seizures included bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic.[5] Those meeting criteria entered a 6-week baseline period, then were randomized to adjunctive treatment with enteral ganaxolone or matching placebo. Those with various other neurological conditions, abnormal liver function, considerable renal insufficiency, or on non-AED interacting medications were excluded.[4,5] Detailed inclusion and exclusion are included in **table 5**. After randomization, a weekly weight-based titration of study agents occurred over 4 weeks, followed 13 weeks of maintenance dosing.[5] If the patient weighed 28 kg or less, the medication was initiated at 6 mg/kg/**dose** and titrated to a maximum of 21 mg/kg/**dose**, given three times a day.[5] Those over 28 kg started 150 mg three times daily and were titrated to a maximum dose of 600 mg three times daily.[5] Daily seizure frequency and type were assessed by the patient's caregiver and entered into a daily electronic diary.[5] The primary efficacy endpoint was percentage change in major motor seizure frequency at week 17 compared to the 6-week baseline period.[5] Participants were primarily female (79%) and either White (92%) or Asian (5%). The population included a small proportion of Hispanic/Latino participants (9.9%) and the median age was 6 years (IQR 3-11 years).[5]

The median percentage change in 28-day major motor seizure frequency from baseline to week 17 was greater in the ganaxolone group (-30.7%; IQR -49.5 to -1.9) when compared to placebo (-6.9%; IQR -24.1 to 39.7).[5] The difference in changes between groups was -27.1% (95% CI -47.9 to -6.6%; p=0.0036).[5]

Bias was low to unclear. While the overall population studied was small (n=101), baseline characteristics related to demographics were generally balanced. There were differences in seizure type and frequencies **(table 5)** between groups, with ganaxolone patients having a higher median and IQR for baseline seizures. Baseline use of AEDs was similar (within 5%) for most of the 23 agents reported.[2] Lamotrigine use was less common in the ganaxolone group (6% vs. 12%) and while oxcarbazepine was more common (6% vs. 0%) when compared to placebo. These were only the 9th and 10th most frequently used AED and unlikely to affect overall findings.[5] Caregiver training and consistency related to assessment of frequency and type of seizures was not described.[4,5] Additionally, sedation from ganaxolone use in some patients could potentially result in unblinding. Ganaxolone use for drug-resistant partial-seizures in the adult population

(n=405) was studied in a phase 3 trial (1042-0603, NCT01963208) and did not meet the primary efficacy endpoint in 2016, though efficacy and safety results are not available in published literature or clinicaltrials.gov.[12,13] The open-label extension was terminated.[12,13]

An open-label extension study is ongoing for long term efficacy data of ganaxolone in CDD. Efficacy and safety data are lacking in patients under 2 years of age. A study (NCT05249556) is planned for patients with CDD aged 6 months to 2 years for this important age group, given early age of onset of CDD.[14]

Clinical Safety:
Ganaxolone was generally well tolerated and there were no deaths and few discontinuations due to adverse events. Somnolence (ganaxolone 36% vs. placebo 16%) and pyrexia (ganaxolone 18% vs. placebo 8%) were the most common TEAE.[5] Somnolence and sedation are the most common adverse reactions resulting dose interruption and reduction of ganaxolone.[5] Use with other sedating agents (e.g. opioids, antidepressants, etc.) could increase side effects.[1] Use with certain cytochrome P450 inducers may decrease the serum concentration of ganaxolone and necessitate dosage adjustments, though the maximum dose should not be exceeded.[1]

There are no safety data available for people under 2 years of age. An open-label extension study beyond 17 weeks is ongoing. The most common adverse events noted in the drug labeling are detailed in **table 3**. This drug is controlled substance schedule V due to potential for abuse and dependence.

Table 3. Adverse Reactions[1]

Adverse Reaction	Ganaxolone (n=50)	Placebo (n=51)
Somnolence	38%	20%
Pyrexia	18%	8%
Upper respiratory tract infection	10%	6%
Sedation	6%	4%
Salivary Hypersecretion	6%	2%
Seasonal allergy	6%	0%
Bronchitis	4%	0%
Influenza	4%	2%
Gait disturbance	4%	2%
Nasal congestion	4%	2%

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduction in seizure frequency, duration, and/or severity
2) Improved quality of life
3) Reduction of global developmental impairment
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percentage change in major motor seizure frequency

Table 4. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	• Not fully known • Hypothesized as positive allosteric modulation of the gamma-aminobutyric acid type A ($GABA_A$) receptor in the central nervous system.
Oral Bioavailability	• Time to maximum plasma concentration (T_{max}) 2 to 3 hours. • High-fat meal increased maximum plasma concentration (C_{max}) 3-fold & area under the curve (AUC) 2-fold • Drug was administered with food during efficacy testing
Distribution and Protein Binding	99% protein bound
Elimination	55% fecal (2% unchanged) 18% renal (~0% unchanged)
Half-Life	34 hours
Metabolism	Metabolized via CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6

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
1. Knight et al.[4,5] DB, PC, Phase 3, MC, RCT	1. Ganaxolone (50 mg/mL) enterally TID 2. Placebo solution enterally TID Administered with food Titration over 4 weeks then 13 wk maintenance dosing -Max dose 63 mg/kg/day (pts ≤ 28 kg) or 1800 mg/day (pts >28 kg) -8 wk historical seizure period -6 wk prospective period to collect baseline date -17 wk DB treatment period -OL follow-up phase 1:1 randomization	Demographics: -Female: 79% -Median age: 6 years (range 3-11) -Median previous anti-Sz meds: 7 -Median current anti-Sz meds: 2 -White 92% -Asian 5% -Hispanic/Latino 9.9% -Concomitant Sz meds Valproate 33.7% Levetiracetam 25.7% Clobazam 24.8% Vigabatrin 21.8% -Baseline 28 d major motor sz frequency Median (IQR) 1. 54.0 (31.3-147.3) 2. 48.2 (18.7-120.0) -Seizure types Bilateral tonic 1. 71% 2. 76% Generalized tonic-clonic 1. 49% 2. 39% Atonic 1. 18% 2. 24% Bilateral clonic 1. 12% 2. 6% Focal to bilateral tonic-clonic 1. 14% 2. 12% Key Inclusion Criteria: -2 to 21 years -molecularly confirmed CDKL5 variant -hx of early-onset seizures uncontrolled despite trial of ≥2 antiseizure medications	ITT: 1. 50* 2. 51 Attrition: 1. 2 (4.0%) 2. 4 (7.8%)	Primary Endpoint: % change in major motor seizure frequency (28 day median value) from 6 week baseline assessment 1. -30.7% 2. -6.9 % Difference – 27.1% (95% CI, -47.9 to -9.6) p-value=0.0036 Secondary Endpoints: Proportion of patients with ≥ 50% reduction in major motor seizure frequency from baseline 1. 12/49 (24%) 2. 5/51 (10%) Difference 14.7% (95% CI, -4.7 to 33.8) p-value=0.064	NA NS	Outcome Death: 1. 0 2. 0 Serious TEAE: 1. 6 (12%) 2. 5 (10%) Any TEAE: 1. 43 (86%) 2. 45 (88%) Discontinuation due to TEAE: 1. 2 (4.0%)† 2. 4 (7.8%) Dose reduction or temporary discontinuation due to TEAE: 1. 11 (22%) 2. 8 (16%) Most frequent TEAE: Somnolence 1. 18 (36%) 2. 8 (16%) Pyrexia 1. 9 (18%) 2. 4 (8%) TRAE: 1. 35 (70%) 2. 22 (43%) Most frequent TRAE: Somnolence 1. 17 (34%) 2. 3 (6%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized centrally via interactive web response system. Baseline characteristics generally balanced, higher baseline median and IQR seizure frequency in ganaxolone group. Performance Bias: (Low) Identical taste and appearance of ganaxolone and placebo. Detection Bias: (Unclear) Staff, patients, caregivers, investigators, and sponsor masked to treatment randomization. Parent/caregiver maintained electronic daily seizure calendar. Parent/caregiver training for seizure identification and type not described. Possible unblinding secondary to side effects. Attrition Bias: (Low) Minimal and balanced attrition. Method for analyzing missing data not described. Reporting Bias: (Unclear) Phase 3 trial in different epilepsy population with negative outcomes unpublished.[12,13] Other Bias: (unclear) Sponsor contributed to study design, data collection, data analysis, data interpretation, data verification, and writing of the report. **Applicability**: Patient: Rare disease. Racial and ethnic makeup not reflective of Medicaid population. Intervention: Appropriate based on earlier phase testing. Comparator: Placebo. No standard comparator available. Outcomes: Appropriate. Longer term outcomes needed. Setting: 39 outpatient clinics (Australia, France, Israel, Italy, Poland, United Kingdom, United States [41.6%])

		-≥16 major motor sz per 28 d in each 4 wk period of 8 wk historic period before screening -up to 4 concomitant antiseizure medications with stable dosing for at least 1 mo before screening (exception: felbamate stable x6 mo) -Note: vagus nerve stimulation, ketogenic diet, modified Atkins diet do not count toward anti-sz medication limit but must be stable x3 mo before screening <u>Key Exclusion Criteria</u>: -West Syndrome -Sz of predominantly infantile spasm type -active CNS infx, demyelinating dz, degenerative neurologic dz, CNS dz deemed progressive via brain imaging -abnormal liver function -eGFR < 30 ml/min -use of adrenocorticotropic hormone or systemic corticosteroid -THC or CBD positive without Rx for EPIDIOLEX -moderate or strong inducers/inhibitors of cytochrome P450 3A4, 3A5, 3A7 *except* anti-sz medication (e.g. carbamazepine, phenytoin)				Seizure 1. 4 (8%) 2. 4 (8%)		

<u>Abbreviations</u>: ARR = absolute risk reduction; CBD = cannabidiol; CDKL5 = cyclin-dependent kinase-like 5 protein; CGI-I = Clinical Global Impression of Improvement; CI = confidence interval; CNS = central nervous system; d = days; DB = double-blind; dz = disease; eGFR = estimated glomerular filtration rate; hx = history; IQR = interquartile range; infx = infection; ITT = intention to treat; MC = multi-country; mITT = modified intention to treat; mo = month; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; OL = open-label; PC = placebo controlled; PP = per protocol; pts = patients; RCT = randomized controlled trial; Rx = prescription; sz = seizure; TEAE = treatment-emergent adverse event; THC = tetrahydrocannabinol; TID = three times daily; TRAE = treatment-related adverse event; wk = week
*one patient missing baseline seizure frequency and excluded from seizure frequency analysis
†one additional patient discontinued due to somnolence but remained in the study

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
carbamazepine	CARBAMAZEPINE	ORAL	ORAL SUSP	Y
carbamazepine	TEGRETOL	ORAL	ORAL SUSP	Y
carbamazepine	CARBAMAZEPINE	ORAL	TAB CHEW	Y
carbamazepine	CARBAMAZEPINE ER	ORAL	TAB ER 12H	Y
carbamazepine	TEGRETOL XR	ORAL	TAB ER 12H	Y
carbamazepine	CARBAMAZEPINE	ORAL	TABLET	Y
carbamazepine	EPITOL	ORAL	TABLET	Y
carbamazepine	TEGRETOL	ORAL	TABLET	Y
diazepam	DIASTAT	RECTAL	KIT	Y
diazepam	DIASTAT ACUDIAL	RECTAL	KIT	Y
diazepam	DIAZEPAM	RECTAL	KIT	Y
divalproex sodium	DEPAKOTE SPRINKLE	ORAL	CAP DR SPR	Y
divalproex sodium	DIVALPROEX SODIUM	ORAL	CAP DR SPR	Y
divalproex sodium	DEPAKOTE ER	ORAL	TAB ER 24H	Y
divalproex sodium	DIVALPROEX SODIUM ER	ORAL	TAB ER 24H	Y
divalproex sodium	DEPAKOTE	ORAL	TABLET DR	Y
divalproex sodium	DIVALPROEX SODIUM	ORAL	TABLET DR	Y
ethosuximide	ETHOSUXIMIDE	ORAL	CAPSULE	Y
ethosuximide	ZARONTIN	ORAL	CAPSULE	Y
ethosuximide	ETHOSUXIMIDE	ORAL	SOLUTION	Y
ethosuximide	ZARONTIN	ORAL	SOLUTION	Y
gabapentin	GABAPENTIN	ORAL	CAPSULE	Y
gabapentin	NEURONTIN	ORAL	CAPSULE	Y
gabapentin	GABAPENTIN	ORAL	TABLET	Y
gabapentin	NEURONTIN	ORAL	TABLET	Y
lacosamide	LACOSAMIDE	ORAL	TABLET	Y
lacosamide	VIMPAT	ORAL	TABLET	Y
lamotrigine	LAMICTAL	ORAL	TABLET	Y
lamotrigine	LAMOTRIGINE	ORAL	TABLET	Y
lamotrigine	SUBVENITE	ORAL	TABLET	Y
levetiracetam	KEPPRA	ORAL	SOLUTION	Y
levetiracetam	LEVETIRACETAM	ORAL	SOLUTION	Y
levetiracetam	KEPPRA	ORAL	TABLET	Y
levetiracetam	LEVETIRACETAM	ORAL	TABLET	Y
levetiracetam	ROWEEPRA	ORAL	TABLET	Y
methsuximide	CELONTIN	ORAL	CAPSULE	Y
oxcarbazepine	OXCARBAZEPINE	ORAL	ORAL SUSP	Y

oxcarbazepine	TRILEPTAL	ORAL	ORAL SUSP	Y
oxcarbazepine	OXCARBAZEPINE	ORAL	TABLET	Y
oxcarbazepine	TRILEPTAL	ORAL	TABLET	Y
phenobarbital	PHENOBARBITAL	ORAL	ELIXIR	Y
phenobarbital	PHENOBARBITAL	ORAL	TABLET	Y
phenytoin	DILANTIN-125	ORAL	ORAL SUSP	Y
phenytoin	PHENYTOIN	ORAL	ORAL SUSP	Y
phenytoin	DILANTIN	ORAL	TAB CHEW	Y
phenytoin	PHENYTOIN	ORAL	TAB CHEW	Y
phenytoin sodium extended	DILANTIN	ORAL	CAPSULE	Y
phenytoin sodium extended	PHENYTEK	ORAL	CAPSULE	Y
phenytoin sodium extended	PHENYTOIN SODIUM EXTENDED	ORAL	CAPSULE	Y
primidone	MYSOLINE	ORAL	TABLET	Y
primidone	PRIMIDONE	ORAL	TABLET	Y
rufinamide	BANZEL	ORAL	TABLET	Y
rufinamide	RUFINAMIDE	ORAL	TABLET	Y
tiagabine HCl	GABITRIL	ORAL	TABLET	Y
tiagabine HCl	TIAGABINE HCL	ORAL	TABLET	Y
topiramate	TOPAMAX	ORAL	TABLET	Y
topiramate	TOPIRAMATE	ORAL	TABLET	Y
valproic acid	VALPROIC ACID	ORAL	CAPSULE	Y
valproic acid (as sodium salt)	VALPROIC ACID	ORAL	SOLUTION	Y
zonisamide	ZONISAMIDE	ORAL	CAPSULE	Y
carbamazepine	EQUETRO	ORAL	CPMP 12HR	V
lamotrigine	LAMICTAL (BLUE)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL (GREEN)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (BLUE)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (GREEN)	ORAL	TAB DS PK	V
lamotrigine	LAMOTRIGINE (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (BLUE)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (GREEN)	ORAL	TAB DS PK	V
lamotrigine	SUBVENITE (ORANGE)	ORAL	TAB DS PK	V
lamotrigine	LAMICTAL XR	ORAL	TAB ER 24	V
lamotrigine	LAMOTRIGINE ER	ORAL	TAB ER 24	V
lamotrigine	LAMICTAL ODT	ORAL	TAB RAPDIS	V
lamotrigine	LAMOTRIGINE ODT	ORAL	TAB RAPDIS	V
lamotrigine	LAMICTAL	ORAL	TB CHW DSP	V
lamotrigine	LAMOTRIGINE	ORAL	TB CHW DSP	V
lamotrigine	LAMICTAL XR (BLUE)	ORAL	TB ER DSPK	V

lamotrigine	LAMICTAL XR (GREEN)	ORAL	TB ER DSPK	V
lamotrigine	LAMICTAL XR (ORANGE)	ORAL	TB ER DSPK	V
lamotrigine	LAMICTAL ODT (BLUE)	ORAL	TB RD DSPK	V
lamotrigine	LAMICTAL ODT (GREEN)	ORAL	TB RD DSPK	V
lamotrigine	LAMICTAL ODT (ORANGE)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (BLUE)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (GREEN)	ORAL	TB RD DSPK	V
lamotrigine	LAMOTRIGINE ODT (ORANGE)	ORAL	TB RD DSPK	V
brivaracetam	BRIVIACT	ORAL	SOLUTION	N
brivaracetam	BRIVIACT	ORAL	TABLET	N
cannabidiol (CBD)	EPIDIOLEX	ORAL	SOLUTION	N
carbamazepine	CARBAMAZEPINE ER	ORAL	CPMP 12HR	N
carbamazepine	CARBATROL	ORAL	CPMP 12HR	N
cenobamate	XCOPRI	ORAL	TAB DS PK	N
cenobamate	XCOPRI	ORAL	TABLET	N
clobazam	SYMPAZAN	ORAL	FILM	N
clobazam	CLOBAZAM	ORAL	ORAL SUSP	N
clobazam	ONFI	ORAL	ORAL SUSP	N
clobazam	CLOBAZAM	ORAL	TABLET	N
clobazam	ONFI	ORAL	TABLET	N
diazepam	VALTOCO	NASAL	SPRAY	N
eslicarbazepine acetate	APTIOM	ORAL	TABLET	N
felbamate	FELBAMATE	ORAL	ORAL SUSP	N
felbamate	FELBATOL	ORAL	ORAL SUSP	N
felbamate	FELBAMATE	ORAL	TABLET	N
felbamate	FELBATOL	ORAL	TABLET	N
fenfluramine HCl	FINTEPLA	ORAL	SOLUTION	N
gabapentin	GABAPENTIN	ORAL	SOLUTION	N
gabapentin	NEURONTIN	ORAL	SOLUTION	N
gabapentin	GRALISE	ORAL	TAB ER 24H	N
gabapentin	GRALISE	ORAL	TAB24HDSPK	N
gabapentin enacarbil	HORIZANT	ORAL	TABLET ER	N
lacosamide	LACOSAMIDE	ORAL	SOLUTION	N
lacosamide	VIMPAT	ORAL	SOLUTION	N
lacosamide	VIMPAT	ORAL	TAB DS PK	N
levetiracetam	ELEPSIA XR	ORAL	TAB ER 24H	N
levetiracetam	KEPPRA XR	ORAL	TAB ER 24H	N
levetiracetam	LEVETIRACETAM ER	ORAL	TAB ER 24H	N
levetiracetam	SPRITAM	ORAL	TAB SUSP	N
midazolam	NAYZILAM	NASAL	SPRAY	N

oxcarbazepine	OXTELLAR XR	ORAL	TAB ER 24H	N
perampanel	FYCOMPA	ORAL	ORAL SUSP	N
perampanel	FYCOMPA	ORAL	TABLET	N
phenobarbital	PHENOBARBITAL	ORAL	ELIXIR	N
pregabalin	LYRICA	ORAL	CAPSULE	N
pregabalin	PREGABALIN	ORAL	CAPSULE	N
pregabalin	LYRICA	ORAL	SOLUTION	N
pregabalin	PREGABALIN	ORAL	SOLUTION	N
rufinamide	BANZEL	ORAL	ORAL SUSP	N
rufinamide	RUFINAMIDE	ORAL	ORAL SUSP	N
stiripentol	DIACOMIT	ORAL	CAPSULE	N
stiripentol	DIACOMIT	ORAL	POWD PACK	N
topiramate	TROKENDI XR	ORAL	CAP ER 24H	N
topiramate	QUDEXY XR	ORAL	CAP SPR 24	N
topiramate	TOPIRAMATE ER	ORAL	CAP SPR 24	N
topiramate	TOPAMAX	ORAL	CAP SPRINK	N
topiramate	TOPIRAMATE	ORAL	CAP SPRINK	N
topiramate	EPRONTIA	ORAL	SOLUTION	N
vigabatrin	SABRIL	ORAL	POWD PACK	N
vigabatrin	VIGABATRIN	ORAL	POWD PACK	N
vigabatrin	VIGADRONE	ORAL	POWD PACK	N
vigabatrin	SABRIL	ORAL	TABLET	N
vigabatrin	VIGABATRIN	ORAL	TABLET	N
gabapentin	NEURONTIN	ORAL	SOLUTION	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 31st, 2022

☐	1	Carbamazepine/tu [Therapeutic Use]	5227
☐	2	Diazepam/tu [Therapeutic Use]	4409
☐	3	divalproex.mp. or Valproic Acid/	13918
☐	4	Ethosuximide/tu [Therapeutic Use]	363
☐	5	Gabapentin/tu [Therapeutic Use]	345
☐	6	Lacosamide/tu [Therapeutic Use]	113
☐	7	Lamotrigine/tu [Therapeutic Use]	216
☐	8	Levetiracetam/tu [Therapeutic Use]	409
☐	9	methsuximide.mp.	103
☐	10	Oxcarbazepine/tu [Therapeutic Use]	66
☐	11	Phenobarbital/tu, th [Therapeutic Use, Therapy]	3449
☐	12	Phenytoin/tu [Therapeutic Use]	4397
☐	13	Primidone/tu [Therapeutic Use]	512
☐	14	rufinamide.mp.	325
☐	15	Tiagabine/tu [Therapeutic Use]	3
☐	16	Topiramate/tu [Therapeutic Use]	160
☐	17	Zonisamide/tu [Therapeutic Use]	54
☐	18	brivaracetam.mp.	384
☐	19	Cannabidiol/tu [Therapeutic Use]	740
☐	20	cenobamate.mp.	77
☐	21	Clobazam/tu [Therapeutic Use]	45
☐	22	eslicarbazepine.mp.	432
☐	23	Felbamate/tu [Therapeutic Use]	5
☐	24	Fenfluramine/tu [Therapeutic Use]	715

☐	25	Midazolam/tu [Therapeutic Use]	1609
☐	26	perampanel.mp.	751
☐	27	Pregabalin/tu [Therapeutic Use]	589
☐	28	rufinamide.mp.	325
☐	29	stiripentol.mp.	337
☐	30	Vigabatrin/tu [Therapeutic Use]	423
☐	31	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	34719
☐	32	limit 31 to yr="2021 -Current"	2021
☐	33	limit 32 to (adaptive clinical trial or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	350
☐	34	limit 33 to humans	344

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 12th, 2022

☐	# ▲	Searches	Results
☐	1	ganaxolone.mp.	156
☐	2	limit 1 to (english language and (clinical trial, all or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review"))	20
☐	3	limit 2 to humans	12

Appendix 3: Prescribing Information Highlights

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

ZTALMY® (ganaxolone) oral suspension, CXX [pending controlled substance scheduling]
Initial U.S. Approval: [pending controlled substance scheduling]

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

ZTALMY is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. (1)

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

- Administer ZTALMY orally three times daily with food. (2.1)
- Titrate ZTALMY gradually according to the recommended schedules. See full prescribing information. (2.1)
- Dosage for patients weighing 28 kg or less (2.1):
  - the starting dosage is 6 mg/kg three times daily (18 mg/kg/day)
  - the maximum dosage is 21 mg/kg three times daily (63 mg/kg/daily).
- Dosage for patients weighing over 28 kg (2.1):
  - the starting dosage is 150 mg three times daily (450 mg daily)
  - the maximum dosage is 600 mg three times daily (1800 mg daily).

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

Oral suspension 50 mg/mL (3)

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

None. (4)

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

- Somnolence and Sedation: Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience with ZTALMY. Concomitant use with other CNS depressants or alcohol could potentiate adverse effects. (5.1)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.2)
- Withdrawal of Antiepileptic Drugs: ZTALMY should be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. (5.3)

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

Most common adverse reactions (incidence of at least 5% for ZTALMY and at least twice the rate of placebo) are somnolence, pyrexia, salivary hypersecretion, and seasonal allergy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Marinus Pharmaceuticals, Inc. at 844-627-4687 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Cytochrome P450 inducers will decrease ganaxolone exposure. It is recommended to avoid concomitant use with strong or moderate CYP3A4 inducers; if unavoidable, consider a dosage increase of ZTALMY, but do not exceed the maximum recommended dosage. (7.1)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2022

Appendix 4: Key Inclusion Criteria

Population	People with seizures or other conditions with crossover use of anti-epileptic therapy (e.g. neuropathy).
Intervention	Antiepileptic therapy
Comparator	vs. other antiepileptic therapy (for established medications in drug class) vs. placebo (for new agent ganaxolone)
Outcomes	Reduction in seizure frequency per month
Timing	Maintenance dosing
Setting	Outpatient

Cannabidiol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cannabidiol

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 renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication AND is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5 Document current seizure frequency_____	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescribed dose greater than 25 mg/kg/day?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
6. Are baseline liver function tests (LFTs) on file (serum transaminases and total bilirubin levels)? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1? LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent LFT's documented in patient records? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?	**Yes:** Go to # 2 Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3 Document baseline and current seizure frequency_____	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 25mg/kg/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4
4. Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment[1]

Hepatic Impairment	Starting Dosage	Maintenance Dosage Range in Patients with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome (DS)	Maintenance Dosage in Patients with Tuberous Sclerosis Complex (TSC)
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 to 10 mg/kg twice daily (10 to 20 mg/kg/day)	12.5 mg/kg twice daily (25 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 to 5 mg/kg twice daily (5 to 10 mg/kg/day)	6.25 mg/kg twice daily (12.5 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 to 2 mg/kg twice daily (2 to 4 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. July 2020.

P&T/DUR Review: 10/22 (SF); 10/21 (DM); 10/20; 6/20; 3/19; 1/19
Implementation: 11/1/20; 5/1/19; 3/1/19

Clobazam

Goal(s): To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:

- 12 months

Requires PA:

Clobazam

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 renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is the patient 2 years of age or older?	**Yes:** Go to #4	**No:** Go to # 5
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a diagnosis of Dravet Syndrome and is the patient 2 years of age or older?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

Limitations of Use:

- Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut.
- National Institute for Health and Care Excellence (NICE) guidance recommends clobazam as a second line agent for management of Dravet Syndrome.[1]

1. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. nice.org.uk/guidance/cg137. Accessed July 30, 2018

P&T Review: *10/22 (SF); 10/21 (DM); 10/20; 6/20; 1/19; 3/18; 7/16; 3/15; 5/12*
Implementation: *3/1/19; 8/16, 8/12*

Fenfluramine

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Fenfluramine

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 renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have uncontrolled seizures on current baseline therapy with at least one other antiepileptic medication AND is fenfluramine intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5 Document seizure frequency_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the prescribed dose greater than 0.7 mg/kg/day or 26 mg/day OR 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
6. Is baseline echocardiogram on file that was performed within past 6 months?	**Yes:** Approve for 12 months Document results here: Date of echocardiogram_____ Results_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has an echocardiogram been obtained within the past 6 months?	**Yes:** Go to # 2 Document results here: Date of echocardiogram____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3 Document baseline and current seizure frequency_____	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 0.7mg/kg/day or 26 mg/day or greater than 0.2 mg/kg/day or 17 mg/day in patients taking stiripentol plus clobazam?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4

Renewal Criteria		
4. Is fenfluramine prescribed as adjuvant therapy and is patient adherent to all prescribed seizure medications?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *10/22 (SF); 10/21 (DM); 10/20*
Implementation: *11/1/20*

Pregabalin

Goal(s):
- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:
- 90 days to lifetime (criteria-specific)

Requires PA:
- Pregabalin and pregabalin extended release

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 this a request for renewal of a previously approved prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is the request for pregabalin immediate release?	**Yes:** Go to #4	**No:** Go to #5

Approval Criteria		
4. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to #5
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. Pregabalin formulations for specific indications based on available evidence

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	

Non-funded		
Fibromyalgia	X	

P&T Review: *10/22 (SF); 10/21 (DM); 10/20; 1/19; 7/18; 3/18; 3/17*
Implementation: *10/1/18; 8/15/18; 4/1/17*

Stiripentol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:

- Up to 12 months

Requires PA:

- Stiripentol capsules and powder for oral suspension

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 renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for the FDA approved indication of Dravet syndrome in patients 2 years of age and older taking clobazam?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is baseline white blood cell (WBC) and platelet counts on file within the past 3 months? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent WBC and platelet counts documented in patient records? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Go to #2 Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

P&T/DUR Review: 10/22 (SF); 10/21 (DM); 10/20; 6/20; 1/19
Implementation: 3/1/2019

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate 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. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime.	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime.	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP AND weight loss drugs excluded by state plan.	**No:** Pass to RPh. Go to #7

Approval Criteria	
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."

P&T Review: *10/22 (SF); 10/21 (DM); 10/20; 6/20; 5/19; 1/19; 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*

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: Multiple Sclerosis

Date of Review: October 2022

Date of Last Review: June 2021
Dates of Literature Search: 03/01/2021 – 06/23/2022

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

Plain Language Summary:

- Should the Oregon Health Authority change the current policy for multiple sclerosis (MS) medicines based on new available evidence?
- Multiple sclerosis (MS) is a condition where the body's immune system, which defends the body against disease and infection, mistakenly attacks the brain and spinal cord. This damage can cause many problems such as pins and needles pain, blurred vision, and trouble with balance and walking. These are called symptoms of MS. MS is a lifelong condition, and these symptoms can cause serious disability.
- There are several types of MS. Most people have “attacks” when new symptoms develop or existing symptoms worsen (called a relapse), followed by periods with no changes to their symptoms (called remittance). This type of MS is called relapsing-remitting MS. But some people’s symptoms may slowly and continually worsen. When symptoms change from occasional relapses to symptoms that continue to get worse over time, this is called secondary progressive MS. In primary progressive MS, people's symptoms gradually worsen over time.
- There are many medicines that the Food and Drug Administration has approved to treat MS. Medicines to treat MS include ocrelizumab, siponimod, ozanimod, and fingolimod. New evidence shows:
    - Ocrelizumab reduces the number and severity of relapses and slows the worsening of symptoms in relapsing-remitting MS and primary progressive MS. Evidence shows that ocrelizumab probably has the same side effects as interferon beta-1a. Interferon beta-1a is a medicine which is the standard treatment for MS.
    - It is not clear if siponimod is an effective treatment for people with relapsing-remitting MS, or if it causes serious side effects because the studies were pretty short. But studies of up to 6 months show that siponimod may reduce relapses and may help prevent disability of people with MS.
    - People taking siponimod, ozanimod, and fingolimod may have side effects such as a slow heart rate or high blood pressure compared to other medicines used to treat MS such as interferon beta, glatiramer acetate, or natalizumab. People taking fingolimod may also have an increased risk of unwanted infections.
- No changes are recommended for the current policy based on new evidence. Current policy is to prefer glatiramer and interferon products and not require prior authorization. Prior authorization is required for all oral medications used to treat MS, as well as ocrelizumab and natalizumab which are administered by a provider in a health care setting. Peginterferon and ofatumumab, which can be self-injected, also require prior authorization.

Purpose for Class Update:
Evidence for the comparative effectiveness of disease modifying drugs (DMDs) for MS was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in June 2021. This review examines new comparative evidence of DMDs for MS published since March 2021.

Research Questions:
1. What is the comparative effectiveness and efficacy of DMDs for management of different forms of MS?
2. Do DMDs for MS differ in harms?
3. Are there patients with MS, based on demographics characteristics (i.e., age, race, ethnicity, gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer adverse events?

Conclusions:
- Four high-quality systematic reviews,[1-4] four National Institute for Care and Excellence (NICE) guidelines,[5-8] and two Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[9,10] have been published since the previous P & T Committee review in 2021.
- A 2022 Cochrane review evaluated the benefits, harms, and tolerability of ocrelizumab in patients with relapsing-remitting MS (RRMS) and primary progressive (PPMS).[1] For patients with RRMS, ocrelizumab probably results in a large reduction in relapse rate and little to no difference in adverse events (AEs) when compared with interferon beta-1a at 96 weeks (based on moderate-certainty evidence).[1] Ocrelizumab may result in a large reduction in disability progression, treatment discontinuation caused by AEs, and may result in little to no difference in serious AEs (low-certainty evidence) in patients with RRMS.[1] For patients with PPMS, ocrelizumab probably results in a higher rate of AEs when compared with placebo for at least 120 weeks (moderate-certainty evidence).[1] Ocrelizumab may result in a reduction in disability progression and little to no difference in serious AEs and treatment discontinuation caused by AEs (based on low-certainty evidence).[1]
- A 2021 Cochrane review assessed the benefits and adverse effects of siponimod for patients diagnosed with MS.[2] There is low-certainty evidence to support use of siponimod 2 mg daily to reduce the annualized relapse and improve worsening of disability at 6 months versus placebo based on randomized controlled trials (RCTs).[2]
- A 2021 systematic review evaluated the risk of cardiovascular AEs in patients with MS treated with sphingosine-1-phosphate (S1P) receptor modulators.[3] A total of 8,157 were treated with S1P receptor modulators and 5,138 were treated with a placebo or other active DMD (interferon beta, glatiramer acetate, or natalizumab).[3] The overall rate of cardiovascular AEs was 10.9% in the S1P receptor modulator-treated group versus 4.8% in the control group (relative risk [RR] 2.21; 95% confidence interval [CI], 1.58–3.10; moderate quality evidence).[3]
- A 2021 systematic review sought to determine the risk of infection in patients with MS treated with fingolimod. Compared with the control (placebo, interferon beta, glatiramer, and natalizumab), fingolimod significantly increased the risk of infection (RR 1.16; 95% CI, 1.07 to 1.27; moderate quality evidence).[4] Fingolimod use was associated with a higher risk of lower respiratory and herpes virus infection.[4]
- There is insufficient evidence to identify subgroups of patients with MS based on specific demographic characteristics (i.e., age, race, ethnicity or gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer AEs.
- NICE recommends diroximel fumarate as a first-line DMD treatment option in adults with active RRMS (defined as 2 clinically significant relapses in the previous 2 years) if they do not have highly active or rapidly evolving severe RRMS.[5] Dimethyl fumarate is not recommended for people with highly active or rapidly evolving severe RRMS due to lack of evidence.[5]
- NICE recommends ponesimod for treating RRMS in adults with active disease defined by clinical or imaging features based on evidence that shows people who take ponesimod have fewer relapses than people who take teriflunomide.[6]

- NICE and CADTH do not recommend ozanimod for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations given the uncertainty of clinical effectiveness relative to other DMDs.[7,10]
- NICE concluded that in people with RRMS, ofatumumab reduces the number of relapses and slows disease progression when compared with teriflunomide.[8] NICE recommends ofatumumab as an option for treating RRMS in adults with active disease defined by clinical or imaging features.[8]
- CADTH recommends ofatumumab in adults with RRMS if the patient has an Expanded Disability Status Scale (EDSS) score of less than 6 and evidence of active disease.[9]

Recommendations:
- No changes to the Preferred Drug List (PDL) based on clinical evidence are warranted.
- Compare medication costs in the executive session.

Summary of Prior Reviews and Current Policy:
- At the June 2021 P&T Committee meeting, evidence for ofatumumab, ponesimod and other DMDs for MS was reviewed. Clinical prior authorization (PA) criteria was updated to include both medications.
- The PDL status of MS drugs is presented in **Appendix 1**. During the second quarter of 2022, 5 fee-for-service (FFS) patients had pharmacy claims processed for MS drugs. All of the claims were for the nonpreferred medications fingolimod (32%), dimethyl fumarate (11%), ofatumumab (21%), and peginterferon beta-1A (21%).

Background:
Multiple sclerosis is a chronic, immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination, and neuronal destruction which results in progressive, irreversible disability.[11] Common neurological manifestations of MS include optic neuritis, diplopia, sensory loss, limb weakness, gait ataxia, loss of bladder control, and cognitive dysfunction.[11] The mean age of diagnosis is 32 years, with most patients presenting with periodic neurological relapses.[11,12] One to two decades after onset, many patients with MS enter a progressive phase of the disease.[11] The prevalence of MS worldwide is approximately 36 per 100,000 people and more commonly impacts women (female to male sex distribution of nearly 2:1).[12] In 2020, the estimated number of people with MS was estimated as 2.8 million.[12] Greater sun exposure and higher vitamin D levels are postulated to protect against MS.[11] North Africa, sub-Saharan Africa, Latin America, Asia, Oceania, and the Middle East have the lowest incidence of MS.[11] The populations with the highest prevalence of MS are at higher latitudes including North America and Western Europe.[11]

Diagnosis of MS is based on a combination of history, examination, radiographic findings (e.g., MRI), and laboratory findings (e.g., cerebrospinal fluid–specific oligoclonal bands), which are components of the 2017 McDonald Criteria.[13] The diagnosis of MS is defined by demonstration of MS disease characteristics in space and time.[13] Dissemination in space refers to the presence of lesions in distinct CNS locations.[13] Dissemination in time refers to the development of new lesions over time or multiple distinct clinical attacks.[13] Four distinct MS clinical courses have been identified: Clinically Isolated Syndrome (CIS), Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS), and Primary Progressive MS (PPMS).[14] Clinically Isolated Syndrome is an acute demyelinating episode lasting greater than 24 hours and is the first onset of MS symptoms. Most patients who present with CIS are eventually diagnosed with MS. Patients with RRMS have clearly defined relapses lasting 3 to 6 months with full recovery and minimal disease progression between symptomatic episodes. Relapsing-Remitting MS may be either characterized as active or not active. About 85% of patients with MS are initially diagnosed with RRMS.[15] Secondary progressive MS begins as RRMS, but gradual worsening of neurologic symptoms is observed over time.[16] After 15 to 20 years, about 65% of RRMS patients enter the secondary

progressive phase.[15] Relapsing MS includes CIS, RRMS, and active SPMS in adults. Primary progressive MS is characterized by a steady decline in neurologic function and progressive accumulation of disability without acute attacks or relapses. Approximately 10 to 15% of MS patients have PPMS, and in contrast to RRMS, symptoms typically begin in the patients' fifth or sixth decade.[17] Primary progressive MS is distributed more equally between men and women than RRMS.[17] Most clinical evidence resides with patients with relapsing forms of MS rather than progressing forms of MS.

Progression of MS is assessed by the amount of disability caused by the disease, number of relapses, and MRI activity.[13] The Expanded Disability Status Scale (EDSS) was developed to provide a standardized measure of neurological impairment in MS.[18] The EDSS ranges from 0 (normal neurologic exam) to 5 (ambulatory without aid for 200 meters) to 10 (death due to MS), with lower scores indicating more mobility and activity by the patient.[18] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[19] In addition, it is nonlinear over its range in comparison with the actual level of function and it places a much greater emphasis on ambulation status than other neurologic functions.[18] Despite these limitations, the EDSS continues to be the standard disability measure for MS clinical research. Clinical trials have defined disability progression when assessed over 3 to 6 months as an increase in EDSS of 0.5 points when the score is between 5.6 to 8.5 and 1 point when the score is between 0 and 5.5.[20] Trials with durations of at least 1 year and with 1-2 point changes in the EDSS scores may better identify patients with sustained disability.[21]

The annualized relapse rate is often included as an outcome measure for MS clinical trials because it is easy to quantify. Relapses are generally defined as neurologic symptoms lasting more than 24 hours and which occur at least 30 days after the onset of a preceding event.[20] However, the probability of relapse is not a consistent function and often decreases over time. Patients who get enrolled in a clinical trial at the time of MS diagnosis have higher probability for relapse.[20] In order to have enough power to detect a significant reduction in relapses, clinical trials may need to evaluate efficacy date for at least 1 year. It is likely more meaningful when a trial evaluates the total number of relapses over a longer period of time.[22] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[22] In addition to clinical measures, radiographic measures of disease progression include the development of new T2 lesions, enlarging T2 lesions, or both.[13]

Treatment of MS falls into three main categories: treatment of acute attacks, symptomatic therapy to improve the patient's quality of life, and treatment with DMDs to alter the natural course of the disease and reduce progressive disability over time. Acute relapses are treated with high-dose systemic corticosteroids for 3 to 5 days. Specific symptoms related to spasticity, pain, bladder dysfunction, fatigue, and mood dysregulation are treated accordingly with appropriate agents. Early use of DMDs in patients with relapsing forms of MS has been shown to reduce the frequency of relapses, lessen severity of relapses, and slow progression of disability.[23] All DMDs modulate the immune system through various mechanisms that include sequestration of lymphocytes, interference with DNA synthesis in lymphocytes, depletion of immune cells, or changes in cytokine secretion pattern.[13] The FDA-approved DMDs for MS include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate (S1P) receptor modulators, fumarates, cladribine, and monoclonal antibodies. Efficacy rates of DMDs, defined by reduction in annualized relapse rates compared with placebo or active comparators, range from 29% to 68%.[13]

The two primary treatment approaches for relapsing MS are based on balancing the risks and efficacy of DMDs.[13] The escalation approach starts with the least-potent medications with relatively few adverse effects, such as interferons or fumarates, and if there is evidence of disease activity the treatment is escalated to a more potent medication.[13] This approach minimizes risks but may result in undertreatment, defined as breakthrough disease and accumulated disability.[13] An alternative option is to initiate a medication with higher potency, such as ocrelizumab or natalizumab, at the time of diagnosis.[13] The rationale for this treatment approach is to provide better relapse control and delay accumulation of disability.[13] A limitation of this approach is that patients are exposed to higher risks of adverse events and some patients may not require such intensive treatment.[13] The DMDs approved for the treatment of MS are presented in **Table 1**.

Table 1: FDA-Approved Disease-Modifying Drugs used to manage Multiple Sclerosis[24,25]

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication	REMS Program	Major Safety Concerns	Monitoring
ORAL AGENTS						
Sphingosine 1-Phosphate Receptor Modulators						
Fingolimod (Affects $S1PR_1$, $S1PR_3$, $S1PR_4$, & $S1PR_5$)	GILENYA	≥ 40 kg: 0.5 mg PO once daily < 40 kg: 0.25 mg PO once daily	CIS RRMS SPMS **Approved for patients ≥ 10 years of age**	No	Infections, PML, bradycardia with first dose, hepatotoxicity hypertension, teratogenicity, and macular edema	Cardiac monitoring with the first dose. Ophthalmic screening at baseline and 3-4 months after starting therapy. LFTs and CBC every 6 months.
Siponimod (Affects $S1PR_1$ & $S1PR_5$)	MAYZENT	2 mg PO once daily (maintenance) 1 mg PO once daily for patients with CYP2C9*1/*3 OR *2/*3 genotype	CIS RRMS SPMS	No	Infections, PML, bradycardia, AV conduction delays, hepatotoxicity, macular edema, hypertension, teratogenicity	CYP2C9 genotype determination before treatment initiation. CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Ozanimod (Affects $S1PR_1$ & $S1PR_5$)	ZEPOSIA	0.92 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, PML, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs at baseline and every 6 months. Ophthalmic screening and ECG at baseline.
Ponesimod (Affects $S1PR_1$)	PONVORY	20 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, PML, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Fumarates						
Dimethyl Fumarate	TECFIDERA	240 mg PO twice a day (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Monomethyl Fumarate	BAFIERTAM	190 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Diroximel Fumarate	VUMERITY	462 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Others						

Teriflunomide	AUBAGIO	7 mg or 14 mg PO once daily	CIS RRMS SPMS	No	Black Box Warnings: Hepatotoxicity and Teratogenicity Other Warnings: infections and hypertension	CBC, LFTs, and blood pressure every 6 months
Cladribine	MAVENCLAD	Cumulative dose of 3.5 mg/kg PO divided into 2 yearly treatment courses (1.75 mg/kg per treatment course).	RRMS SPMS	No	Black Box Warnings: Malignancies and Teratogenicity Other Warnings: Bone marrow suppression, PML, lymphopenia, infections, cardiac failure, and hepatoxicity **Due to its safety profile, cladribine is recommended for patients who have had an inadequate response to, or who are unable to tolerate an alternative MS treatment**	CBC with lymphocyte count and LFTs every 6 months
INJECTABLE AGENTS						
Interferons						
Interferon beta-1a	AVONEX	30 mcg IM once weekly (maintenance)	CIS RRMS SPMS	No	Hepatotoxicity, thrombocytopenia, increased risk of spontaneous abortion, depression, and suicidal ideation	Thyroid function, CBC and LFTs every 6 months
Interferon beta-1a	REBIF	22 or 44 mcg SC three times a week				
Peginterferon beta-1a	PLEGRIDY	125 mcg SC every 14 days				
Interferon beta-1b	BETASERON, EXTAVIA	250 mcg SC every other day				
Monoclonal Antibodies						
Alemtuzumab	LEMTRADA	Intravenous infusion for 2 treatment courses. First course: 12 mg IV over 4 hours once a day for 5 consecutive days (total 60 mg). Second course: 12 mg once a day for 3 days (total 36 mg). Begin 12 months after the first treatment course.	RRMS SPMS	Yes	Black Box Warnings: Autoimmunity, Infusion Reactions, Stroke, and Malignancies Other Warnings: Infections, PML, thyroid autoimmunity, glomerular nephropathies, thrombocytopenia, autoimmune hepatitis **Due to safety profile, reserve for patients who have inadequate response to 2 or more MS drugs**	Thyroid function every 3 months. CBC with differential, serum creatinine, and urinalysis every month. Baseline and yearly LFTs and skin exams.

Natalizumab	TYSABRI	300 mg via IV infusion every 4 weeks	CIS RRMS SPMS	Yes	Black Box Warnings: PML Other Warnings: infections, hypersensitivity, teratogenicity, thrombocytopenia, hepatotoxicity **consider risk of PML vs. benefit of therapy**	JCV antibody testing and brain MRI every 6 months. CBC and LFTs every 6 months.
Ocrelizumab	OCREVUS	600 mg IV every 6 months (maintenance)	CIS RRMS SPMS PPMS	No	Infusion reactions, infections and PML	Hepatitis B virus screening prior to starting therapy.
Ofatumumab	KESIMPTA	20 mg SC every 4 weeks	CIS RRMS SPMS	No	Infusion reactions and infections	Hepatitis B virus screening prior to starting therapy
Others						
Mitoxantrone	NOVANTRONE	12 mg/m^2 IV infusion every 3 months – duration of therapy limited to 2 years and cumulative dose of 140 mg/m^2	RRMS SPMS	No	Black Box Warning: Dose-related Cardiotoxicity **Considered as last resort treatment for patients that have failed other therapies**	ECG and LVEF before each infusion. CBC and LFTs every 6 months.
Glatiramer Acetate	COPAXONE, GLATOPA	20 mg SC once daily; OR 40 mg SC three times a week	CIS RRMS SPMS	No	Transient post injection reactions (chest pain, dyspnea, tachycardia, anxiety, palpitations, flushing, urticaria) and hepatoxicity	None required

Abbreviations: AML = acute myeloid leukemia; CBC = complete blood count; CIS = clinically isolated syndrome; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; IM = Intramuscular; IV = Intravenous; JCV = John Cunningham Virus; LFTs = liver function tests; LVEF= left ventricular ejection fraction; MS = multiple sclerosis; MRI = magnetic resonance imaging; PO = Oral; PPMS = primary progressive multiple sclerosis; PML = progressive multifocal leukoencephalopathy; REMS = Restricted Evaluation and Mitigation Strategy; RRMS = relapsing-remitting multiple sclerosis; SC= Subcutaneous, S1PR = sphingosine 1-phosphate receptor; SPMS = secondary progressive multiple sclerosis

Methods:

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

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

New Systematic Reviews

Cochrane Systematic Review: Ocrelizumab for Multiple Sclerosis

A 2022 Cochrane review evaluated the benefits, harms, and tolerability of ocrelizumab in people with RRMS and PPMS.[1] Literature was searched through October 2021 for RCTs involving adults diagnosed with RRMS or PPMS according to the McDonald criteria, comparing ocrelizumab alone or associated with other medications, at the approved dose of 600 mg every 24 weeks for any duration, versus placebo or any other active drug therapy.[1] Four RCTs met inclusion criteria.[1] The overall population included 2551 patients; 1370 treated with ocrelizumab 600 mg and 1181 treated with controls.[1] Among the controls, 298 patients received placebo and 883 received interferon beta-1a.[1] The treatment duration was 24 weeks in one study, 96 weeks in 2 studies, and at least 120 weeks in one study.[1] One study was at high risk of allocation concealment and blinding of participants and personnel; all 4 studies were at high risk of bias for incomplete outcome data.[1] Primary outcomes included the number of patients experiencing at least one relapse at one year, number of patients experiencing disability progression at 24 to 96 weeks, and the number of patients experiencing AEs, serious AEs, or treatment discontinuation caused by AEs.[1]

For RRMS, ocrelizumab was associated with a lower relapse rate versus interferon beta-1a (RR 0.61; 95% CI, 0.52 to 0.73; 2 studies, n=1656; moderate-certainty evidence) and a lower number of participants with disability progression (hazard ratio (HR) 0.60; 95% CI, 0.43 to 0.84; 2 studies, n=1656; low-certainty evidence).[1] No difference in AEs (RR 1.00; 95% CI, 0.96 to 1.04; 2 studies, n=1651; moderate-certainty evidence) or serious AE (RR 0.79; 95% CI 0.57 to 1.11; 2 studies, n=1651; low-certainty evidence) were found between the groups. A lower number of participants discontinued treatment from an AE with ocrelizumab therapy versus interferon beta-1a (RR 0.58; 95% CI, 0.37 to 0.91; 2 studies, n=1651; low-certainty evidence).[1]

For PPMS, ocrelizumab was associated with a lower number of participants with disability progression versus placebo (HR 0.75; 95% CI, 0.58 to 0.98; 1 study, n=731; low-certainty evidence).[26] A higher number of patients with any AEs were observed in patients receiving ocrelizumab versus placebo (RR 1.06; 95% CI, 1.01 to 1.11; 1 study, n=725; moderate-certainty evidence). No difference any serious AE (RR 0.92; 95% CI, 0.68 to 1.23; 1 study, n=725; low-certainty evidence) or the number of participants who discontinued treatment from an AE (RR 1.23; 95% CI, 0.55 to 2.75; 1 study, n=725; low-certainty evidence) were found for at least 120 weeks.[1] The most common AEs reported with ocrelizumab were infusion-related reactions, nasopharyngitis, urinary tract infections, and upper respiratory tract infections.[1]

In summary, ocrelizumab probably reduces the relapse rate with little difference in AEs versus interferon beta-1a for people with RRMS over 96 weeks (moderate-certainty evidence).[1] Ocrelizumab may reduce disability progression and result in less treatment discontinuation than interferon beta-1a in people with RRMS with little difference in serious AEs (low-certainty evidence).[1] In patients with PPMS, ocrelizumab may reduce disability progression, but it is associated with higher rates of AEs versus placebo over 120 weeks (moderate-certainty evidence) without much difference in serious AEs or treatment discontinuation from AEs (low-certainty evidence).[1]

Cochrane Systematic Review: Siponimod for Multiple Sclerosis

A 2021 Cochrane review assessed the benefits and AEs of siponimod for adults diagnosed with MS.[2] The literature search was completed through September 2021.[1] Any RCT that evaluated siponimod versus placebo or active comparator met selection critiera.[2] There were no restrictions on dose or administration frequency.[2] Two studies (n=1948) met selection criteria which compared siponimod with placebo in patients with SPMS (n=1651) and RRMS (n=297).[2] Both studies had a high risk of bias due to selective reporting and attrition.[2] Primary outcomes included the number of patients experiencing new relapses, the number of patients who experienced disability worsening as measured by the EDSS, and the number of patients who withdrew due to any AE.[2]

Only one RCT assessed the number of patients who experienced at least one relapse at 6 months.[2] Overall, the risk of new relapse in patients receiving 10 mg, 2 mg and 0.5 mg siponimod was 18%, 10.2% and 23.3% respectively.[2] To investigate the effect these doses, a subgroup analysis was performed which did not find

difference between 0.5 mg and 10 mg of siponimod (RR 0.87; 95% CI, 0.42 to 1.81 and RR 0.68; 95% CI, 0.31 to 1.45, respectively.[2] Siponimod 2 mg reduced disability progression at 6 months versus placebo (56 fewer people per 1000; RR 0.78; 95% CI, 0.65 to 0.94; 1 study, n=1641; low-certainty evidence) and reduced the annualized relapse rate (RR 0.43; 95% CI, 0.34 to 0.56; 2 studies, n=1739; low-certainty evidence) but it is unknown whether siponimod 2 mg reduced the number of patients with new relapse (166 fewer people per 1000; RR 0.38, 95% CI 0.15 to 1.00; 1 study, n=94; very low-certainty evidence).[2]

No difference in AEs were observed between siponimod and placebo (14 more people per 1000; RR 1.52, 95% CI 0.85 to 2.71; 2 studies, n=1739, low-certainty evidence).[2] Both studies had high attrition bias resulting from the unbalanced reasons for dropouts among groups and high risk of bias due to conflicts of interest.[2] No difference was observed between groups in the number of patients with at least one serious AE excluding relapses (113 more people per 1000; RR 1.80, 95% CI 0.37 to 8.77; 2 studies, n=1739; low-certainty evidence) at 6 months.[2] No data were available regarding serious cardiac adverse events.[2] In terms of safety profile, the most common AEs associated with siponimod were headache, back pain, bradycardia, dizziness, fatigue, influenza, urinary tract infection, lymphopenia, nausea, alanine amino transferase increase and upper respiratory tract infection.[2]

No difference was observed in the number of patients who withdrew due to AEs at 6 months between siponimod 0.5 mg (RR 2.62; 95% CI, 0.54 to 12.77) and 2 mg dosing (RR 1.52; 95% CI, 0.85 to 2.71) versus placebo.[2] The risk of discontinuing 10 mg of siponimod due to AEs was statistically significantly higher than placebo (RR 4.50; 95% CI, 1.04 to 19.45).[2] The AEs associated with siponimod have dose-related effects and rarely led to discontinuation of treatment.[2]

In summary, it is uncertain whether siponimod is beneficial for patients with MS.[2] There was low-certainty evidence to support siponimod 2 mg daily over 6 months to reduce the annualized relapse rate and the number of patients who experienced disability worsening.[2] The certainty of the evidence of siponimod to reduce the number of people with a relapse is very low.[2] The overall body of evidence for siponimod was low to very low due to serious study limitations, imprecision and indirectness.[2] More studies with robust methodology and longer follow-up are needed to evaluate the benefit of siponimod for the management of MS and to observe long-term adverse effects.[2] Head-to-head studies would help us compare siponimod to other available therapeutics.[2]

Risk for Cardiovascular Adverse Events Associated With Sphingosine-1-Phosphate Receptor Modulators

A 2021 systematic review with meta-analysis evaluated the risk of cardiovascular AEs in patients with MS treated with S1P receptor modulators.[3] Due to extensive S1P expression on cardiomyocytes and vascular endothelial cells, all S1P receptor modulators have some cardiovascular effect.[3] Literature was searched through January 2021 to identify RCTs that used S1P receptor modulator to treat patients with MS.[3] Outcomes evaluated were overall cardiovascular AEs (including general and serious cardiovascular AEs) and specific cardiovascular AEs (any arrhythmia, bradyarrhythmia, tachyarrhythmia, hypertension, hypotension, heart failure, coronary artery disease, acute coronary syndrome, and chronic coronary syndrome).[3] Serious cardiovascular AEs were defined as life-threatening or fatal AEs, or AEs that resulted in hospitalization (or extended hospital stay if already hospitalized).[3] Seventeen RCTs (12 for fingolimod; 3 for ozanimod; 2 for siponimod) met inclusion critiera.[3] A total of 13,295 patients were enrolled, among which 8,157 were treated with S1P receptor modulators and 5,138 were treated with a placebo or other active DMD (interferon beta, glatiramer acetate, or natalizumab).[3] Of the 17 trials, 12 (70.6%) had a low risk of bias, 4 had an unclear risk of bias due to unknown random sequence generation and incomplete outcome data, and 1 had a high risk of bias due to allocation concealment and blinding issues.[3]

The rate of cardiovascular AEs was 10.9% in the S1P receptor modulator group versus 4.8% in the control group (RR 2.21; 95% CI; 1.58–3.10; I^2 =75.6%).[3] The high-risk cardiovascular AEs associated with S1P receptor modulators were bradyarrhythmia (RR 2.92; 95% CI, 1.91–4.46; I^2 =30.8%) and hypertension (RR 2.00; 95% CI, 1.49–2.67; I^2 =56.5%).[3] Subgroup analyses were consistent with the primary analysis except that ozanimod was associated with a higher risk of hypertension (RR 1.76; 95% CI, 1.10-2.82; I^2 =0.0%) and siponimod was associated with higher risk of bradyarrhythmia (RR 2.75; 95% CI, 1.75-4.31; I^2 =0.0%).[3]

In summary, S1P receptor modulators increased risk of cardiovascular AEs by 1.21 times in MS patients, and the incidence for both general and serious cardiovascular AEs were increased significantly relative to control groups.[3] Patients treated with S1P receptor modulators were at 2.92- and 2.00-fold increased risk for bradyarrhythmia and hypertension, respectively.[3] The risk for bradyarrhythmia and hypertension may not differ between S1P receptor modulators or dose used.[3] Several limitations of this study were described by the authors. First, the incidence timing, duration and severity of cardiovascular AEs between patients treated with S1P receptor modulators versus control could not be compared due to limited data.[3] The limited number of ozanimod and siponimod trials studied prevent a robust comparative analysis of all S1P receptor modulators.[3] Third, analyses are based on the data from RCTs which have carefully selected participants who are usually be younger in age, which limits the ability to evaluate patients with late-onset MS whose cardiovascular AE risk might be higher.[3]

Incidence and Risk of Infection Associated With Fingolimod in Patients With Multiple Sclerosis

A 2021 systematic review and meta-analysis sought to determine the risk of infection in patients with MS treated with fingolimod.[4] Literature was searched through April 2020 to identify RCTs that reported the occurrence of infection associated with fingolimod treatment.[4] The primary outcome of this study was the overall infection rate. Secondary outcomes included general infection, serious infection, and other different types of infection.[4] Twelve RCTs conducted over 6 weeks to 24 months and including 8,448 patients met inclusion criteria.[4] Sixty-two percent of patients were treated with fingolimod and 38% of patients were treated with a placebo or first-generation DMD (interferon beta, glatiramer, or natalizumab).[4] Of these 12 trials, all studies (6,508 patients) involved fingolimod 0.5 mg daily and four studies (1,940 patients) involved fingolimod 1.25 mg daily.[4] Most trials had low risk of bias, but four trials were at high risk of bias due to selection, performance, attrition, and reporting biases.[4]

The overall rate of infection was 55.13% (56.78% vs. 52.20% for fingolimod and control groups, respectively).[4] Fingolimod was associated with increased risk of infection versus control (RR 1.16; 95% CI, 1.07 to 1.27; I^2 =81%), regardless of whether the infection was a general infection (RR 1.14; 95% CI, 1.05 to 1.25; I^2 =78%) or serious infection (RR 1.49; 95% CI, 1.06 to 2.10; I^2 =0%).[4] Analyses of subgroups found that fingolimod increased the risk of lower respiratory infection (RR 1.48; 95% CI, 1.19 to 1.85; I^2 =0%) and herpes virus infection (RR 1.34; 95% CI, 1.01 to 1.78; I^2 =9%).[4] No dose-dependent increase in risk of infection was observed with fingolimod (0.5 mg: RR 1.15; 95% CI, 1.07 to 1.25; I^2 =91% and 1.25 mg: RR 1.11; 95% CI, 0.97 to 1.28; I^2 =81%; p=0.66).[4] In summary, fingolimod increased the risk of overall infection by 16%, including both general and serious infections. Fingolimod was associated with higher risk of lower respiratory and herpes virus infection. The risk of infection did not appear to be dose-dependent.[4]

After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[27-32] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

National Institute For Health and Care Excellence: Diroximel fumarate for Treating RRMS

NICE published guidance for the use of diroximel fumarate for treatment of RRMS in June 2022.[5] Canadian regulatory approval for diroximel fumarate was granted because it has the same active metabolite as dimethyl fumarate and pharmacokinetic analyses have demonstrated bioequivalence.[5] The NICE concluded that diroximel fumarate and dimethyl fumarate are expected to be equally effective.[5] Results from the phase 3 RCT (EVOLVE-MS-2) suggest that diroximel fumarate is associated with fewer gastrointestinal side effects than dimethyl fumarate.[5]

- Diroximel fumarate is recommended as a first-line DMD option for treatment of active RRMS (defined as 2 clinically significant relapses in the previous 2 years) in adults if they do not have highly active or rapidly evolving severe RRMS.[5] Dimethyl fumarate is not recommended for people with highly active or rapidly evolving severe MS because of lack of evidence.[5]

National Institute For Health and Care Excellence: Ponesimod for Treating RRMS

NICE published guidance for the use of ponesimod for treatment of RRMS in February 2022.[6] Clinical trial evidence shows that people on ponesimod have fewer relapses than people who take teriflunomide.[6] The effect of ponesimod on disability progression is not clear.[6] Ponesimod cannot be compared with other DMDs due to the limitations in the clinical evidence.[6] Use in pregnancy is also an important area for research and ponesimod is not indicated for pregnant women.[6] NICE concluded that ponesimod may not be the most effective treatment, but individual risks and benefits should be considered.[6]

- Ponesimod is recommended as a treatment option for RRMS in adults with active disease defined by clinical or imaging features.[6]

National Institute For Health and Care Excellence: Ozanimod for Treating RRMS

NICE published guidance for the use of ozanimod in treatment of RRMS in June 2021.[7] Clinical trial evidence shows that ozanimod reduces the number of relapses and brain lesions compared with interferon beta-1a. The effect of ozanimod on progression of disability is unclear.[7]

- Ozanimod is not recommended for treating RRMS in adults with clinical or imaging features of active disease due to high cost of treatment (United Kingdom [UK] National Health Service [NHS] data).[7]

Canadian Agency for Drugs and Technologies in Health Drug Review: Ozanimod

The CADTH recommended that ozanimod should not be recommended for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations.[10] There is insufficient evidence to determine if ozanimod offers any meaningful clinical benefits compared with other DMDs for RRMS. Direct comparative evidence for ozanimod 1 mg with DMDs other than interferon beta-1a was not identified; however, interferon beta-1a is no longer a routinely used treatment option in current clinical practice, in part because of its modest efficacy, which limits the scope of the results obtained from RADIANCE Part B and SUNBEAM studies.[10] Furthermore, limitations associated with the indirect comparison provided by the manufacturer and reviewed by CADTH precluded any conclusions regarding the comparative efficacy and safety advantages of ozanimod with other DMDs for RRMS.[10] Given the uncertainty in the clinical effectiveness of ozanimod relative to other DMDs, the cost-effectiveness of ozanimod is highly uncertain (Canada, CADTH data).[10]

National Institute For Health and Care Excellence: Ofatumumab for Treating RRMS

NICE published guidance for the use of ofatumumab in treatment of RRMS in May 2021.[8] Clinical trial evidence shows that ofatumumab reduces the number of relapses and slows disease progression in people with RRMS when compared with teriflunomide.[8] The ASCLEPIOS trials showed that ofatumumab is more effective than teriflunomide for all main clinical outcomes and had no unexpected safety concerns.[8] There is no evidence directly comparing ofatumumab with the other treatments.[8] Ofatumumab is cost effective and is an acceptable use of NHS resources (UK, NHS data).[8]

- Ofatumumab is recommended as an option for treatment of RRMS in adults with active disease defined by clinical or imaging features.[8]

Canadian Agency for Drugs and Technologies in Health Drug Review: Ofatumumab

The CADTH based their recommendation for ofatumumab on 2 randomized, double-blind, active comparator–controlled trials (ASCLEPIOS I and ASCLEPIOS II) which demonstrated that ofatumumab was superior to teriflunomide in reducing the annualized relapse rate of MS based on annualized relapse rates (RR 0.50; 95% CI, 0.37 to 0.65; $P < 0.001$ in ASCLEPIOS I and RR 0.42; 95% CI, 0.31 to 0.56; $P < 0.001$ in ASCLEPIOS II).[9]

No deaths were reported in the ASCLEPIOS I and II trials.[9] Most patients reported at least one treatment-emergent AE (82.2% vs. 82.3% in ASCLEPIOS I and 85.0% vs. 86.1% in ASCLEPIOS II for the ofatumumab and teriflunomide groups, respectively).[9] The most commonly reported AEs were injection-related reactions, nasopharyngitis, headache, and upper respiratory tract infections.[9] In both studies, injection site reactions and a decrease in blood immunoglobulin M were reported more in the ofatumumab groups.[9] In contrast, alopecia and diarrhea were more common in patients in the teriflunomide groups.[9] Specific to each trial, upper respiratory tract infections were reported more in patients on ofatumumab versus teriflunomide in the ASCLEPIOS I trial and injection-related reactions were reported more in patients on ofatumumab versus teriflunomide in the ASCLEPIOS II trial.[9]

Ofatumumab is recommended for the treatment of adults with RRMS if the following conditions are met:

Initiation Criteria

1. Patients must have all of the following characteristics at the time of initiating treatment with ofatumumab:
    - An Expanded Disability Status Scale (EDSS) score of less than 6; and
    - Evidence of active disease defined as at least 1 of the following:
        - One relapse during the previous year; or
        - Two relapses during the previous 2 years; or
        - A positive gadolinium (Gd)-enhancing magnetic resonance imaging (MRI) scan during the year before starting treatment with ofatumumab.[9]
2. Ofatumumab should not be used in combination with other DMDs to treat MS.[9]
3. Patients must be under the care of a specialist with experience in the diagnosis and management of MS.[9]

Renewal Criteria

1. Ofatumumab may only be renewed for patients who do not exhibit evidence of disease progression since the previous assessment.[9]
2. Patients should be assessed for response to ofatumumab every 12 months.[9]
3. Patients must not have experienced more than 1 relapse in the previous year.[9]

New Formulations:

A new formulation of fingolimod lauryl sulfate (TASCENSO ODT) received FDA approval in December 2021.[33] The orally disintegrating tablets are indicated for treatment of relapsing forms of MS including CIS, RRMS, and SPMS in pediatric patients aged 10 years of age and older and weighing less than or equal to 40 kg.[33] The recommended dose in this population is 0.25 mg orally once daily, with or without food.[33] TASCENSO ODT is not approved for use in any patients who weigh more than 40 kg.[33] Pediatric patients whose weight exceeds 40 mg after starting TASCENSO ODT should be switched another fingolimod product approved for use in this population.[33]

The capsule formulation of fingolimod (GILENYA) received FDA approval for use in pediatric patients 10 years of age and older with relapsing forms of MS in December 2019.[34] The recommended dose of GILENYA is 0.25 mg once a day in patients aged 10 years and above who weigh less than or equal to 40 kg.[34] In patients 10 years of age and older who weigh more than 40 kg, the FDA-approved dose is 0.5mg once daily.[34]

Safety and effectiveness of fingolimod for the treatment of relapsing forms of multiple sclerosis in pediatric patients 10 years to less than 18 years of age were established in one randomized, double-blind clinical study in 215 patients in which the 0.25 mg fingolimod dose was compared to intramuscular interferon beta-

1a (fingolimod n = 107; intramuscular interferon beta-1a n = 108).[33] Median duration of exposure to study drug was 634 days in the fingolimod group and 547 days in the interferon beta-1a group.[33] In the fingolimod group, 6.5% of patients did not complete the study, compared to 18.5% in the interferon beta-1a group.[33] The primary endpoint was the annualized relapse rate. The annualized relapse rate was lower in patients treated with fingolimod than in patients who received interferon beta-1a (0.122 vs. 0.675 respectively; $p<0.001$).[33] The safety profile in pediatric patients (10 years to less than 18 years of age) receiving fingolimod capsules daily was similar to that seen in adult patients.[33] In the pediatric study, cases of seizures were reported in 5.6% of fingolimod-treated patients and 0.9% of interferon beta-1a-treated patients.[33]

New FDA Safety Alerts:
The FDA issued an alert on 8/18/2022 regarding cross-compatibility issues with glatiramer acetate autoinjector devices.[35] Autoinjector devices that are optional for use with glatiramer acetate injection may not be compatible for use across FDA-approved glatiramer acetate injection drug products.[35] FDA has received reports that using an autoinjector that is not compatible with the patient's specific glatiramer acetate injection drug product has resulted in missed and partial doses.[35] Currently, there are 3 FDA-approved glatiramer acetate injection drug products on the market—all available in a single-dose prefilled syringe with an attached needle for subcutaneous administration.[35] Glatiramer acetate may be injected using only the syringe or by inserting the syringe into an autoinjector.[35] The autoinjectors are reusable, designed to facilitate injections in patients with limited dexterity, and are available by prescription separately.[35] FDA has requested that drug product manufacturers update their labeling to instruct users to confirm the autoinjector is compatible before using it to inject glatiramer acetate.[35] The FDA-approved glatiramer acetate injection drug products and their compatible autoinjector device are listed in **Table 1.** A description of additional new FDA safety alerts is presented in **Table 2**.

Table 1. Glatiramer Acetate Injection Products and Compatible Autoinjector Device (Optional for Use With Drug Product)[35]

Drug Product Name	Drug Manufacturer	Compatible Autoinjector Device
COPAXONE (glatiramer acetate)	Teva	Autoject 2
GLATOPA (glatiramer acetate)	Sandoz	Glatopa*ject*
Glatiramer acetate	Viatris/Mylan	*Whisper*JECT

Table 2. Description of new FDA Safety Alerts[36]

Generic Name	Brand Name	Month/Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Teriflunomide	AUBAGIO	4/2021	Warnings and Precautions	**Pancreatitis in Pediatric Patients** AUBAGIO is not approved for use in pediatric patients. Effectiveness of AUBAGIO for the treatment of relapsing form of multiple sclerosis in pediatric patients (10 to 17 years of age) was not established in an adequate and well-controlled clinical study in 166 patients (109 patients received once daily doses of AUBAGIO and 57 patients received placebo) for up to 96 weeks. In this pediatric clinical trial, cases of pancreatitis were observed in 1.8% (2/109) of patients receiving AUBAGIO; one of these cases was serious. If pancreatitis is suspected, discontinue teriflunomide and start an accelerated elimination procedure.

Ozanimod	ZEPOSIA	5/2021	Warnings and Precautions	**Bradyarrhythmia** In UC Study 1 and Study 3, bradycardia was reported on the day of treatment initiation in 1 patient (0.2%) treated with ZEPOSIA compared to none in patients who received placebo. After Day 1, bradycardia was reported in 1 patient (0.2%) treated with ZEPOSIA. In UC Study 2, bradycardia was not reported. **Liver Injury** In UC Study 1, elevations of ALT to 5-fold the ULN or greater occurred in 0.9% of patients treated with ZEPOSIA 0.92 mg and 0.5% of patients who received placebo, and in UC Study 2 elevations occurred in 0.9% of patients receiving ZEPOSIA and no patients receiving placebo. In UC Study 1, elevations of ALT to 3-fold the ULN or greater occurred in 2.6% of UC patients treated with ZEPOSIA 0.92 mg and 0.5% of patients who received placebo, and in UC Study 2 elevations occurred in 2.3% of patients and no patients, respectively. In controlled and uncontrolled UC studies, the majority (96%) of patients with ALT greater than 3-fold the ULN continued treatment with ZEPOSIA with values returning to less than 3-fold the ULN within approximately 2 to 4 weeks. Overall, the discontinuation rate because of elevations in hepatic enzymes was 0.4% in patients treated with ZEPOSIA 0.92 mg, and none in patients who received placebo in the controlled UC studies. Individuals with an AST or ALT greater than 1.5 times ULN were excluded from MS Study 1 and Study 2 and greater than 2 times the ULN for UC Study 1 and Study 3. There are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking ZEPOSIA. Use of ZEPOSIA in patients with hepatic impairment is not recommended. **Increased Blood Pressure** The mean increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in UC patients treated with ZEPOSIA is similar to patients with MS. In UC Study 1 and Study 3, the average increase from baseline in SBP was 3.7 mm Hg in patients treated with ZEPOSIA and 2.3 mm Hg in patients treated with placebo. In UC Study 2, the average increase from baseline in SBP was 5.1 mm Hg in patients treated with ZEPOSIA and 1.5 mm Hg in patients treated with placebo. There was no effect on DBP. Hypertension was reported as an adverse reaction in 1.2% of patients treated with ZEPOSIA 0.92 mg and none in patients treated with placebo in UC Study 1 and Study 3, and in 2.2% and 2.2% of patients in UC Study 2, respectively. Hypertensive crisis was reported in two patients receiving ZEPOSIA and one patient receiving placebo. **Respiratory Effects**

				In UC Study 1 the mean difference in decline in absolute FEV1 from baseline in patients treated with ZEPOSIA compared to patients who received placebo was 22 mL (95% CI: -84, 39) at 10 weeks. The mean difference in percent predicted normal (PPN) FEV1 at 10 weeks between patients treated with ZEPOSIA compared to those who received placebo was 0.8% (95% CI: -2.6, 1.0). The difference in reductions in FVC (absolute value and %-predicted) seen at Week 10 in UC Study 1, comparing patients who were treated with ZEPOSIA to those who received placebo was 44 mL, 95% CI (-114, 26); 0.5%, 95% CI (-2.3, 1.2), respectively. There is insufficient information to determine the reversibility of observed decreases in FEV1 or FVC after discontinuation of ZEPOSIA, or whether changes could be progressive with continued use.
Ozanimod	ZEPOSIA	5/2021	Warnings and Precautions	**Progressive Multifocal Leukoencephalopathy** Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. PML has been reported in patients treated with S1P receptor modulators, including ZEPOSIA, and other multiple sclerosis (MS) and UC therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation. If PML is confirmed, treatment with ZEPOSIA should be discontinued.
Peginterferon Beta-1A	PLEGRIDY	11/2021	Warnings and Precautions	**Injection Site Reactions Including Necrosis** Injection site abscesses and cellulitis have been reported in the post marketing setting with use of interferon beta. Some cases required treatment with hospitalization for surgical drainage and intravenous antibiotics. Periodically evaluate patient understanding and use of aseptic self-injection techniques and procedures, particularly if injection site necrosis has occurred.

Peginterferon Beta-1A	PLEGRIDY	03/2022	Warnings and Precautions	**Hepatic Injury** Cases of noninfectious hepatitis have been reported in the post marketing setting with use of PLEGRIDY.
Interferon Beta-1A	AVONEX	11/2021	Warnings and Precautions	**Injection Site Reactions Including Necrosis** Injection site reactions, including injection site necrosis, can occur with the use of interferon beta products, including AVONEX. In controlled clinical trials, injection site reactions (e.g., injection site pain, bruising or erythema) occurred in 18% of patients receiving AVONEX and 13% in the placebo group. These reactions included injection site inflammation (6%), injection site pain (8%), injection site mass (<1%), nonspecific reactions. Injection site abscesses and cellulitis and injection site necrosis have been reported in the post marketing setting with interferon beta products, including AVONEX. Some cases required treatment with hospitalization for surgical drainage and intravenous antibiotics. Periodically evaluate patient understanding and use of aseptic self-injection techniques and procedures, particularly if injection site necrosis has occurred. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with AVONEX after injection site necrosis has occurred, avoid administration of AVONEX into the affected area until it is fully healed. If multiple lesions occur, change injection site or discontinue therapy until healing occurs.
Alemtuzumab	LEMTRADA	01/2022	Warnings and Precautions	**Adults Onset Still's Disease** During post marketing use, Adult Onset Still's Disease (AOSD) has been reported in patients treated with LEMTRADA. AOSD is a rare inflammatory condition that requires urgent evaluation and treatment. Patients with AOSD may have a combination of the following signs and symptoms: fever, arthritis, rash, and leukocytosis in the absence of infections, malignancies, and other rheumatic conditions. Patients with manifestations of AOSD should be evaluated immediately and LEMTRADA should be discontinued if an alternate etiology for the signs or symptoms cannot be established.
Alemtuzumab	LEMTRADA	05/2022	Warnings and Precautions	**Autoimmune Encephalitis (AIE)** During post marketing use, cases of AIE have been reported in patients treated with LEMTRADA. AIE can present with a variety of clinical manifestations, including subacute onset of memory impairment, altered mental status, psychiatric symptoms, neurological findings, and seizures. LEMTRADA should be discontinued if AIE is confirmed by the presence of neural autoantibodies or an alternate etiology cannot be established.

Randomized Controlled Trials:

A total of 123 citations were manually reviewed from the initial literature search. After further review, 123 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
glatiramer acetate	COPAXONE	SUBCUT	SYRINGE	Y
interferon beta-1a	AVONEX PEN	INTRAMUSC	PEN IJ KIT	Y
interferon beta-1a	AVONEX	INTRAMUSC	SYRINGE	Y
interferon beta-1a	AVONEX	INTRAMUSC	SYRINGEKIT	Y
interferon beta-1a/albumin	REBIF REBIDOSE	SUBCUT	PEN INJCTR	Y
interferon beta-1a/albumin	REBIF	SUBCUT	SYRINGE	Y
interferon beta-1a/albumin	AVONEX	INTRAMUSC	KIT	Y
interferon beta-1b	EXTAVIA	SUBCUT	KIT	Y
interferon beta-1b	BETASERON	SUBCUT	KIT	Y
alemtuzumab	LEMTRADA	INTRAVEN	VIAL	N
cladribine	MAVENCLAD	ORAL	TABLET	N
dalfampridine	DALFAMPRIDINE ER	ORAL	TAB ER 12H	N
dalfampridine	AMPYRA	ORAL	TAB ER 12H	N
dimethyl fumarate	TECFIDERA	ORAL	CAPSULE DR	N
dimethyl fumarate	DIMETHYL FUMARATE	ORAL	CAPSULE DR	N
diroximel fumarate	VUMERITY	ORAL	CAPSULE DR	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	N
glatiramer acetate	GLATOPA	SUBCUT	SYRINGE	N
glatiramer acetate	GLATIRAMER ACETATE	SUBCUT	SYRINGE	N
glatiramer acetate	COPAXONE	SUBCUT	SYRINGE	N
interferon beta-1b	EXTAVIA	SUBCUT	VIAL	N
interferon beta-1b	BETASERON	SUBCUT	VIAL	N
monomethyl fumarate	BAFIERTAM	ORAL	CAPSULE DR	N
ocrelizumab	OCREVUS	INTRAVEN	VIAL	N
ofatumumab	KESIMPTA PEN	SUBCUT	PEN INJCTR	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAP DS PK	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAPSULE	N
peginterferon beta-1a	PLEGRIDY PEN	SUBCUT	PEN INJCTR	N
peginterferon beta-1a	PLEGRIDY	INTRAMUSC	SYRINGE	N
peginterferon beta-1a	PLEGRIDY	SUBCUT	SYRINGE	N
ponesimod	PONVORY	ORAL	TAB DS PK	N
ponesimod	PONVORY	ORAL	TABLET	N
siponimod	MAYZENT	ORAL	TAB DS PK	N
siponimod	MAYZENT	ORAL	TABLET	N

teriflunomide	AUBAGIO	ORAL	TABLET	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to June Week 3 2022, and , Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to June 23, 2022

1	exp Multiple Sclerosis/	50544
2	exp Glatiramer Acetate/	1459
3	exp Interferons/	106404
4	exp Alemtuzumab/	2201
5	exp Cladribine/	1365
6	dalfampridine.mp. or exp 4-Aminopyridine/	2612
7	exp Dimethyl Fumarate/	906
8	exp Fingolimod Hydrochloride/	2586
9	exp Fumarates/ or monomethyl fumarate.mp.	3610
10	ocrelizumab.mp.	544
11	ofatumumab.mp.	590
12	ozanimod.mp. or exp Sphingosine-1-Phosphate Receptors/	1012
13	peginterferon.mp.	6398
14	Sphingosine 1 Phosphate Receptor Modulators/ or ponesimod.mp.	190
15	siponimod.mp.	162
16	teriflunomide.mp.	694
17	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	121630
18	1 and 17	7516
19	limit 18 to (english language and humans and yr="2021 -Current")	639
20	limit 19 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	123

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying drugs for multiple sclerosis or ulcerative colitis.
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 6 months

Requires PA:
- All oral MS therapy including:
  - Sphingosine 1-phosphate receptor modulators (e.g. fingolimod, ozanimod, ponesimod, siponimod, etc.)
  - Teriflunomide
  - Fumarate salts (e.g., dimethyl fumarate, monomethyl fumarate, diroximel fumarate, etc.)
  - Cladribine

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 ozanimod to treat moderate-to-severe ulcerative colitis?	**Yes:** Go to #3	**No:** Go to #4

Approval Criteria		
3. Has the patient failed to respond or had an inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication these conventional therapies? AND • Has the patient tried and failed a 3-month trial of a Humira® product?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Is the medication being prescribed by or in consultation with a neurologist or gastroenterologist (if the diagnosis is ulcerative colitis)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1b, glatiramer acetate, interferon beta-1a, natalizumab, ofatumumab, ocrelizumab, or mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #9
9. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the prescription for teriflunomide?	**Yes:** Go to #11	**No:** Go to #14
11. Is the patient of childbearing potential?	**Yes:** Go to #12	**No:** Approve for up to 6 months.
12. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #15	**No:** Go to #18
15. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #16
16. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #17	**No:** Go to #21
17. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Go to #21	**No:** Pass to RPh. Deny; medical appropriateness.
18. Is the prescription for a fumarate product?	**Yes:** Go to # 19	**No:** Go to #20
19. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
20. Is the request for cladribine?	**Yes:** Go to #21	**No:** Go to #24
21. Is the patient of child bearing potential?	**Yes:** Go to #22	**No:** Go to #24
22. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #23

Approval Criteria		
23. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #24	**No:** Pass to RPh. Deny; medical appropriateness.
24. Has the patient had an inadequate response to or they are unable to tolerate alternative MS (or alternative UC treatment if the request is for ozanimod) treatment?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1. Dosing And FDA-Approved Indications for Oral MS Drugs

Generic Name	FDA Indication (Adults unless otherwise indicated)			
	CIS	RRMS	SPMS	Ulcerative Colitis
Cladribine		X	X	
Fingolimod	X *(≥ 10 years)*	X *(≥ 10 years)*	X *(≥ 10 years)*	
Siponimod	X	X	X	
Ozanimod	X	X	X	X
Ponesimod	X	X	X	
Teriflunomide	X	X	X	
Dimethyl Fumarate	X	X	X	
Monomethyl Fumarate	X	X	X	
Diroximel Fumarate	X	X	X	
Abbreviations: CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis				

Table 2. FDA-recommended Baseline Safety Assessments (see clinical notes for details)

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Varicella Zoster Antibodies	CYP2C9 genotype	Other Screening
Fumarate salts		X	X (>500)				
Fingolimod*	X	X	X	X	X		
Ozanimod*	X	X	X	X	X		
Ponesimod*	X	X	X	X	X		
Siponimod*	X	X	X	X	X	X	
Teriflunomide	X (box warning)	X (box warning)	X				
Cladribine	X (box warning)	X	X (WNL)		X		TB; HBV; HIV; HCV; MRI for PML
Abbreviations: HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; WNL = within normal limits							

* sphingosine 1-phosphate receptor modulators

Sphingosine 1-Phosphate Receptor Modulators (fingolimod, ozanimod, ponesimod, siponimod) Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for 4 to 6 hours after initial dose in a clinically appropriate area (fingolimod, ponesimod, siponimod).
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod, ozanimod, ponesimod, or siponimod with caution. A cardiology evaluation should be performed before considering treatment.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod, ozanimod, ponesimod, or siponimod initiation with subsequent evaluations based on clinical symptoms.
- Patients starting on siponimod therapy must be tested for CYP2C9 variants to determine CYP2C9 genotype before starting siponimod. Siponimod is contraindicated in patients with a CYP2C9*3/*3 genotype. The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg. The recommended maintenance dosage in all other patients is 2 mg.

Teriflunomide Clinical Notes:

- Before starting teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in individuals of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting teriflunomide, monitor ALT levels at least monthly for 6 months. Consider additional ALT monitoring when teriflunomide is given with other potentially hepatotoxic drugs. Consider stopping teriflunomide if serum transaminase levels increase (>3-times the upper limit of normal). Monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue teriflunomide and start accelerated elimination in those with suspected teriflunomide-induced liver injury and monitor liver tests weekly until normalized. Check blood pressure

periodically and manage hypertension. Check serum potassium level in teriflunomide-treated patients with hyperkalemia symptoms or acute renal failure. Monitor for signs and symptoms of infection.

- Monitor for hematologic toxicity when switching from teriflunomide to another agent with a known potential for hematologic suppression because systemic exposure to both agents will overlap.

Fumarate Salts (Dimethyl Fumarate, Monomethyl Fumarate, Diroximel Fumarate) Clinical Notes:

- Fumarate salts may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 $x10^3$ cells/mm^3 (equivalent to <0.8 cells/µL). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Fumarate salts should be held if the WBC falls below 2 $x10^3$ cells/mm^3 or the lymphocyte count is below 0.5 $x10^3$ cells/mm^3 (cells/µL) and permanently discontinued if the WBC did not increase to over 2 $x10^3$ cells/mm^3 or lymphocyte count increased to over 0.5 $x10^3$ cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored every 6 to 12 months.

Cladribine Clinical Notes:

- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Prior to initiating cladribine follow standard cancer screening guidelines because of the risk of malignancies.
- Obtain a CBC with differential including lymphocyte count. Lymphocytes must be: within normal limits before initiating the first treatment course and at least 800 cells per microliter before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with cladribine.
- Infection screening: exclude HIV infection, perform TB and hepatitis screening. Evaluate for active infection; consider a delay in cladribine treatment until any acute infection is fully controlled.
- Administer all immunizations according to immunization guidelines prior to starting cladribine. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting cladribine.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

P&T/DUR Review: *10/22 (DM); 10/21(DM); 8/21 (DM); 6/21 (DM); 8/20 (DM); 6/20; 11/17; 11/16; 9/15; 9/13; 5/13; 3/12*
Implementation: *1/1/2023, 1/1/2022, 9/1/20; 1/1/18; 1/1/17; 1/1/14; 6/21/2012*

Dalfampridine

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization:

- Up to 12 months

Requires PA:
Dalfampridine

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 Multiple Sclerosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy previously approved by the FFS program (patient has completed 2-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Is a documented estimated glomerular filtration rate (eGFR) showing the product is not contraindicated? Note: Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min)	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~7. Is the patient ambulatory with a walking disability requiring use of a walking aid **OR;** have moderate ambulatory dysfunction and does not require a walking aid AND able to complete the baseline timed 25-foot walk test between 8 and 45 seconds?	**Yes:** Approve initial fill for 2-month trial.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking dalfampridine for ≥2 months with documented improvement in walking speed while on dalfampridine (≥20% improvement in timed 25-foot walk test)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Clinical Notes:

- Because fewer than 50% of MS patients respond to therapy and therapy has risks, a trial of therapy should be used prior to beginning ongoing therapy.
- The patient should be evaluated prior to therapy and then 4 weeks to determine whether objective improvements which justify continued therapy are present (i.e. at least a 20% improvement from baseline in timed walking speed).
- Dalfampridine is contraindicated in patients with moderate to severe renal impairment.
- Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.

P&T Review: *10/22 (DM); 6/21(DM); 8/20 (DM); 6/20; 11/17; 5/16; 3/12*
Implementation: *TBD, 8/16, 9/1/13*

Ocrelizumab (Ocrevus™)

Goal(s):

- Restrict use of ocrelizumab in patients with relapsing-remitting multiple sclerosis (RRMS) to those who have failed multiple drugs for the treatment of RRMS.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Ocrevus™ (ocrelizumab) pharmacy or 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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication FDA-approved or compendia-supported for the requested indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis?	**Yes:** Go to #6	**No:** Go to #7
6. Has the patient failed trials for at least 2 drugs indicated for the treatment of relapsing multiple sclerosis?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the drug prescribed by or in consultation with a neurologist who regularly treats multiple sclerosis?	**Yes**: Approve ocrelizumab 300 mg every 2 weeks x 2 doses followed by 600mg IV every 6 months for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1.Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *10/22 (DM); 6/21(DM); 6/20; 11/17 (DM); 1/17*
Implementation: *TBD, 7/1/20; 1/1/18; 4/1/17*

Peginterferon Beta-1a (Plegridy®)

Goal(s):

- Approve therapy for covered diagnosis that are supported by the medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.

Approval Criteria		
3. Will the prescriber consider a change to a Preferred MS product?	**Yes:** Inform provider of covered alternatives in the class.	**No:** Go to #4.
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny for medical appropriateness.
5. Does the patient have any of the following: • Adherence issues necessitating less frequent administration • Dexterity issues limiting ability to administer subcutaneous injections	**Yes:** Approve for up to one year.	**No:** Pass to RPH; Deny for medical appropriateness.

P&T / DUR Action: *1022 (DM); 6/21(DM); 8/20 (DM); 6/20; 11/17; 9/23/14*
Implementation: *TBD, 10/15*

Ofatumumab (Kesimpta™)

Goal(s):

- Restrict drug use to patient populations in which the drug has been shown to be effective and safe.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Kesimpta™ (ofatumumab) pharmacy or physician administered claims
- Requests for Arzerra™ should be reviewed under the Oncology 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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication FDA-approved or compendia-supported for the requested indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient of childbearing potential?	**Yes:** Go to #7	**No:** Go to #9
7. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Has the patient failed trials for at least 2 drugs indicated for the treatment of relapsing multiple sclerosis?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the drug prescribed by or in consultation with a neurologist?	**Yes**: Approve ofatumumab 20 mg SC at week 0, 1 and 2 followed by 20 mg once monthly starting at week 4 for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *10/22 (DM); 6/21 (DM)*
Implementation: *TBD, 7/1/2021*

Natalizumab (Tysabri®)

Goal(s):

- Approve therapy for covered diagnosis which are supported by the medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Natalizumab (Tysabri®) pharmacy or physician administered claims

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Has the patient been screened for John Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness

Approval Criteria		
3. Does the patient have a diagnosis of relapsing multiple sclerosis (CIS, RRMS, or SPMS)?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny for medical appropriateness.
6. Does the patient have Crohn's Disease?	**Yes:** Go to #7	No: Pass to RPH; Deny for medical appropriateness.
7. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #8	**No:** Pass to RPH; Deny for medical appropriateness**.**
8. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • Has the patient tried and failed a 3 month trial of Humira?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.

P&T / DUR Action: *10/22 (DM); 6/21(DM); 10/20 (DM); 11/17*
Implementation: *TBD, 1/1/18*

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 Literature Scan: HIV

Date of Review: October 2022

Date of Last Review: August 2021
Literature Search: 05/24/21 – 08/16/22

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

Conclusions:

- Six new randomized controlled trials (RCT) are included (**Appendix 2**) in this literature scan.
- Two RCT support recent approval by the FDA for cabotegravir (APRETUDE) in pre-exposure prophylaxis (PrEP). When compared with tenofovir disoproxil fumarate/emtricitabine, incident human immunodeficiency virus (HIV) infections were reduced in female participants at high risk of HIV acquisition (hazard ratio [HR] 0.12; 95% confidence interval [CI] 0.05 to 0.31; p=<0.0001; superiority design)[1] and in cisgender men who have sex with men (MSM) and transgender women who have sex with men (HR 0.34; 95% CI 0.18 to 0.62; P<0.001; non-inferiority design).[2] Cabotegravir with rilpivirine for HIV-1 treatment has received expanded indications for both population age (12 years and older) and approved dosing regimens (monthly and every two-months), with or without oral-lead in therapy.
- One RCT compared incident HIV infection at 96 weeks in MSM and transgender women who have sex with men with use tenofovir alafenamide fumarate/emtracitabine versus tenofovir disoproxil fumarate/emtracitabine for PrEP (incident rate ratio [IRR] 0.54; 95% CI 0.23 to 1.26; non-inferiority design).[3]
- One RCT found a doravirine-based regimen was non-inferior to an efavirenz-based regimen in treatment-naïve adults for the outcome of viral suppression defined as a HIV RNA less than 50 copies/mL at 96 weeks (77.5% vs. 73.6%, difference 3.8%; 95% CI -2.4% to 10.0%).[4]
- One RCT compared dolutegravir/emtracitabine/(tenofovir disoproxil fumarate or tenofovir alafenamide fumarate) to an efavirenz/emtricitabine/tenofovir disoproxil fumarate regimen in pregnant women. Viral suppression at delivery in the combined dolutegravir (DTG) groups (98%) was compared to the efavirenz group (91%) (est. difference 6.5%; 95% CI 2.0 to 10.7%; P=0.0052; non-inferiority design with prespecified superiority criteria). Composite adverse pregnancy outcomes were lower in the dolutegravir/emtracitabine/ tenofovir alafenamide fumarate (24%) when compared to dolutegravir/emtracitabine/ tenofovir disoproxil fumarate (33%; est. difference -8.8%; 95% CI -17.3 to -0.3; P=0.043) or the efavirenz group (33%; est. difference -8.6%; 95% CI -17.1 to -0.1; P=0.047).[5]
- One RCT compared dolutegravir (DTG) based 3 drug regimens to non-DTG based 3 drug regimens in children requiring 1st or 2nd line therapy. Prespecified non-inferiority criteria were met for the outcome of treatment failure with DTG versus non-DTG based therapy (difference in proportion -0.08; 95% CI -0.14 to -0.03; P=0.004; non-inferiority design).[6]
- Bictegravir/emtricitabine/tenofovir alafenamide fumarate (BIKTARVY) and abacavir/dolutegravir/lamivudine (TRIUMEQ/TRIUMEQ PD) both received expanded indications for pediatric populations and introduced new formulations to accommodate smaller pediatric patients.

Author: Sara Fletcher, PharmD, MPH, BCPS

- Several older agents, including stavudine, didanosine, saquinavir and nelfinavir, are no longer recommended in current guidelines. An evaluation of claims data did not identify any current Medicaid patients with claims for these agents.

Recommendations:
- Change stavudine, didanosine, saquinavir, and nelfinavir to non-preferred.

Summary of Prior Reviews and Current Utilization
HIV drugs were added to the PDL in 2015. At the time, all agents were made preferred. Guidelines and literature for HIV drugs were re-evaluated in 2021. Evidence demonstrated variation amongst guidelines related to the recommended initial treatment regimens and alternative regimens in adults. Guideline methodology and quality varies significantly. However, recommendations for initial therapy for most patients consisted of:
- A two-drug nucleoside reverse transcriptase inhibitor backbone combined with:
- An add-on therapy of a non-nucleoside reverse transcriptase inhibitor (NNRTI), integrase strand transfer inhibitor (INSTI), or boosted protease inhibitor (PI)

Guidelines from the Department of Health and Human Services (HHS), also list several agents which are no longer recommended for treatment of HIV. Drugs which are not recommended for use include the following:[7,8]
- Nucleoside reverse transcriptase inhibitors (NRTIs): stavudine, and didanosine. These are older drugs which are no longer recommended because of high rates of serious toxicities, and they have generally been replaced by newer NRTIs with decreased risk of serious adverse events.
- Protease inhibitors (PIs): saquinavir and nelfinavir. These older agents have disadvantages such as greater pill burden, lower efficacy, or increased toxicity. Newer protease inhibitors such as atazanavir and darunavir are more commonly recommended.

During the first quarter of 2022, there were over 150 FFS patients with claims for HIV therapy. The most commonly prescribed HIV therapies included:
- Single-tablet 3-drug regimens and
- Combination 2-drug NRTI regimens with indications for PrEP

This trend for commonly prescribed therapies has been consistent over the past few years for both FFS and CCO patients enrolled in Oregon Medicaid. Only a small proportion of patients had claims for 2-drug single-tablet regimens. Overall, about one-third of patients had paid claims for drugs commonly used in multi-tablet regimens. The most common drugs use for multi-tablet regimens from each class were dolutegravir (INSTI), darunavir (PI), and rilpivirine (NNRTI). There was no recent FFS or CCO utilization for drugs which are no longer recommended by U.S. guidelines including saquinavir, nelfinavir, stavudine, and didanosine.

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:

After review, 3 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:
After review, 2 guidelines were excluded due to poor quality or general lack of applicability to PDL assessment.

New Formulations:[9]
Bictegravir/emtricitabine/tenofovir alafenamide (BIKTARVY)-low dose tablet (Oct 2021)
Cabotegravir (APRETUDE)-Extended-release injectable for pre-exposure prophylaxis (Dec 2021)
Abacavir/dolutegravir/lamivudine (TRIUMEQ PD)-tablets for oral suspension (March 2022)

Table 1: New Indications:[9]

Generic Name	Brand Name	Month / Year of Change	New or Expanded Indication
Abacavir/dolutegravir/lamivudine tablet	TRIUMEQ; TRIUMEQ PD	March 2022	Pediatric patients with HIV-1 infection weighing at least 10 kg
Bictegravir; emtricitabine; tenofovir alafenamide tablet	BIKTARVY	Oct 2021	Pediatric patients with HIV-1 infection weighing at least 14 kg
Cabotegravir extended-release intramuscular suspension	APRETUDE	Dec 2021	At-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV.
Cabotegravir tablet	VOCABRIA	Dec 2021 March 2022	Expanded to include use as an oral lead-in for APRETUDE for HIV-1 pre-exposure prophylaxis (PrEP) for adults and pediatric patients 12 to less than 19 years of age and weighing at least 35 kg and as short-term oral therapy for HIV-1 PrEP for patients who will miss a planned injection dosing of APRETUDE. Expands use in combination with rilpivirine as an oral, short-term treatment regimen followed by every two-month or monthly CABENUVA injection

			dosing regimen for the treatment of HIV-1 virus infection in adolescents 12 years of age and older and weighing at least 35 kg.
Cabotegravir/rilpivirine extended-release intramuscular suspension	CABENUVA kit	Jan 2022 March 2022 March 2022	Expanded to include every 2-month dosing regimen for treatment of HIV-1 in adults to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no known or suspected resistance to cabotegravir or rilpivirine. Removal of need for mandatory oral, lead-in therapy. Treatment of HIV-1 infection in adolescents 12 years of age and older and weighing at least 35 kg with use of monthly and every 2-month dosing.
Doravirine tablet Doravirine/lamivudine/tenofovir disoproxil tablet	PIFELTRO DELSTRIGO	Jan 2022	Pediatric patients with HIV-1 infection weighing at least 35 kg
Rilpivirine tablet	EDURANT	March 2022	Expand, in combination with VOCABRIA (cabotegravir), as an oral, short-term treatment regimen, followed by CABENUVA injection dosing regimen for the treatment of HIV-1 virus infection in adolescents 12 years of age and older and weighing at least 35 kg.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
abacavir sulfate	ABACAVIR	ORAL	SOLUTION	Y
abacavir sulfate	ZIAGEN	ORAL	SOLUTION	Y
abacavir sulfate	ABACAVIR	ORAL	TABLET	Y
abacavir sulfate	ZIAGEN	ORAL	TABLET	Y
abacavir sulfate/lamivudine	ABACAVIR-LAMIVUDINE	ORAL	TABLET	Y
abacavir sulfate/lamivudine	EPZICOM	ORAL	TABLET	Y
abacavir/dolutegravir/lamivudi	TRIUMEQ PD	ORAL	TAB SUSP	Y
abacavir/dolutegravir/lamivudi	TRIUMEQ	ORAL	TABLET	Y
abacavir/lamivudine/zidovudine	ABACAVIR-LAMIVUDINE-ZIDOVUDINE	ORAL	TABLET	Y
abacavir/lamivudine/zidovudine	TRIZIVIR	ORAL	TABLET	Y
atazanavir sulfate	ATAZANAVIR SULFATE	ORAL	CAPSULE	Y
atazanavir sulfate	REYATAZ	ORAL	CAPSULE	Y
atazanavir sulfate	REYATAZ	ORAL	POWD PACK	Y
atazanavir sulfate/cobicistat	EVOTAZ	ORAL	TABLET	Y
bictegrav/emtricit/tenofov ala	BIKTARVY	ORAL	TABLET	Y
cabotegravir	APRETUDE	INTRAMUSC	SUSER VIAL	Y
cabotegravir	CABOTEGRAVIR ER	INTRAMUSC	SUSER VIAL	Y
cabotegravir	APRETUDE	INTRAMUSC	SUSER VIAL	Y
cabotegravir sodium	VOCABRIA	ORAL	TABLET	Y
cabotegravir/rilpivirine	CABENUVA	INTRAMUSC	SUSER VIAL	Y
cobicistat	TYBOST	ORAL	TABLET	Y
darunavir ethanolate	PREZISTA	ORAL	ORAL SUSP	Y
darunavir ethanolate	PREZISTA	ORAL	TABLET	Y
darunavir/cob/emtri/tenof alaf	SYMTUZA	ORAL	TABLET	Y
darunavir/cobicistat	PREZCOBIX	ORAL	TABLET	Y
didanosine	DIDANOSINE	ORAL	CAPSULE DR	Y
didanosine/sodium citrate	VIDEX	ORAL	PACKET	Y
dolutegravir sodium	TIVICAY PD	ORAL	TAB SUSP	Y
dolutegravir sodium	TIVICAY	ORAL	TABLET	Y
dolutegravir sodium/lamivudine	DOVATO	ORAL	TABLET	Y
dolutegravir/rilpivirine	JULUCA	ORAL	TABLET	Y
doravirine	PIFELTRO	ORAL	TABLET	Y
doravirine/lamivu/tenofov diso	DELSTRIGO	ORAL	TABLET	Y
efavirenz	EFAVIRENZ	ORAL	CAPSULE	Y
efavirenz	SUSTIVA	ORAL	CAPSULE	Y
efavirenz	EFAVIRENZ	ORAL	TABLET	Y
efavirenz	SUSTIVA	ORAL	TABLET	Y
efavirenz/emtricit/tenofovr df	ATRIPLA	ORAL	TABLET	Y
efavirenz/emtricit/tenofovr df	EFAVIRENZ-EMTRIC-TENOFOV DISOP	ORAL	TABLET	Y
efavirenz/lamivu/tenofov disop	EFAVIRENZ-LAMIVU-TENOFOV DISOP	ORAL	TABLET	Y

efavirenz/lamivu/tenofov disop	SYMFI	ORAL	TABLET	Y
efavirenz/lamivu/tenofov disop	SYMFI LO	ORAL	TABLET	Y
elviteg/cob/emtri/tenof alafen	GENVOYA	ORAL	TABLET	Y
elviteg/cob/emtri/tenofo disop	STRIBILD	ORAL	TABLET	Y
emtricita/rilpivirine/tenof DF	COMPLERA	ORAL	TABLET	Y
emtricitab/rilpiviri/tenof ala	ODEFSEY	ORAL	TABLET	Y
emtricitabine	EMTRICITABINE	ORAL	CAPSULE	Y
emtricitabine	EMTRIVA	ORAL	CAPSULE	Y
emtricitabine	EMTRIVA	ORAL	SOLUTION	Y
emtricitabine/tenofov alafenam	DESCOVY	ORAL	TABLET	Y
emtricitabine/tenofovir (TDF)	EMTRICITABINE-TENOFOVIR DISOP	ORAL	TABLET	Y
emtricitabine/tenofovir (TDF)	TRUVADA	ORAL	TABLET	Y
enfuvirtide	FUZEON	SUBCUT	VIAL	Y
etravirine	ETRAVIRINE	ORAL	TABLET	Y
etravirine	INTELENCE	ORAL	TABLET	Y
fosamprenavir calcium	LEXIVA	ORAL	ORAL SUSP	Y
fosamprenavir calcium	FOSAMPRENAVIR CALCIUM	ORAL	TABLET	Y
fosamprenavir calcium	LEXIVA	ORAL	TABLET	Y
ibalizumab-uiyk	TROGARZO	INTRAVEN	VIAL	Y
lamivudine	EPIVIR	ORAL	SOLUTION	Y
lamivudine	LAMIVUDINE	ORAL	SOLUTION	Y
lamivudine	EPIVIR	ORAL	TABLET	Y
lamivudine	LAMIVUDINE	ORAL	TABLET	Y
lamivudine/tenofovir disop fum	CIMDUO	ORAL	TABLET	Y
lamivudine/tenofovir disop fum	TEMIXYS	ORAL	TABLET	Y
lamivudine/zidovudine	COMBIVIR	ORAL	TABLET	Y
lamivudine/zidovudine	LAMIVUDINE-ZIDOVUDINE	ORAL	TABLET	Y
lopinavir/ritonavir	KALETRA	ORAL	SOLUTION	Y
lopinavir/ritonavir	LOPINAVIR-RITONAVIR	ORAL	SOLUTION	Y
lopinavir/ritonavir	KALETRA	ORAL	TABLET	Y
lopinavir/ritonavir	LOPINAVIR-RITONAVIR	ORAL	TABLET	Y
maraviroc	SELZENTRY	ORAL	SOLUTION	Y
maraviroc	MARAVIROC	ORAL	TABLET	Y
maraviroc	SELZENTRY	ORAL	TABLET	Y
nelfinavir mesylate	VIRACEPT	ORAL	TABLET	Y
nevirapine	NEVIRAPINE	ORAL	ORAL SUSP	Y
nevirapine	NEVIRAPINE ER	ORAL	TAB ER 24H	Y
nevirapine	VIRAMUNE XR	ORAL	TAB ER 24H	Y
nevirapine	NEVIRAPINE	ORAL	TABLET	Y
nevirapine	VIRAMUNE	ORAL	TABLET	Y
raltegravir potassium	ISENTRESS	ORAL	POWD PACK	Y
raltegravir potassium	ISENTRESS	ORAL	TAB CHEW	Y

raltegravir potassium	ISENTRESS	ORAL	TABLET	Y
raltegravir potassium	ISENTRESS HD	ORAL	TABLET	Y
rilpivirine	RILPIVIRINE ER	INTRAMUSC	SUSER VIAL	Y
rilpivirine HCl	EDURANT	ORAL	TABLET	Y
ritonavir	NORVIR	ORAL	POWD PACK	Y
ritonavir	NORVIR	ORAL	SOLUTION	Y
ritonavir	NORVIR	ORAL	TABLET	Y
ritonavir	RITONAVIR	ORAL	TABLET	Y
saquinavir mesylate	INVIRASE	ORAL	TABLET	Y
stavudine	STAVUDINE	ORAL	CAPSULE	Y
tipranavir	APTIVUS	ORAL	CAPSULE	Y
zidovudine	RETROVIR	INTRAVEN	VIAL	Y
zidovudine	RETROVIR	ORAL	CAPSULE	Y
zidovudine	ZIDOVUDINE	ORAL	CAPSULE	Y
zidovudine	RETROVIR	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	TABLET	Y

Appendix 2: New Comparative Clinical Trials

Since the last review, a total of 609 and 312 citations were identified through PubMed and OVID medline, respectively. After further screening and manual review, all except 6 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). These trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes
Delany-Moretlwe et al.[1] DB, DD, RCT	Long-acting CAB 600 mg IM every 8 weeks TDF/FTC 300/200mg tablet orally daily 185 weeks	N=3224 total -Patients 18-45 years assigned female sex at birth at high-risk of HIV infection	Incident HIV infection (superiority)	CAB = 4 infections; incidence 0.2/100 person-years TDF/FTC = 36 infections; incidence 1.85/100 person-years CAB vs. TDF/FTC HR 0.12 (95% CI 0.05 to 0.31; p<0.0001)	All patients from sub-Saharan Africa CAB cases: 1 case determined to have been present at enrollment, 2 cases did not receive any CAB injections, 1 occurred in patient with delayed injection visits. TDF-FTC cases: Poor or non-adherence (<2 doses/week) observed in 35 of 36 cases, partial adherence (4-6 doses/week) observed in 1 of 36 cases.
Ladovitz et al.[2] DB, DD, RCT	Long-acting CAB 600 mg IM every 8 weeks TDF/FTC 300/200mg tablet orally daily 153 weeks	N=4566 total -Cisgender MSM -At-risk transgender women who have sex with men (N=570)	Incident HIV infection (non-inferiority) -Non-inferiority margin predetermined HR 1.23	CAB = 13 infections; incidence 0.41/100 person-years TDF/FTC = 39 infections; incidence 1.22/100 person-years CAB vs. TDF/FTC HR 0.34 (95% CI 0.18 to 0.62; p<0.001)	Patients from US, Latin America, Asia, and Africa -96.6% adherence during oral tablet lead-in -74.2% with TDF concentrations consistent with daily use Stopped early for efficacy at preplanned interim analysis.
Lockman et al.[5] RCT	1. DTG/FTC/TAF 2. DTG/FTC/TDF 3. EFV/FTC/TDF	N=643 total -Treatment-naïve pregnant, adult, women with HIV-1 and 14-28 weeks gestation	-Viral suppression (HIV-1 RNA < 200 copies/mL) at or within 14 days of delivery (non-inferiority vs. EFV group) -Composite adverse pregnancy outcome	<u>Viral Suppression</u> Combined DTG groups: 98% EFV group: 91% Est difference 6.5% (95% CI 2.0 to 10.7%; p=0.0052) <u>Composite adverse pregnancy outcome</u> 1. 24%	Open-label Patients from Brazil, India, sub-Saharan Africa, Thailand, & US Stratified by gestation and country Composite adverse pregnancy outcomes include spontaneous abortion, stillbirth,

			-Occurrence of grade 3 or higher maternal and infant adverse events	2. 33% 3. 33% 1 vs. 2 Est difference -8.8% (95% CI -17.3 to -0.3; p=0.043) 1 vs. 3 Est difference -8.6% (95% CI -17.1 to -0.1; p=0.047) 2 vs. 3 NS <u>Grade 3 or higher maternal and infant adverse events</u> 1. 21% 2. 26% 3. 22% NS between groups	preterm delivery, or the infant being born small for gestational age.
Ogbuagu et al.[3] DB, RCT	TAF/FTC (25/200mg) TDF/FTC (300/200mg) 96 weeks	N=5387 total -Cisgender MSM -At-risk transgender women who have sex with men	Incident HIV infection at 96 weeks (non-inferiority)	TAF/FTC: 8 infections incidence 0.16/100 person-years TDF/FTC: 15 infections incidence 0.3/100 person-years TAF/FTC vs TDF/FTC IRR 0.54 (95% CI 0.23 to 1.26)	Patients from Europe and North America Adherence was similar between groups and assessed by dry blood spot, self-report, and pill count.
Orkin et al.[4] DRIVE-AHEAD DB, RCT	DOR/3TC/TDF (100/300/300mg FDT) EFV/FTC/TDF (600/200/300mg FDT) 96 weeks	N=728 total Treatment naïve adults	HIV-1 RNA levels <50 copies/mL at week 96 (non-inferiority)	DOR/3TC/TDF: 77.5% EFV/FTC/TDF: 73.6% Treatment difference 3.8% (95% CI -2.4% to 10.0%)	Participants from Africa, Asia/Pacific, Europe, Latin America, and North America. Neuropsychiatric adverse events more common in EFV based group.

Turkova et al.[6] RCT	DTG based 3-drug ART Non-DTG based 3-drug ART standard care 96 weeks	N=707 total Children 4 weeks to < 18 years old weighing at least 14kg with HIV-1 Requiring 1st or 2nd line ART	Virologic or clinical treatment failure by 96 weeks (non-inferiority)	DTG based: 47 failure (estimated probability 0.14) Non-DTG based: 75 failure (estimated probability 0.22) Difference in proportion -0.08 (95% CI -0.14 to -0.03, P=0.004)	Open-label Those <14 kg enrolled in different, ongoing trial cohort. Most participants from sub-Saharan Africa, some sites in Thailand and Europe. 1st and 2nd line cohort enrollments similar (44% vs. 56%)
Abbreviations: ART = antiretroviral treatment; CAB = cabotegravir; CI = confidence interval; DB = double-blind; DD = double-dummy; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; FDT = fixed-dose tablet; FTC = emtricitabine; HIV = human immunodeficiency virus; HR = hazard ratio; IM = intramuscular; IRR = incidence rate ratio; MSM = men who have sex with men; NS = not significant; RCT = randomized clinical trial; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; US = United States; 3TC = lamivudine.					

Appendix 3: Abstracts of Comparative Clinical Trials

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial[1]

BACKGROUND: Oral pre-exposure prophylaxis has been introduced in more than 70 countries, including many in sub-Saharan Africa, but women experience considerable barriers to daily pill-taking, such as stigma, judgement, and the fear of violence. Safe and effective long-acting agents for HIV prevention are needed for women. We aimed to evaluate the safety and efficacy of injectable cabotegravir compared with daily oral tenofovir diphosphate plus emtricitabine (TDF-FTC) for HIV prevention in HIV-uninfected women. METHODS: HPTN 084 was a phase 3, randomised, double-blind, double-dummy, active-controlled, superiority trial in 20 clinical research sites in seven countries in sub-Saharan Africa. Participants were eligible for enrolment if they were assigned female sex at birth, were aged 18-45 years, reported at least two episodes of vaginal intercourse in the previous 30 days, were at risk of HIV infection based on an HIV risk score, and agreed to use a long-acting reversible contraceptive method. Participants were randomly assigned (1:1) to either active cabotegravir with TDF-FTC placebo (cabotegravir group) or active TDF-FTC with cabotegravir placebo (TDF-FTC group). Study staff and participants were masked to study group allocation, with the exception of the site pharmacist who was responsible for study product preparation. Participants were prescribed 5 weeks of daily oral product followed by intramuscular injections every 8 weeks after an initial 4-week interval load, alongside daily oral pills. Participants who discontinued injections were offered open-label daily TDF-FTC for 48 weeks. The primary endpoints of the study were incident HIV infection in the intention-to-treat population, and clinical and laboratory events that were grade 2 or higher in all women who had received at least one dose of study product. This study is registered with ClinicalTrials.gov, NCT03164564. FINDINGS: From Nov 27, 2017, to Nov 4, 2020, we enrolled 3224 participants (1614 in the cabotegravir group and 1610 in the TDF-FTC group). Median age was 25 years (IQR 22-30); 1755 (54·7%) of 3209 had two or more partners in the preceding month. 40 incident infections were observed over 3898 person-years (HIV incidence 1·0% [95% CI 0·73-1·40]); four in the cabotegravir group (HIV incidence 0·2 cases per 100 person-years [0·06-0·52]) and 36 in the TDF-FTC group (1·85 cases per 100 person-years [1·3-2·57]; hazard ratio 0·12 [0·05-0·31]; p<0·0001; risk difference -1·6% [-1·0% to -2·3%]. In a random subset of 405 TDF-FTC participants, 812 (42·1%) of 1929 plasma samples had tenofovir concentrations consistent with daily use. Injection coverage was 93% of the total number of person-years. Adverse event rates were similar across both groups, apart from injection site reactions, which were more frequent in the cabotegravir group than in the TDF-FTC group (577 [38·0%] of 1519 vs 162 [10·7%] of 1516]) but did not result in injection discontinuation. Confirmed pregnancy incidence was 1·3 per 100 person-years (0·9-1·7); no congenital birth anomalies were reported. INTERPRETATION: Although both products for HIV prevention were generally safe, well tolerated, and effective, cabotegravir was superior to TDF-FTC in preventing HIV infection in women.

Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women[2]

BACKGROUND: Safe and effective long-acting injectable agents for preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection are needed to increase the options for preventing HIV infection. METHODS: We conducted a randomized, double-blind, double-dummy, noninferiority trial to compare long-acting injectable cabotegravir (CAB-LA, an integrase strand-transfer inhibitor [INSTI]) at a dose of 600 mg, given intramuscularly every 8 weeks, with daily oral tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) for the prevention of HIV infection in at-risk cisgender men who have sex with men (MSM) and in at-risk transgender women who have sex with men. Participants were randomly assigned (1:1) to receive one of the two regimens and were followed for 153 weeks. HIV testing and safety evaluations were performed. The primary end point was incident HIV infection. RESULTS: The intention-to-treat population included 4566 participants who underwent randomization; 570 (12.5%) identified as transgender women, and the median age was 26 years (interquartile range, 22 to 32). The trial was stopped early for efficacy on review of the results of the first preplanned interim end-point analysis. Among 1698 participants from the United States, 845 (49.8%) identified as Black. Incident HIV infection occurred in 52 participants: 13 in the cabotegravir group (incidence, 0.41 per 100 person-years) and 39 in the TDF-FTC group (incidence, 1.22 per 100 person-years) (hazard ratio, 0.34; 95% confidence interval, 0.18 to 0.62). The effect was consistent across prespecified subgroups. Injection-site reactions were reported in 81.4% of the participants in the cabotegravir group and in 31.3% of those in the TDF-FTC group. In the participants in whom HIV infection was diagnosed after exposure to CAB-LA, INSTI resistance and delays in the detection of HIV infection were noted. No

safety concerns were identified. CONCLUSIONS: CAB-LA was superior to daily oral TDF-FTC in preventing HIV infection among MSM and transgender women. Strategies are needed to prevent INSTI resistance in cases of CAB-LA PrEP failure. (Funded by the National Institute of Allergy and Infectious Diseases and others; HPTN 083 ClinicalTrials.gov number, NCT02720094.).

Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial[5]

BACKGROUND: Antiretroviral therapy (ART) during pregnancy is important for both maternal health and prevention of perinatal HIV-1 transmission; however adequate data on the safety and efficacy of different ART regimens that are likely to be used by pregnant women are scarce. In this trial we compared the safety and efficacy of three antiretroviral regimens started in pregnancy: dolutegravir, emtricitabine, and tenofovir alafenamide fumarate; dolutegravir, emtricitabine, and tenofovir disoproxil fumarate; and efavirenz, emtricitabine, and tenofovir disoproxil fumarate. METHODS: This multicentre, open-label, randomised controlled, phase 3 trial was done at 22 clinical research sites in nine countries (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the USA, and Zimbabwe). Pregnant women (aged ≥18 years) with confirmed HIV-1 infection and at 14–28 weeks' gestation were eligible. Women who had previously taken antiretrovirals in the past were excluded (up to 14 days of ART during the current pregnancy was permitted), as were women known to be pregnant with multiple fetuses, or those with known fetal anomaly or a history of psychiatric illness. Participants were randomly assigned (1:1:1) using a central computerised randomisation system. Randomisation was done using permuted blocks (size six) stratified by gestational age (14–18, 19–23, and 24–28 weeks' gestation) and country. Participants were randomly assigned to receive either once-daily oral dolutegravir 50 mg, and once-daily oral fixed-dose combination emtricitabine 200 mg and tenofovir alafenamide fumarate 25 mg; once-daily oral dolutegravir 50 mg, and once-daily oral fixed-dose combination emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg; or once-daily oral fixed-dose combination of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg. The primary efficacy outcome was the proportion of participants with viral suppression, defined as an HIV-1 RNA concentration of less than 200 copies per mL, at or within 14 days of delivery, assessed in all participants with an HIV-1 RNA result available from the delivery visit, with a prespecified non-inferiority margin of −10% in the combined dolutegravir-containing groups versus the efavirenz-containing group (superiority was tested in a pre-planned secondary analysis). Primary safety outcomes, compared pairwise among treatment groups, were the occurrence of a composite adverse pregnancy outcome (ie, either preterm delivery, the infant being born small for gestational age, stillbirth, or spontaneous abortion) in all participants with a pregnancy outcome, and the occurrence of grade 3 or higher maternal and infant adverse events in all randomised participants. This trial was registered with ClinicalTrials.gov, NCT03048422. FINDINGS: Between Jan 19, 2018, and Feb 8, 2019, we enrolled and randomly assigned 643 pregnant women: 217 to the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group, 215 to the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group, and 211 to the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group. At enrolment, median gestational age was 21·9 weeks (IQR 18·3–25·3), the median HIV-1 RNA concentration among participants was 902·5 copies per mL (152·0–5182·5; 181 [28%] of 643 participants had HIV-1 RNA concentrations of <200 copies per mL), and the median CD4 count was 466 cells per µL (308–624). HIV-1 RNA concentrations at delivery were available for 605 (94%) participants. Of these, 395 (98%) of 405 participants in the combined dolutegravir-containing groups had viral suppression at delivery compared with 182 (91%) of 200 participants in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (estimated difference 6·5% [95% CI 2·0 to 10·7], p=0·0052; excluding the non-inferiority margin of −10%). Significantly fewer participants in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (52 [24%] of 216) had a composite adverse pregnancy outcome than those in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (70 [33%] of 213; estimated difference −8·8% [95% CI −17·3 to −0·3], p=0·043) or the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (69 [33%] of 211; −8·6% [–17·1 to −0·1], p=0·047). The proportion of participants or infants with grade 3 or higher adverse events did not differ among the three groups. The proportion of participants who had a preterm delivery was significantly lower in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (12 [6%] of 208) than in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (25 [12%] of 207; −6·3% [–11·8 to −0·9], p=0·023). Neonatal mortality was significantly higher in the efavirenz, emtricitabine, and tenofovir

disoproxil fumarate group (ten [5%] of 207 infants) than in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (two [1%] of 208; p=0·019) or the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (three [2%] of 202; p=0·050). INTERPRETATION: When started in pregnancy, dolutegravir-containing regimens had superior virological efficacy at delivery compared with the efavirenz, emtricitabine, and tenofovir disoproxil fumarate regimen. The dolutegravir, emtricitabine, and tenofovir alafenamide fumarate regimen had the lowest frequency of composite adverse pregnancy outcomes and of neonatal deaths.

Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial[3]

BACKGROUND: In DISCOVER, a multinational, randomised controlled trial, emtricitabine and tenofovir alafenamide compared with emtricitabine and tenofovir disoproxil fumarate showed non-inferior efficacy for HIV prevention and improved bone mineral density and renal safety biomarkers at week 48. We report outcomes analysed after all participants had completed 96 weeks of follow-up. METHODS: This study is an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial done at 94 community, public health, and hospital-associated clinics located in Europe and North America. Adult cisgender men and transgender women who have sex with men, both with a high risk of acquiring HIV as determined by self-reported sexual behaviour or recent sexually transmitted infections, were randomly assigned (1:1) to receive either emtricitabine and tenofovir alafenamide (200/25 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir alafenamide group), or emtricitabine and tenofovir disoproxil fumarate (200/300 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir disoproxil fumarate group). The primary efficacy outcome was incident HIV infection. Incidence of HIV-1 infection per 100 person-years was assessed when the last participant had completed 96 weeks of follow-up. This trial is registered with ClinicalTrials.gov , number NCT02842086 .FINDINGS: Between Sept 13, 2016, and June 30, 2017, 5387 participants were randomly assigned to receive emtricitabine and tenofovir alafenamide (n=2694) or emtricitabine and tenofovir disoproxil fumarate (n=2693), contributing 10 081 person-years of follow-up. At 96 weeks of follow-up, there were eight HIV infections in participants who had received emtricitabine and tenofovir alafenamide (0·16 infections per 100 person-years [95% CI 0·07–0·31]) and 15 in participants who had received emtricitabine and tenofovir disoproxil fumarate (0·30 infections per 100 person-years [0·17–0·49]). Emtricitabine and tenofovir alafenamide maintained its non-inferiority to emtricitabine and tenofovir disoproxil fumarate for HIV prevention (IRR 0·54 [95% CI 0·23–1·26]). Approximately 78–82% of participants reported taking study medication more than 95% of the time across all study visits. Rates of sexually transmitted infections remained high and similar across groups (21 cases per 100 person-years for rectal gonorrhoea and 28 cases per 100 person-years for rectal chlamydia). Emtricitabine and tenofovir alafenamide continued to show superiority over emtricitabine and tenofovir disoproxil fumarate in all but one of the six prespecified bone mineral density and renal biomarkers. There was more weight gain among participants who had received emtricitabine and tenofovir alafenamide (median weight gain 1·7 kg vs 0·5 kg, p<0·0001). INTERPRETATION: Emtricitabine and tenofovir alafenamide is safe and effective for longer-term pre-exposure prophylaxis in cisgender men and transgender women who have sex with men.

Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) Versus Efavirenz/Emtricitabine/TDF in Treatment-naive Adults With Human Immunodeficiency Virus Type 1 Infection: Week 96 Results of the Randomized, Double-blind, Phase 3 DRIVE-AHEAD Noninferiority Trial[4]

BACKGROUND: Doravirine (DOR) is a nonnucleoside reverse-transcriptase inhibitor. In the phase 3 DRIVE-AHEAD trial in treatment-naive adults with human immunodeficiency virus type 1 (HIV-1) infection, DOR demonstrated noninferior efficacy compared with efavirenz (EFV) and superior profiles for neuropsychiatric tolerability and lipids at 48 weeks. We present data through week 96. METHODS: DRIVE-AHEAD is a phase 3, multicenter, double-blind, noninferiority trial in antiretroviral treatment-naive adults with HIV-1 RNA >/=1000 copies/mL. Participants were randomized to a daily fixed-dose tablet of DOR (100 mg), lamivudine (3TC; 300 mg) and tenofovir disoproxil fumarate (TDF; 300 mg) (DOR/3TC/TDF) or EFV (600 mg), emtricitabine (FTC; 200 mg) and TDF (300 mg) (EFV/FTC/TDF). The efficacy end point of interest at week 96 was the proportion of participants with HIV-1 RNA levels <50 copies/mL (Food and Drug Administration Snapshot Approach) with a predefined noninferiority margin of 10% to support week 48 results. Safety end points of interest included

prespecified neuropsychiatric adverse events and the mean change in fasting lipids at week 96. RESULTS: Of 734 participants randomized, 728 received study drugs and were included in analyses. At week 96, HIV-1 RNA <50 copies/mL was achieved by 77.5% of DOR/3TC/TDF vs 73.6% of EFV/FTC/TDF participants, with a treatment difference of 3.8% (95% confidence interval, -2.4% to 10%). Virologic failure rates were low and similar across treatment arms, with no additional resistance to DOR observed between weeks 48 and 96. Prespecified neuropsychiatric adverse events and rash were less frequent in DOR/3TC/TDF than in EFV/FTC/TDF participants through week 96. At week 96, fasting low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol (HDL-C) levels increased in the EFV/FTC/TDF group but not in the DOR/3TC/TDF group; the mean changes from baseline in total cholesterol/HDL-C ratio were similar. CLINICAL TRIALS REGISTRATION: NCT02403674.

Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children[6]

BACKGROUND: Children with human immunodeficiency virus type 1 (HIV-1) infection have limited options for effective antiretroviral treatment (ART). METHODS: We conducted an open-label, randomized, noninferiority trial comparing three-drug ART based on the HIV integrase inhibitor dolutegravir with standard care (non-dolutegravir-based ART) in children and adolescents starting first- or second-line ART. The primary end point was the proportion of participants with virologic or clinical treatment failure by 96 weeks, as estimated by the Kaplan-Meier method. Safety was assessed. RESULTS: From September 2016 through June 2018, a total of 707 children and adolescents who weighed at least 14 kg were randomly assigned to receive dolutegravir-based ART (350 participants) or standard care (357). The median age was 12.2 years (range, 2.9 to 18.0), the median weight was 30.7 kg (range, 14.0 to 85.0), and 49% of the participants were girls. By design, 311 participants (44%) started first-line ART (with 92% of those in the standard-care group receiving efavirenz-based ART), and 396 (56%) started second-line ART (with 98% of those in the standard-care group receiving boosted protease inhibitor-based ART). The median follow-up was 142 weeks. By 96 weeks, 47 participants in the dolutegravir group and 75 in the standard-care group had treatment failure (estimated probability, 0.14 vs. 0.22; difference, -0.08; 95% confidence interval, -0.14 to -0.03; P = 0.004). Treatment effects were similar with first- and second-line therapies (P = 0.16 for heterogeneity). A total of 35 participants in the dolutegravir group and 40 in the standard-care group had at least one serious adverse event (P = 0.53), and 73 and 86, respectively, had at least one adverse event of grade 3 or higher (P = 0.24). At least one ART-modifying adverse event occurred in 5 participants in the dolutegravir group and in 17 in the standard-care group (P = 0.01). CONCLUSIONS: In this trial involving children and adolescents with HIV-1 infection who were starting first- or second-line treatment, dolutegravir-based ART was superior to standard care. (Funded by ViiV Healthcare; ODYSSEY ClinicalTrials.gov number, NCT02259127; EUDRACT number, 2014-002632-14; and ISRCTN number, ISRCTN91737921.).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to August 16, 2022
1 exp HIV/ or exp Anti-HIV Agents/ or exp HIV-1/ 155430
2 limit 1 to (yr="2021 -Current" and (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)) 312

PubMed.gov:
(HIV infection) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))
Filters applied: from 2021/6/1 - 2022/8/16
609 results

After manual review of results above, 2 guidelines, 3 systematic reviews, and 10 comparative trials were identified for additional quality assessment.

Appendix 5: Key Inclusion Criteria

Population	Adults and children with HIV-1 or at risk of acquiring HIV-1
Intervention	See **Appendix 1**
Comparator	See **Appendix 1**
Outcomes	HIV RNA copies, HIV acquisition
Timing	Prophylaxis or Treatment
Setting	Outpatient

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 with New Drug Evaluation: GLP-1 Receptor Agonists and SGLT-2 Inhibitors

Date of Review: October 2022

Date of Last Review: GLP-1 receptor agonists (August 2020)
SGLT-2 inhibitors (August 2021)

Dates of Literature Search: 08/01/2020 - 08/08/2022

Generic Name: tirzepatide

Brand Name (Manufacturer): Mounjaro (Eli Lilly and Company)

Dossier Received: yes

Plain Language Summary:

- Drugs used to treat diabetes lower sugar levels in the blood. Drugs work to lower sugar levels in different ways. Diabetes drugs are divided into classes based on how they work. Drugs that lower sugars the same way are put into the same class. This report is reviewing two classes of drugs. The first class is called sodium-glucose cotransporter 2 (SGLT2) inhibitors and the second class is called glucagon-like peptide-1 receptor agonist (GLP-1 RA). A new drug will also be reviewed that is part of new class called GLP1 RAs / glucose-dependent insulinotropic polypeptide (GIP) agonists.
- A review was done that looked at SGLT2 inhibitors in people that had type 2 diabetes (T2D) and heart disease or had a high chance of getting heart disease. The review found SGLT2 drugs, when compared to treatment with a sugar pill, was more effective at reducing the risk dying from heart disease or having to go into the hospital because of a failing heart, dying due to any cause, or having any major heart related issue (such as a heart attack or stroke). The results were the same for different ages of people, men and women and for those of different races.
- A report found using GLP-1 RAs, compared to other drugs used to lower sugar levels, may cause an increased risk of gallbladder or biliary diseases. Biliary diseases are diseases that affect the bile ducts, gallbladder and other structures involved in the production and transportation of bile.
- A respected organization that produces guidelines for managing diabetes recommends that most people needing medication to lower sugars for the first time should try metformin. People that also have heart issues should consider using a SGLT2 inhibitor with metformin.
- A respected organization that produces guidelines for managing diabetes recommends that adults who have kidney disease, even if they don't have diabetes, should consider using the drug dapagliflozin, which is a type of SGLT2 inhibitor.
- A medication which is part of the GLP-1 RA class is called semaglutide. It was previously available just as a weekly injectable but is now formulated as an oral tablet that is taken once a day to reduce sugars in the blood.
- The Food and Drug Administration (FDA) reviews the proper uses of drugs and they recently evaluated dapagliflozin, which is part of the SGLT2 inhibitor class. They have authorized dapagliflozin to be used to reduce the risk of worsening kidney disease and death from heart disease and reduce the chance of going to the hospital for heart disease.
- The FDA reviewed exenatide, which is part of the GLP-1 RA class, and found that it is effective in lowering sugar concentrations in children with diabetes who are 10 years and older.

Author: Kathy Sentena, PharmD

- Empagliflozin, which is part of the SGLT2 inhibitor class, was reviewed by the FDA. They evaluated the use of empagliflozin in people with heart failure and decreased ability for the heart to pump blood well and in those with heart failure and normal ability to pump blood. Empagliflozin was found to reduce the chance of dying from heart disease or getting hospitalized for heart failure in both of these type of people.
- A combination of 2 products used to treat T2M containing dapagliflozin and metformin was approved by the FDA to be used to decrease the risk of death from heart disease and for going to the hospital for heart failure in people with heart disease and reduced ability to pump blood. This combination was also approved for reducing the risk of worsening kidney disease and dying from heart disease and going to the hospital for heart failure in people with kidney disease they is likely to get worse.
- Harmful effects of drugs are also tracked by the FDA. There are 3 new warnings for drugs that are used for diabetes. The drugs in the GLP-1 RA class have been shown to possibly increase the risk of gallbladder diseases. Exenatide extended release, which is a GLP-1 RA type drug, has shown to interfere with the ability of a component in the blood. A combination product, dapagliflozin and metformin, has shown a risk of possibly increasing the chance of kidney problems in some people.
- A new drug called tirzepatide was approved by the FDA. Tirzepatide was compared to other drugs for T2D and compared to sugar pills. Tirzepatide was found to lower sugars in the blood better than a sugar pill and the drugs it was compared to. Tirzepatide was also shown to cause weight loss of about 4 pounds to 33 pounds more than placebo or other drugs for diabetes.
- The data we have for drugs to treat T2D is most often studied in White people around 50 to 60 years of age, that are overweight, have had diabetes for around 5 years and have tried other drugs for to lower sugars in the blood.

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

- **Purpose for Class Update:** To identify new evidence for the glucagon-like peptide-1 receptor agonist (GLP-1 RA) and sodium-glucose cotransporter 2 (SGLT2) inhibitor classes since the last reviews and to evaluate the evidence for the newly approved drug, tirzepatide, to determine place in therapy. The focus of this review is for the use of SGLT2 inhibitors and GLP-1 RAs for people with T2D. There is evidence that the use of GLP-1 RAs when used in people, with and without T2D, results in weight reduction. The use of drugs that are indicated for weight loss alone are not covered in this review and evidence for this purpose will be presented in future reviews.

Research Questions:
1. In patients with type 2 diabetes (T2D), what is the comparative evidence for efficacy or harms of GLP-1 RA and SGLT2 inhibitors for important outcomes (e.g., hemoglobin A1c [HbA1C], microvascular outcomes, macrovascular outcomes and mortality)?
2. Are there subpopulations of patients with T2D for which GLP-1 RAs and SGLT2 inhibitors may be more effective or associated with less harm?
3. What is the evidence for the effectiveness and harms of tirzepatide in patients with T2DM?
4. Are there specific subpopulations for which tirzepatide may be specifically indicated, more effective, or associated with less harm?

Conclusions:
- Two high quality systematic review and meta-analyses, 2 high quality guidelines, one new formulation, 5 new indications, 3 new safety warnings, 4 randomized controlled trials (RCTs) and one new drug evaluation are included in this update.

- A systematic review and meta-analysis found moderate quality evidence that SGLT2 inhibitors were more effective than placebo in people with T2DM and atherosclerotic cardiovascular disease (ASCVD) or at high risk of ASCVD for the following outcomes: cardiovascular (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.[1] Subgroup analyses found results of findings for SGLT2 inhibitors to be consistent across sex, ethnicities and age.[1]
- A 2022 systematic review and meta-analysis identified GLP-1 RAs were associated with an increased risk of a composite assessment of gallbladder or biliary diseases compared to active treatments or placebo in adult patients (with or without diabetes) (relative risk [RR] 1.37; 95% confidence interval [CI], 1.23 to 1.52; I^2 = 0%; high quality evidence).[2] Other adverse outcomes associated with the use of GLP-1 RAs more than controls were cholelithiasis, cholecystitis, biliary disease, and cholecystectomy.
- The National Institute for Health and Care Excellence (NICE) updated guidance on managing patients with diabetes with an emphasis on the evidence for clinical data related to SGLT2 inhibitors in people with CV disease or at high risk of developing CV disease. In people without comorbidities, metformin is recommended as first-line therapy.[3] Those that have chronic HF or established atherosclerotic CV disease should be offered a SGLT2 inhibitor with proven CV benefit in addition to metformin (e.g., empagliflozin, canagliflozin, and dapagliflozin).[3]
- In adults with or without diabetes, NICE guidance recommends dapagliflozin as an option for adults with chronic kidney disease (CKD) and who meet additional criteria such as T2D, receiving standard of care for CKD and an estimated glomerular filtration rate (eGFR) is between 25 ml/min/1.73 m^2 and 75 ml/min/1.73 m^2 .[4]
- There was one new formulation of semaglutide (Rybelsus®) FDA-approved since the last update.[5] Five drugs have new indications and/or labeling changes: dapagliflozin (Farxiga®), exenatide (Bydureon®), empagliflozin (Jardiance®), dapagliflozin/metformin (Xigduo XR®) and lixisenatide (Adlyxin®).[6, 7, 8, 9, 10]
- Four good quality RCTs provided evidence for use of the following medications: empagliflozin, ertugliflozin, and dapagliflozin.[11–14]
    - There was moderate quality evidence that empagliflozin was more effective than placebo at preventing CV death or hospitalizations for HF in patients with reduced or preserved ejection fraction, with or without diabetes.[11,14]
    - Ertugliflozin was non-inferior to placebo for the risk of major adverse CV outcomes based on moderate evidence.[12]
    - There was moderate quality of evidence that dapagliflozin was more effective than placebo for reduction in the sustained decline of eGFR of at least 50%, end-stage kidney disease, death from renal or CV causes, and the composite outcome of death from CV causes or hospitalization for HF.[15]
- There were 3 new safety alerts pertaining to the following products: GLP-1 RAs, Bydureon® and Qtern®. There is evidence of an increased risk of acute gallbladder disease related to GLP-1 RAs. Exenatide extended release (Bydureon®) may cause drug induced thrombocytopenia. Dapagliflozin/metformin (Qtern®) may cause intravascular volume depletion and hypotension with case reports of acute kidney injury.
- Tirzepatide is a GLP-1 RA and glucose-dependent insulinotropic polypeptide (GIP) approved in May of 2022 for adult patients with T2D.[16] Five phase 3 RCTs were evaluated for approval comparing tirzepatide to placebo or semaglutide, insulin degludec, or insulin glargine. Tirzepatide demonstrated HbA1c lowering of -1.87% to -2.58% ($P<0.05$ for all comparisons; high quality evidence).[17–21] The number of patients obtaining an HbA1c of 7% or less, was more common with tirzepatide versus comparators (placebo and active controls) with number needed to treat (NNT) of 2 to 34 over 40-52 weeks.[17–21] Tirzepatide was associated with weight loss more than placebo, semaglutide, insulin degludec and insulin glargine with differences ranging from -1.9 kg to -15.2 kg. Cardiovascular outcome trials are ongoing.
- A majority of the evidence for SGLT2 inhibitors and GLP-1 RAs comes from trials enrolling predominately people of White ethnicity, people who are overweight and people 50-60 years of age.

Recommendations:

- Include the glucose-dependent insulinotropic polypeptide (GIP) therapies in the prior authorization (PA) criteria with GLP-1 RAs.
- Update the GLP-1 RA PA criteria to remove concomitant prandial insulin restriction.
- Remove clinical PA criteria for the preferred SGLT2 inhibitors due to effectiveness, for people with and without diabetes and non-preferred products would be subject to general non-preferred criteria. If the decision is made to maintain the PA criteria, update PA criteria to clarify that renal function should be evaluated on an annual basis.
- Maintain tirzepatide as non-preferred on the preferred drug list (PDL) and subject to the GLP-1 RA and GLP + GIP agonist PA criteria.
- No changes are recommended to the preferred drug list (PDL) after review of the current literature. Evaluate drug costs in executive session.

Summary of Prior Reviews and Current Policy

- The last review of SGLT2 inhibitors was in 2021. Evidence from systematic reviews and meta-analyses found that SGLT2 inhibitors reduced the risk of all-cause mortality, CV mortality and hospitalizations for HF in patients with and without diabetes. Canagliflozin, dapagliflozin and empagliflozin are preferred therapies in this class.
- A review of newer diabetic agents in August of 2020 identified literature that SGLT-2 inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin) reduce the risk of hospitalizations due to HF. The requirement for step therapy, other than metformin, was removed for the SGLT2 class. Currently step therapy with metformin only applies to non-preferred treatments.
- The GLP-1 RAs were part of a review of the newer diabetes drugs report in August of 2020. Evidence found GLP-1 RAs (e.g. exenatide extended-release, liraglutide, and semaglutide) reduce the risk of all-cause mortality in people with T2D. The evidence for HF outcomes was neutral with no benefits or harms demonstrated. The requirement for step therapy, other than metformin, was removed for GLP-1 RAs. After executive session dulaglutide was designated a preferred therapy on the PDL. Dulaglutide, exenatide and liraglutide are preferred therapies in this class.

Background:

Approximately 287,000 adult Oregonians have T2D.[22] It is estimated that over 38,000 of these patients are Oregon Health Plan (OHP) members.[22] The Oregon Health Plan paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012.[22] The overall cost to the state is estimated at $3 billion a year.[22] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2D by 2050.[23] 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 diabetes.[24,25]

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.[26] 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.[27] Classes of non-insulin antidiabetic agents currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, 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.[3,27,28] There is no consensus on a universally recognized second-line treatment, and therefore, selection should be

dependent on degree of glucose lowering required to assist in obtaining goal HbA1c levels, patient specific characteristics including comorbidities, and harms of therapy.[3] Therapies that have demonstrated renal and CV benefits are outlined in **Table 1.** 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.[27] This update will focus on new evidence for the use of SGLT2 inhibitors and GLP-1 RAs.

In 2008, the Food and Drug Administration (FDA) started requiring evaluation of CV risk for antidiabetic therapies. Cardiovascular studies have been published for each of the newer classes of antidiabetic therapies. These studies are most applicable to patients with CV disease or at high risk of CV disease (e.g., 55 years or older with coronary, carotid, or lower-extremity artery stenosis greater than 50% or left ventricular hypertrophy). A comparison table of effectiveness and harms can be found in **Table 1**. Both the SGLT2 inhibitors and GLP-1 RAs have demonstrated CV benefits. Guidelines have identified the following drugs as having an CV advantage compared to other therapies: canagliflozin, empagliflozin and liraglutide.[29] There is also evidence that SGLT2 inhibitors slow progression of CKD in people with CKD and albuminuria (200 mg/g creatinine or more).[30] For people with T2D and CKD without albuminuria, both SGLT2 inhibitors or GLP-1 RAs are recommended to decrease CV risk.[27]

Table 1. Cardiovascular Outcomes for Newer Diabetes Medications Vs. Placebo[27,30]

Outcome	All-Cause Mortality	Stroke	CV Death/ CV Events	Myocardial Infarction	Hospitalization for Heart Failure	Serious Adverse Events	Chronic Kidney Disease
Drug Class							
GLP-1 RA	*Small risk reduction (moderate quality evidence)* Benefit: Exenatide ER Liraglutide Semaglutide oral Neutral: Albiglutide Dulaglutide Lixisenatide Semaglutide inj	*No effect (low quality evidence)* Benefit: Dulaglutide Neutral: Albiglutide Exenatide ER Liraglutide Lixisenatide Semaglutide oral No evidence: Semaglutide inj	*Reduced risk (moderate quality evidence)* Benefit: Dulaglutide* Liraglutide* Semaglutide inj*	*No conclusion (very low quality evidence)* Benefit: Albiglutide Liraglutide Neutral: Dulaglutide Exenatide ER Lixisenatide Semaglutide oral No evidence: Semaglutide inj	*No effect (moderate quality evidence)* Neutral: Dulaglutide Exenatide ER Liraglutide Lixisenatide Semaglutide (oral and inj) No evidence: Albiglutide	*Reduced risk (low quality evidence)* Benefit: Albiglutide Dulaglutide Semaglutide (oral and inj) No evidence: Exenatide ER Liraglutide Lixisenatide	*Reduced risk of eGFR decline (low quality evidence)* Benefit: Liraglutide
SGLT-2 Inhibitors	*No effect (moderate quality evidence)* Benefit: Empagliflozin	*No effect (low quality evidence)* Neutral: Canagliflozin Dapagliflozin	*Reduced Risk (moderate quality evidence)* Benefit: Canagliflozin* Dapagliflozin*	*No effect (moderate quality evidence)* Neutral: Canagliflozin Dapagliflozin	*Significant risk reduction (moderate quality evidence)* Benefit: Canagliflozin	*Significant risk reduction (moderate quality evidence)* Benefit: Dapagliflozin Empagliflozin	*Reduced risk of eGFR decline, end stage kidney disease CV death and hospitalization for HF in adults with* CKD *(moderate quality evidence)*

	Neutral: Canagliflozin Dapagliflozin	Empagliflozin	Empagliflozin∞*	Empagliflozin	Dapagliflozin* Empagliflozin*	Neutral or benefit: (conflicting results) Canagliflozin	Benefit: Dapagliflozin* Canagliflozin*

Key: ∞ For patients with preserved and reduced ejection fraction
* 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 0.3% or more.[31] 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:
The quarterly costs paid to pharmacies for SGLT2 inhibitors and GLP-1 RAs are substantial. Utilization of preferred agents was 89% for SGLT2 inhibitors and 78% for GLP-1 RAs.

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

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

Systematic Reviews:
Bhattarai, et al – Association of Sodium-Glucose Cotransporter 2 Inhibitors with Cardiovascular Outcomes in Patients with Type 2 Diabetes and Other Risk Factors for Cardiovascular Disease
A 2022 systematic review and meta-analysis evaluated the CV benefit of SGLT2 inhibitors. Randomized controlled trials compared SGLT2 inhibitors to placebo in patients with ASCVD or risk factors for ASCVD, diabetes or HF.[1] Trials studied the following drugs: empagliflozin, canagliflozin, dapagliflozin and sotagliflozin (not approved in the US). Ten trials were identified with 71,553 participants. The mean age was 65 years old, 79.43% were White, 25.57% were Asian, 19% were Black

and 69.4% had established CVD. The mean follow-up was 2.3 years.[1] All of the trials were considered high-quality with a Jadad score of 8. Authors reported no conflicts of interest. Funding source was not disclosed. The primary outcome of interest was CV death and hospitalization for HF. Key secondary outcomes were MACE, hospitalization for heart failure, CV death, acute MI, and all-cause mortality.

SGLT2 inhibitors were associated with a reduced risk of CV death and hospitalization for HF compared to placebo (odds ratio [OR] 0.67; 95% CI, 0.55 to 0.80; P<0.001; I^2= 92%).[1] Major CV adverse events were reduced in those taking SGLT2 inhibitors compared to placebo, 9.82% versus 10.22% (OR 0.90; 95% CI, 0.81 to 0.99; P=0.03; I^2=66%).[1] Participants taking SGLT2 inhibitors demonstrated a decreased risk of hospitalizations for HF and emergency department visits for HF (OR 0.67; 95% CI, 0.62 to 0.72), CV death (OR 0.87; 95% CI, 0.79 to 0.97; P=0.09; I^2=52%) and all-cause mortality (OR 0.87; 95% CI, 0.80 to 0.9; P=0.004; I^2=59%).[1] There was no difference in the incidence of myocardial infarction (MI) between groups. Subgroup analyses found no difference in treatment effect based on sex; however, men were associated with a higher incidence of CV death or HF hospitalization compared to women. Results were similar in groups younger than 65 years of age and those 65 years and older.

Limitations to the analysis include high heterogeneity in outcomes between the study comparisons. The results are most applicable to people who are White with a history of ASCVD or who have high risk of ASCVD.

<u>He, et al – Association of Glucagon-like Peptide-1 Receptor Agonist Use with Risk of Gallbladder and Biliary Diseases</u>

A 2022 systematic review and meta-analysis evaluated the use of GLP-1 RAs and the risk of gallbladder and biliary disease.[2] Seventy-six RCTs (n=103,371) evaluating the use of GLP-1 RAs compared to placebo or active treatment (e.g., rosiglitazone, glimepiride, sitagliptin, orlistat, insulin glargine, canaglifllozin, empagliflozin, metformin, insulin lispro, dapagliflozin, and glibenclamide, (not available in the US) in adult patients were included. Included patients had a mean age of 57.8 years, mean HbA1c of 7.8%, mean body mass index (BMI) of 32.6 kg/m^2.[2] Eighty-four percent of participants had T2D and 40.5% were women. Sixty trials evaluated treatment for diabetes, 13 trials evaluated weight loss and 3 evaluated nonalcoholic steatohepatitis, polycystic ovary syndrome and schizophrenia. Trial durations lasted from 26-104 weeks. Trials were considered to be moderate to high quality. There was no publication bias based on the Egger test and funnel plot analysis. The primary outcome was the composite of gallbladder or biliary diseases, and key secondary outcomes included biliary diseases, biliary cancer, cholecystectomy, cholecystitis, and cholelithiasis.

Treatment with GLP-1 RAs resulted in an increased risk of a composite assessment of gallbladder or biliary diseases compared to controls (RR 1.37; 95% CI, 1.23 to 1.52; I^2 = 0%).[2] There were an additional 27 events per 10,000 patients treated per year compared to controls. Randomization to GLP-1 RAs was also associated with an increased risk of the following outcomes compared to control: cholelithiasis (RR 1.27; 95% CI, 1.10 to 1.47), cholecystitis (RR 1.36; 95% CI, 1.14 to 1.62), biliary disease (RR 1.55; 95% CI, 1.08 to 2.22), and cholecystectomy (RR 1.70; 95% CI, 1.25 to 2.32).[2] There was no evidence of an increased risk of biliary tract cancer. Analysis of individual GLP-1 RAs agents found an increased risk for liraglutide, dulaglutide, subcutaneous semaglutide and exenatide; however, the risk was not statistically significant for subcutaneous semaglutide and exenatide. There was no increased risk with albiglutide, oral semaglutide, and lixisenatide. GLP-1 RA use beyond 26 weeks was associated with increased risk of gallbladder disease or biliary diseases (RR 1.40; 95% CI, 1.26 to 1.56) but shorter treatment durations did not have the associated risk.[2] Trials in which GLP-1 RAs were used for weight loss had a higher risk of the primary outcome compared to use in other populations (e.g. diabetes) which may be a result of higher doses and longer treatment durations used in trials evaluating weight loss.

Limitations to the review include potential for under reporting of biliary events. In many included trials, biliary events were not a predefined safety endpoint, and only a small number of events were reported. Many outcomes or subgroups, may not have sufficient power to detect differences between groups.

After review, 31 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). [32–44, 45–61]

New Guidelines:

High Quality Guidelines:

NICE – Type 2 Diabetes Management in Adults: 2022 Update

The National Institute for Health and Care Excellence updated the original 2015 publication on managing adults with diabetes with new evidence and guidance. Drug treatment included in the review were: dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 RAs, SGLT2 inhibitors, sulfonylureas and metformin.[3] The main focus of the update was the evidence for clinical and cost-effectiveness of the SGLT2 inhibitor class in people with CV disease or at high risk of developing CV disease. Recommendations are for people with T2DM, and use of these therapies in people without T2DM was not discussed.[3]

The guidance maintains the recommendation for standard-release metformin as first-line therapy in people without comorbidities. People should be assessed for CV risk.

- In people with chronic HF, established atherosclerotic CV disease or high risk of developing CV disease, a SGLT2 inhibitor with proven CV benefit is recommended in addition to metformin.[3] If combination therapy is initiated with metformin and a SGLT2 inhibitor, the medications should be started sequentially to ensure metformin is tolerated. If metformin is contraindications or not tolerated, then a SGLT2 inhibitor should be offered in this population.[3]
- For people that are unable to take metformin and who don't have a CV indication, then a DPP-4 inhibitor, pioglitazone, or sulfonylurea is recommended. SGLT2 inhibitors may also be considered in patients without CV indications.[3]
- An SGLT2 inhibitor should be added at any stage after the first-line treatment has been initiated if the person has or develops chronic HF or established atherosclerotic CV disease. The SGLT2 inhibitor can be added to the current treatment or replace the existing treatment. Using ertugliflozin for CV risk reduction is considered off-label if serum glucose is controlled.[3]
- There was insufficient evidence to justify recommending SGLT2 inhibitors for people with T2DM at lower risk of CV disease. SGLT-2 inhibitors demonstrated differences in CV benefits so recommendations for use of a specific SGLT2 inhibitors state that drugs with proven benefit should be used (there was greater uncertainty about the benefits of ertugliflozin).[3]

People who are not meeting glucose targets with monotherapy may be considered for treatment with a DPP-4 inhibitor, pioglitazone, sulfonylurea or SGLT2 inhibitor (if they meet the previous outlined specifications as noted above).[3] If a combination therapy with metformin and an additional oral agent has not succeeded in lowering glucose levels to the desired level, then triple oral therapy with a DPP-4 inhibitor, pioglitazone, sulfonylurea, or SGLT-2 inhibitor can be added. In people who are unable to take metformin and combination therapy with 2 oral drugs does not allow obtainment of goal glucose levels, insulin should be considered.[3]

The clinical effectiveness of GLP-RAs to lower glucose was not included in this review, and therefore, specific recommendations related to GLP-1 RAs were not updated. GLP-1 RAs when used for CV benefit were not cost-effective, and they are only recommended as an alternate treatment option. GLP-1 RAs should be continued if HbA1c has been reduced by at least 1% and weight loss has improved by at least 3% at 6 months (2015 recommendation).[3]

GLP-1 RA therapy should be considered in people who have:

- Inadequate glycemic control while taking triple oral therapy with metformin and 2 other drugs[3]

- BMI of 35 kg/m^2 or higher and specific psychological or other medical problems related to obesity[3]
- BMI of lower than 35 kg/m^2 and which insulin has significant occupational implications or weight loss would benefit other obesity-related comorbidities

SGLT2 inhibitors may also be considered for people with T2DM and CKD taking an ARB or ACE inhibitor if they have an albumin to creatinine ratio (ACR) between 3 and 30 mg/mmol and they meet the eGFR thresholds outlined in the drug labeling.[3] People who are starting SGLT2 inhibitors should be evaluated for risk of diabetic ketoacidosis (DKA). The presence of the following factors may increase risk of DKA: previous episodes of DKA, a current illness, or a very low carbohydrate or ketogenic diet. Risk factors should be modified if possible.

NICE – Dapagliflozin for Chronic Kidney Disease

A Technology Appraisal Guidance was published in March of 2022 on the use of dapagliflozin in treating CKD in adults, with and without diabetes.[4] Recommendations were based on the DAPA-CKD trial (**Table 2**). NICE recommends the use of dapagliflozin as an option for adults with CKD if the following criteria are met:

- Dapagliflozin is added as an adjunct to standard care (e.g., highest tolerated licensed ACE inhibitor or ARB unless contraindicated)[4] AND
- The person's eGFR is between 25 ml/min/1.73 m^2 and 75 ml/min/1.73 m^2 AND
- The person has T2DM OR the person has a urine albumin-to-creatinine ratio (uACR) or 22.6 mg/mmol or greater

Additional Guidelines for Clinical Context:

ADA – Pharmacological Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes 2022

The American Diabetes Association (ADA) updated pharmacological treatment recommendations for managing patients with type 1 diabetes (T1D) and T2D. For the purpose of this review we will focus on the treatment of people with T2D, with a focus on SGLT2 inhibitors and GLP-1 RA.[27] Choice of antidiabetic therapy should be determined by a person's specific preferences, including: comorbidities, hypoglycemia risk, impact on weight, cost, access, and risk for adverse reactions. Antidiabetic treatment should be re-evaluated every 3-6 months and intensification of therapy should not be delayed if glucose goals are not met.[27]

Specific treatment recommendations are as follows[27]:

- Metformin is recommended first-line in combination with lifestyle changes.
- Persons with T2D with or at high risk of atherosclerotic CV disease, HF, and/or CKD should be considered candidates for GLP-1 RAs or SGLT2s with or without metformin.
- Metformin should be continued, if tolerated and not contraindicated, if insulin is started due to the metabolic benefits of metformin.
- Combination therapy at treatment initiation may be considered to extend the time to treatment failure.
- GLP-1 RAs are recommended over insulin for people with T2D if possible.
- If insulin is used in people with T2D, GLP-1 RAs are recommended in combination for greater durability of treatment effect.
- People receiving high doses of basal insulin (0.5 IU/kg/day or more) should be evaluated for additional therapies (not specifically describied).

ADA – Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes 2022

The management of people with diabetes and CKD was updated in the 2022 recommendations by the ADA.[30] The use of SGLT2 inhibitors is recommended for people with T2D, diabetic kidney disease, eGFR of 25 mL/min/1.73 m^2 or greater, and urinary albumin creatinine of 300 mg/g or greater. Evidence has demonstrated a reduction in progression of CKD and CV events.[30]

ADA – Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes 2022

The ADA provided guidance for the management of people with diabetes in regards to CV risk reduction.[62] As mentioned above, SGLT2 inhibitor or GLP-1 RAs with demonstrated CV benefit are recommended for people with T2D who have established atherosclerotic CV disease or established kidney disease to reduce the risk of adverse CV outcomes. SGLT2 inhibitors with demonstrated CV benefit are also recommended for people with T2D and multiple atherosclerotic CV risk factors.[62] Reduction in HF hospitalizations and/or reduction in major CV events have been demonstrated with SGLT2 inhibitors in this population. GLP-1 RAs with demonstrated CV benefit have been shown to reduce the risk of major CV events in people with T2D and established atherosclerotic CV disease or multiple atherosclerotic CV risk factors. In people with T2D and established atherosclerotic CV disease or multiple atherosclerotic CV risk factors, combination therapy with SGLT2 inhibitors and GLP-1 RAs with demonstrated CV benefit may be considered to lower the risk of adverse CV and kidney events. In people with T2DM and established HF with reduced ejection fraction, treatment with a SGLT2 is recommended to reduce the risk of HF and CV death. People with T2D and HF can continue with metformin if eGFR is 30 mL/min/1.73m^2 or above; however, metformin should be discontinued/avoided patients who are unstable or hospitalized.[62]

After review, 2 guidelines were excluded due to poor quality.[63,64]

New Formulations or Indications:

New Formulations:

Semaglutide (Rybelsus®): Semaglutide oral tablets was approved for use in January 2020 as an adjunct to diet and exercise to improve glycemic control in adults with T2D.[5] Semaglutide tablets are given once daily instead of once weekly like the semaglutide injection. Currently, semaglutide oral tablets do not have the same indication for CV disease reduction in adults with T2D as the injectable formulation. There is a boxed warning for the risk of thyroid c-cell tumors with oral semaglutide as with other GLP-1 RA products.[5]

New Indications:

Dapagliflozin (Farxiga®): In April of 2021, dapagliflozin received an expanded to indication for risk reduction of sustained eGFR decline, end stage kidney disease, CV death, and hospitalization for HF in adults with CKD at risk of progression.[6] Details on the evidence used for the expanded indication are provided in **Table 3**.

Exenatide (Bydureon®): The FDA approved an expanded indication for exenatide in pediatric patients 10 years of age and older with T2D in July of 2021.[7] Evidence for the approval was based on one 24-week, double-blind, placebo-controlled RCT in which exenatide was more effective than placebo with an HbA1c reduction of -0.71% (95% CI, -1.42 to 0: $p<0.05$).[7]

Empagliflozin (Jardiance®): In 2021, empagliflozin received an expanded indication to reduce the risk of CV death and hospitalization for HF in adults with HF and reduced ejection fraction (**Table 3**). Empagliflozin has also been shown to be effective in those with preserved ejection fraction; therefore, labeling as of 2/2022 includes an indication for HF, without delineation of ejection fraction.

Dapagliflozin and metformin (Xigduo XR®): The combination product of dapagliflozin and metformin received an expanded indication for reduced risk of CV death and hospitalization for HF in adults with HF (New York Heart Association [NYHA]class II-IV) with reduced ejection fraction in February of 2022.[9] An additional indication was approved in April of 2022 is to reduce the risk of sustained eGFR decline, end-stage kidney disease [ESKD], CV death and hospitalization for HF in adults with CKD at risk of progression (**Table 3**).[9] Both new indications apply to people with and without diabetes.

Lixisenatide (Adlyxin®): The FDA removed the statement that "lixisenatide has not been studied in combination with short acting insulin" from the limitations of use section in the labeling.[10]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts.

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
GLP-1 RAs[65]	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	June 2022	Warnings	Due to the risk of acute gallbladder disease, if cholelithiasis or cholecystitis are suspected then gallbladder studies should be performed.
Exenatide ER[7]	Bydureon	February 2020	Warnings	Risk of drug induced thrombocytopenia has been reported, including serious bleeding which may be fatal. Discontinue exenatide promptly if this occurs.
Dapagliflozin and saxagliptin[66]	Qtern	March 2022	Warnings	Dapagliflozin may cause intravascular volume depletion and hypotension with case reports of acute kidney injury. Monitor for hypotension and renal function after initiating therapy.

Randomized Controlled Trials:
A total of 263 citations were manually reviewed from the initial literature search. After further review, 258 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 5 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
Anker, et al[11] EMPEROR-Preserved DB, PC, MC, NI, RCT	1. Empagliflozin 10 mg orally once daily 2. Placebo Median duration: 26.2 months	Adult patients with class II-IV HF and an ejection fraction of more than 40% (with or without diabetes) N=5988	Composite of CV death or hospitalization for HF	1. Empagliflozin: 415 (13.8%) 2. Placebo: 511 (17.1%) HR 0.79 (95% CI, 0.69 to 0.90) P<0.001	Patients were on background standard of care medications for HF. Results were similar in patients with and without diabetes. Empagliflozin was more effective than placebo at preventing CV death or hospitalizations for HF.
Cannon, et al[12] VERTIS CV DB, PC, MC, NI, RCT	1. Ertugliflozin 5 mg orally once daily 2. Ertugliflozin 15 mg orally once daily 3. Placebo Mean duration: 3.5 years	Adult patients (at least 40 years old) with T2DM and atherosclerotic CV disease N=8238	Incidence of major adverse CV events (a composite of death from CV causes nonfatal MI, or nonfatal stroke)	1. Ertugliflozin (pooled doses): 653 (11.9%) 2. Placebo: 327 (11.9%) HR 0.97 (95% CI, 0.85 to 1.11) P<0.001 for non-inferiority	Ertugliflozin was non-inferior to placebo for the risk of major adverse CV outcomes.
Heerspink, et al[13] DAPA-CKD DB, PC, MC, RCT, Phase 3	1. Dapagliflozin 10 mg orally once daily 2. 2. Placebo Median duration: 2.4 years	Adult patients (with or without diabetes) with eGFR of 25 to 75 ml/min/1.73 m2 and urinary albumin-to-creatinine ratio of 200 to 5000 N = 4304	Sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes	1. Dapagliflozin: 197 (9.2%) 2. Placebo: 312 (14.5%) HR 0.61 (95% CI, 0.51 to 0.72) P<0.001	Results were similar for those with and without diabetes. Trial was stopped early due to efficacy. All patients were on a background ACE or ARB. Dapagliflozin was more effective than placebo for the primary outcome and for the composite outcome of death from CV causes or hospitalization for heart failure.

Packer, et al[14] EMPEROR-Reduced DB, PC, PG, RCT, Phase 3	1. Empagliflozin 10 mg orally once daily 2. 2. Placebo Median duration: 16 months	Adult patients with class II-IV HF and an ejection fraction of 40% or less (with or without diabetes) N=3730	Composite of CV death or hospitalization for worsening HF	1. Empagliflozin: 361 (19.4%) 2. Placebo: 462 (24.7%) HR 0.75 (95% CI, 0.65 to 0.86) P<0.001	Results were similar in patients with or without diabetes. All patients were on standard of care HF treatments (e.g., diuretics, ACE or ARBs, neprilysin, beta-blockers, and mineralocorticoid receptor antagonists) Empagliflozin was more effective than placebo for reducing CV death or hospitalization for HF

Abbreviations: ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; CV – cardiovascular; DB – double-blind: eGFR – estimated glomerular filtration; HF – heart failure; HR – hazard ratio; MC – multi-center; NI – non-inferiority trial; PC – placebo controlled; PG – parallel group; RCT – randomized controlled trial; T2DM – type 2 diabetes mellitus

NEW DRUG EVALUATION:

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

Clinical Efficacy:

Tirzepatide is a dual GIP and GLP-1 RA therapy approved as an adjunct to diet and exercise to improve glycemic control in adult patients with T2D. Approval of tirzepatide was based on 5 phase 3 trials.[17–21] All trials were multi-center, randomized, parallel-group design in patients with T2D. Tirzepatide was compared to placebo in 2 trials and compared to active treatment in the remaining 3 trials (SURPASS trials 1-5). Comparators were insulin glargine, insulin degludec and semaglutide 1 mg. Tirzepatide was studied with stable dose background therapy of insulin glargine (with or without metformin), metformin alone, or combination treatment with metformin, sulfonylurea, and SGLT2 inhibitors. Dosing titration of tirzepatide and comparators are outlined in **Table 4**. Patients from 24 countries, 23.1% from North America, were included. Participants were predominantly White (80%), 55% were male with a mean age of 58 years. The mean BMI across the trials was 33 kg/m^2.[17–21] Most participants did not have significant comorbidities with the exception of SURPASS-4 which enrolled patients at increased CV risk. Baseline HbA1c values ranged from 7 to 10.5%. To meet inclusion criteria, patients had to have an eGFR of at least 30 mL/min/1.73 m^2. There were small protocol amendments to all 5 trials but the FDA concluded that it would have only affected 0.2-0.9% of primary endpoint data so it would be unlikely that it would have made a significant difference in the results.[67] Detailed trial information is available in **Table 5**.

Table 4. Titration and Dosing of Tirzepatide and other Diabetes Medications.

Study	Tirzepatide Titration	Other Diabetes Medications
SURPASS-1[17]	- Tirzepatide initiated at 2.5 mg/week and increased by 2.5 mg every 4 weeks until the assigned dose was reached	- Not applicable
SURPASS-2[18]	- Same as above	- Semaglutide was initiated at a starting dose of 0.25 mg once weekly and the dose was doubled every 4 weeks until 1 mg was reached (dose for diabetes up to 2 mg/week) - Only insulin was allowed for acute therapy if needed - Background therapy with metformin
SURPASS-3[19]	- Same as above	- Insulin degludec was initiated at 10 U/day and titrated once weekly to a fasting self-monitored blood glucose of less than 90 mg /dL - Background therapy with stable dose of metformin +/- a SGLT-2 inhibitor
SURPASS-4[20]	- Same as above	- Insulin glargine was initiated at 10 units/day and adjusted weekly to a treat to target fasting blood glucose of less than 100 mg/dL - Background therapy: stable dose of metformin, SGLT2 inhibitor, and/or SU
SURPASS-5[21]	- Same as above	- Initial 4-week insulin glargine stabilization period followed by a 36-week insulin titration period* - Metformin 1500 mg/day (if taking at baseline)

* Between weeks 5 and 40 patients self-adjusted insulin glargine dose to target fasting blood glucose of less than 100 mg/dL.

Tirzepatide demonstrated improved efficacy over all comparators studied. HbA1c changes from baseline ranged from -1.87% to -2.58% (P<0.05 for all comparisons) (**Table 6**).[17–21] The magnitude of HbA1c lowering was considered clinically meaningful (difference to comparator reductions of -0.4% to -1.6%), with exception of the tirzepatide 5 mg compared to sitagliptin 1 mg which demonstrated a difference of -0.2% (95% CI, -0.3 to -0.0).[18] Glucose lowering was sustained in all trials and all doses reached near normal blood glucose levels suggesting there is no dose-response effect of tirzepatide.[68] Patients receiving tirzepatide achieved HbA1c less than 7% more than comparators ranging from 75.1% to 89.6% of the population studied (P<0.05 for all comparisons).[67] Weight loss was more significant in the tirzepatide groups versus comparators with losses of -5.3 kg to -11.3 kg. Hierarchical testing was not performed for the effect of tirzepatide on blood pressure and lipids; however a beneficial effect was demonstrated with tirzepatide. Tirzepatide lowered systolic blood pressures 6-9 mmHg and diastolic blood pressure 3-4 mmHg compared to changes of 2 mmHg in diastolic and systolic blood pressures with placebo.[67] Small reductions in triglyceride (TG), total cholesterol (TC) and very-low-density lipoprotein-C (VLDL-C) and increases in HDL-C were demonstrated with tirzepatide.

There is insufficient evidence on the effect of tirzepatide on cardiovascular outcomes in patients with T2DM. There is an ongoing trial (SURPASS-CVOT) which should delineate the CV impact. Until trial results are available, tirzepatide is not recommended to reduce CV events in adults with CV disease or CV risk factors as demonstrated with other GLP-1 RAs and SGLT-2 inhibitors. There is insufficient evidence for the use of tirzepatide to reduce the risk of HF or CKD progression. There was limited evidence for non-White populations (12% of the population studied) and those 75 years and older. There is insufficient data in patients with an eGFR of 30 mL/min/1.73 m^2 or less.

Clinical Safety:
Tirzepatide safety data comes from the analysis of 5119 patients, with a mean treatment exposure of approximately 43 weeks. The most common adverse reactions seen with tirzepatide occurring in 5% or more of patients were: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain.[16] Serious adverse events occurred in 5.5% of patients in the placebo arm compared to 5.4% with tirzepatide.[67] Tirzepatide has been associated with pancreatitis (less than 0.1%), hypoglycemia with concomitant use of insulin secretagogues or insulin, hypersensitivity reactions, acute kidney injury (less than 0.1%), severe gastrointestinal disease (less than 0.1%), diabetic retinopathy complications in patients with a history of diabetic retinopathy, and acute gallbladder disease.[16] There is a boxed warning for the risk of thyroid c-cell tumors, and tirzepatide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma.[16] In placebo comparisons, tirzepatide had a higher rate of discontinuations, 86.6% versus 91.1%, that were dose-related.[67] Tirzepatide may reduce the effectiveness of oral hormonal contraceptives and patients should be advised to switch to non-oral contraceptive method.[16] Long-term treatment with tirzepatide will assist in informing safety profile in patients who likely will require chronic use over many years. Discontinuation rates across the trials ranged from 9 to 15% across all 5 trials.[67]

Table 5. Adverse Reactions in 5% or More of Patients Treated with Tirzepatide in Placebo-Controlled Trials

Adverse Reaction	Placebo (n=235) %	Tirzepatide 5 mg (n=237) %	Tirzepatide 10 mg (n=240) %	Tirzepatide 15 mg (n=241) %
Nausea	4	12	15	18
Diarrhea	9	12	13	17
Decreased Appetite	1	5	10	11
Vomiting	2	5	5	9
Constipation	1	6	6	7
Dyspepsia	3	8	8	5
Abdominal Pain	4	6	5	5

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Mortality
2) Cardiovascular events
3) Reduction in A1C
4) Reductions in weight
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Changes in A1C from baseline

Table 5. Pharmacology and Pharmacokinetic Properties[16]

Parameter	
Mechanism of Action	Glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist
Oral Bioavailability	NA
Distribution and Protein Binding	10.3 Liters Highly bound to plasma albumin (99%)
Elimination	0.061 Liters/hour
Half-Life	5 days
Metabolism	Proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Rosenstock, et al [17] SURPASS-1 Phase 3, DB, MC, PG, RCT	1. Tirzepatide 5 mg SC once weekly 2. Tirzepatide 10 mg SC once weekly 3. Tirzepatide 15 mg SC once weekly 4. Placebo SC once weekly Duration: 40 weeks	Demographics: Female: 48% Age: 54.1 years White: 36% Asian: 35% American Indian or Alaska Native: 25% Baseline A1C: 7.94% Weight: 85.9 kg Previous diabetes medication use: 46% Key Inclusion Criteria: - Age ≥18 years - T2DM inadequately controlled with diet and exercise - A1C of 7.0 to 9.5% - BMI ≥23 kg/m^2 (stable for the previous 3 months) Key Exclusion Criteria: - T1DM - Use of antidiabetic medication within previous 3 months - eGFR of ≤30 mL/min/1.73 m^2 - history of pancreatitis - diabetic retinopathy requiring urgent treatment or diabetic maculopathy	mITT: 1. 121 2. 121 3. 121 4. 115 PP: 1. 110 2. 109 3. 95 4. 98 Attrition: 1. 11 (9.1%) 2. 12 (9.9%) 3. 26 (21.5%) 4. 17 (14.8%)	Primary Endpoint: Change in A1C level from baseline at 40 weeks: 1. -1.87% 2. -1.89% 3. -2.07% 4. 0.04% Tirzepatide 5 mg vs. placebo: ETD -1.91 (95% CI, -2.18 to -1.63); P<0.0001 Tirzepatide 10 mg vs. placebo: ETD -1.93 (95% CI, -2.21 to -1.65); P<0.0001 Tirzepatide 15 mg vs. placebo: ETD -2.11 (95% CI, -2.39 to -1.83); P<0.0001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 105 (87%) 2. 108 (92%) 3. 102 (88%) 4. 22 (19%) Tirzepatide 5 mg vs. placebo: OR 49.0 (95% CI, 21.1 to 113.7); P<0.0001 Tirzepatide 10 mg vs. placebo: OR 80.4 (95% CI, 31.8 to 203.2); P<0.0001 Tirzepatide 15 mg vs. placebo: OR 52.9 (95% CI, 22.3 to 125.7); P<0.0001 Changes in body weight from baseline to week 40 1. -7.0 kg 2. -7.8 kg 3. -9.5 kg 4. -0.7 kg Tirzepatide 5 mg vs. placebo: MD -6.3 kg (95% CI, -7.8 to -4.7); P<0.0001 Tirzepatide 10 mg vs. placebo: MD -7.1 kg (95% CI, -8.6 to -5.5); P<0.0001 Tirzepatide 15 mg vs. degludec: MD -8.8 kg (95% CI, -10.3 to -7.2); P<0.0001	NA NA NA ARR 68 NNT 2 ARR 73 NNT 2 ARR 69 NNT 2 NA NA NA	Nausea: 1. 14 (12%) 2. 16 (13%) 3. 22 (18%) 4. 7 (6%) Diarrhea: 1. 14 (12%) 2. 17 (14%) 3. 14 (12%) 4. 9 (8%) Vomiting: 1. 4 (3%) 2. 3 (2%) 3. 7 (6%) 4. 2 (2%) Hypoglycemia: 1. 7 (6%) 2. 8 (7%) 3. 8 (7%) 4. 1 (1%) DC due to adverse events: 1. 4 (3%) 2. 6 (5%) 3. 8 (7%) 4. 3 (3%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1:1:1 via computer generated random sequence. Baseline characteristics were well matched. Performance Bias: (Low) All patients, investigators, and sponsor were blinded to treatment assignment. All pens were similar in appearance. Detection Bias: (Unclear) No details on the outcome assessment were reported. Attrition Bias: (High) Attrition was high in two of the four groups which could bias results. Missing values imputed by mixed model and repeated measures. Reporting Bias: (Low) Trial was conducted according to protocol and outcomes reported as pre-specified. Other Bias: (High) The study was funded by the manufacturer. **Applicability**: Patient: Studied in patients with T2DM inadequately controlled with diet and exercise. Results are most applicable to White, Asian and American Indian with early T2DM as demonstrated by less than half of participants on antihyperglycemic therapy. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Placebo. Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate surrogate outcomes. Setting: 52 medical centers in India, Japan, Mexico, and the U.S. (number of sites not provided).

2. Frias, et al[68] SURPASS-2 Phase 3, MC, OL, PG, RCT	1. Tirzepatide 5 mg† SC once weekly 2. Tirzepatide 10 mg† SC once weekly 3. Tirzepatide 15 mg† SC once weekly 4. Semaglutide 1 mg SC once weekly Duration: 40 weeks Background therapy: metformin † Doses of tirzepatide were blinded, other assessments were open-label	Demographics: Female: 53% Age: 56.6 years White: 82.6% Baseline A1C: 8.28% Weight: 93.7 kg Metformin use: 100% Key Inclusion Criteria: - Age ≥18 years - T2DM that was inadequately controlled with metformin (≥1500 mg/day) - A1C 7.0 to 10.5% - BMI ≥25 kg/m^2 (stable for the previous 3 months) Key Exclusion Criteria: - T1DM - eGFR ≤45 mL/min/1.73 m^2 - history of pancreatitis - diabetic retinopathy requiring urgent treatment or diabetic maculopathy	mITT: 1. 471 2. 469 3. 470 4. 469 PP: 1. 431 2. 411 3. 408 4. 428 Attrition: 1. 40 (8.5%) 2. 58 (12.4%) 3. 62 (13.2%) 4. 41 (8.7%)	Primary Endpoint: Change in HbA1C level from baseline at 40 weeks: 1. -2.01% 2. -2.24% 3. -2.30% 4. -1.86% Tirzepatide 5 mg vs. semaglutide: ETD -0.15 (95% CI, -0.28 to -0.03); P=0.02 Tirzepatide 10 mg vs. semaglutide: ETD -0.39 (95% CI, -0.51 to -0.26); P<0.001 Tirzepatide 15 mg vs. semaglutide: ETD -0.45 (95% CI, -0.57 to -0.32); P<0.001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 386 (82%) 2. 404 (86%) 3. 404 (86%) 4. 371 (79%) Tirzepatide 5 mg vs. semaglutide*: P<0.05 Tirzepatide 10 mg vs. semaglutide*: P<0.05 Tirzepatide 15 mg vs. semaglutide*: P<0.001 Changes in body weight from baseline to week 40 1. -7.6 kg 2. -9.3 kg 3. -11.2 kg 4. -5.7 kg Tirzepatide 5 mg vs. semaglutide: ETD -1.9 kg (95% CI, -0.28 to -1.0); P<0.001 Tirzepatide 10 mg vs. semaglutide: ETD -3.6 kg (95% CI, -4.5 to -2.7); P<0.001 Tirzepatide 15 mg vs. semaglutide: ETD -5.5 kg (95% CI, -6.4 to -4.6); P<0.001	NA NA NA ARR 3/ NNT 34 ARR 7/ NNT 15 ARR 7/ NNT 15 NA NA NA	Nausea: 1. 6 (1.3%) 2. 7 (1.5%) 3. 4 (0.9%) 4. 4 (0.9%) Diarrhea: 1. 1 (0.2%) 2. 3 (0.6%) 3. 6 (1.3%) 4. 1 (0.2%) Vomiting: 1. 1 (0.2%) 2. 4 (0.9%) 3. 4 (0.9%) 4. 3 (0.6%) Hypoglycemia: 1. 29 (0.6%) 2. 10 (0.2%) 3. 80 (1.7%) 4. 19 (0.4%) DC due to adverse events: 1. 28 (6%) 2. 40 (8.5%) 3. 40 (8.5%) 4. 19 (4.1%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Baseline characteristics were well matched. Patients were randomized 1:1:1:1 and stratified by country and baseline A1C (> 8.5% or ≤ 8.5%); however details on randomization process were not provided. Performance Bias: (High). Open-label study design lends itself to potential bias towards study treatment. Detection Bias: (Unclear) Blinding of outcome assessors was not described. Attrition Bias: (High) Attrition rates exceeded 10% in the tirzepatide 10 mg and 15 mg groups. Conservative multiple imputation method used for missing data. Reporting Bias: (Low) Study was performed as described in the protocol. Other Bias: (High) Study funded by the manufacturer. **Applicability**: Patient: Studied in patients not previously controlled on metformin. The gender demographics are similar to the Medicaid FFS population in Oregon. American Indians, African American and Hispanics were under represented compared to Oregon and National statistics. Patients were overweight with a BMI of at least 25 and predominantly white. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Semaglutide is an appropriate comparator; however, the maximum dose is 2 mg once weekly which would provide additional glucose lowering and weight loss. Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes. Setting: Study sites included 128 locations in the United States, Argentina, Australia, Brazil, Canada, Israel, Mexico and the

								United Kingdom. Twenty-five percent were from the U.S.
3. Ludvik, et al SURPASS-3[19] Phase 3, MC, NI, OL, PG, RCT Non-inferiority boundary set at 0.3%	1. Tirzepatide 5 mg SC once weekly 2. Tirzepatide 10 mg SC once weekly 3. Tirzepatide 15 mg SC once weekly 4. Insulin degludec SC once daily Duration: 52 weeks Background therapy: stable dose of metformin +/- a SGLT-2 inhibitor	Demographics: Female: 44% Age: 57 years White: 91% Baseline A1C: 8.17% Bodyweight: 94.3 kg Metformin use: 68% Metformin and SGLT-2 use: 32% Key Inclusion Criteria: - Age ≥18 years - T2DM - A1C 7.0% to 10.5% - Insulin naïve - Metformin alone or in combination with an SGLT-2 inhibitor - BMI ≥25 kg/m^2 Key Exclusion Criteria: - T1DM - eGFR ≤30 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2 for patients taking metformin - history of pancreatitis - hepatitis - proliferative diabetic retinopathy requiring urgent treatment or diabetic maculopathy - use of other antihyperglycemic medications in 3 months prior to screening	mITT: 1. 358 2. 360 3. 359 4. 360 PP: 1. 431 2. 411 3. 408 4. 428 Attrition: 1. 40 (8.5%) 2. 58 (12.4%) 3. 62 (13.2%) 4. 41 (8.7%)	Primary Endpoint: Change in A1C level from baseline at week 52: 1. -1.93% 2. -2.20% 3. -2.37% 4. -1.34% Tirzepatide 5 mg vs. degludec: ETD -0.59% (95% CI, -0.73 to -0.45);P<0.0001 Tirzepatide 10 mg vs. degludec: ETD -0.86% (95% CI, -1.00 to -0.72); P<0.001 Tirzepatide 15 mg vs. degludec: ETD -1.04% (95% CI, -1.17 to -0.90); P<0.001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 291 (82%) 2. 314 (90%) 3. 327 (93%) 4. 215 (61%) Tirzepatide 5 mg vs. degludec: OR 3.45 (95% CI, 2.38 to 5.01); P<0.0001 Tirzepatide 10 mg vs. degludec: OR 7.02 (95% CI, 4.55 to 10.84); P<0.001 Tirzepatide 15 mg vs. degludec: OR 10.79 (95% CI, 6.65 to 17.48); P<0.0001 Changes in body weight from baseline to week 52 1. -7.5 kg 2. -10.7 kg 3. -12.9 kg 4. 2.3 kg Tirzepatide 5 mg vs. degludec: ETD -9.8 kg (95% CI, -10.8 to -8.8); P<0.001 Tirzepatide 10 mg vs. degludec: ETD -13.0 kg (95% CI, -14.0 to -11.9); P<0.0001 Tirzepatide 15 mg vs. degludec: ETD -15.2 kg (95% CI, -16.2 to -14.2); P<0.0001	NA NA NA ARR 21 NNT 5 ARR 29 NNT 4 ARR 32 NNT 4 NA NA NA	Nausea: 1. 3 (1%) 2. 7 (2.0%) 3. 9 (3%) 4. 1 (<1%) Diarrhea: 1. 4 (1%) 2. 1 (<1%) 3. 3 (1%) 4. 0 Vomiting: 1. 3 (1%) 2. 6 (2%) 3. 3 (1%) 4. 0 Hypoglycemia (less than or equal to 70 mg/dL): 1. 30 (8%) 2. 49 (14%) 3. 51 (14%) 4. 170 (48%) DC due to adverse events: 1. 25 (7%) 2. 37 (10%) 3. 39 (11%) 4. 5 (1%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1:1:1 by a computer generated random sequence interactive web-response system. Baseline characteristics were well matched. Performance Bias: (High) Open-label study design lends itself to potential bias towards study treatment. Detection Bias: (Unclear) Blinding of outcome assessors was not described Attrition Bias: (High) Analysis was done on mITT population. High attrition rates (greater than 10%) may bias results. Missing values were imputed using the predicted value from primary endpoint mixed model for repeated measures analysis and then dichotomised. Reporting Bias: (Low) Trial was conducted as outlined in methods. Other Bias: (High) Manufacturer was involved in funding, study design, data collection, data review, data analysis, and drafting of report. **Applicability**: Patient: The gender demographics are similar to the Medicaid FFS population in Oregon. American Indians, African American and Hispanics were under represented compared to Oregon and National statistics. Patients were overweight with a BMI of at least 25 and predominantly white. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Insulin degludec is an appropriate comparator and titration was appropriate. Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes.

								Setting: One hundred twenty-two sites and 13 countries (description of sites not provided).
4. Del Prato, et al[20] SURPASSS- 4 Phase 3, OL, MC, NI, PG, RCT	1. Tirzepatide 5 mg SC once weekly 2. Tirzepatide 10 mg SC once weekly 3. Tirzepatide 15 mg SC once weekly 4. Insulin glargine SC once weekly Duration: 52 weeks and variable treatment period of up to an additional 52 weeks to collect additional CV outcome data Background therapy: stable dose of metformin, SGLT2 inhibitor, and/or SU	Demographics: Female: 38% Age: 63.6 years White: 82% Baseline A1C: 8.52% Bodyweight: 90.3 kg History of CV disease‡: 87% Metformin use: 95% SGLT-2 use: 25% SU use: 54% Key Inclusion Criteria: - Age ≥18 years - T2DM - A1C 7.0% to 10.5% - Stable doses of AHA (metformin, SGLT2i, and/or SU) for ≥3 months - BMI ≥25 kg/m^2 - Increased CV risk (peripheral arterial or cerebrovascular disease or 50 or older with a history of CKD and eGFR <60 mL/min/1.73 m^2 or history of CHF [NYHA II-III]) Key Exclusion Criteria: - T1DM - pancreatitis - proliferative diabetic retinopathy or diabetic maculopathy - cancer - NYHA IV heart failure	mITT: 1. 329 2. 330 3. 338 4. 1005 PP: 1. 294 2. 312 3. 313 4. 882 Attrition: 1. 35 (10.6%) 2. 18 (5.4%) 3. 25 (7.4%) 4. 123 (12.2%)	Primary Endpoint: Change in A1C level from baseline at week 52: 1. -2.24% 2. -2.43% 3. -2.58% 4. -1.44% Non-inferiority margin: 0.3% Tirzepatide 5 mg vs. degludec: ETD -0.80% (95% CI, -0.92 to -0.68);P<0.0001 Tirzepatide 10 mg vs. degludec: ETD -0.99% (95% CI, -1.11 to -0.87);P<0.0001 Tirzepatide 15 mg vs. degludec: ETD -1.14% (95% CI, -1.26 to -1.02); P<0.0001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 264 (81%) 2. 283 (88%) 3. 303 (91%) 4. 496 (51%) Tirzepatide 5 mg vs. degludec: OR 4.78 (95% CI, 3.47 to 6.58); P<0.0001 Tirzepatide 10 mg vs. degludec: OR 9.23 (95% CI, 6.31 to 13.49); P<0.0001 Tirzepatide 15 mg vs. degludec: OR 11.87 (95% CI, 7.88 to 17.89); P<0.0001 Changes in body weight from baseline to week 52 1. -7.1 kg 2. -9.5 kg 3. -11.7 kg 4. 1.9 kg Tirzepatide 5 mg vs. degludec: ETD -9.0 kg (95% CI, -9.8 to -8.3); P<0.0001	NA NA NA ARR 30 NNT 4 ARR 37 NNT 3 ARR 40 NNT 3 NA	Nausea: 1. 39 (12%) 2. 53 (16%) 3. 76 (23%) 4. 23 (2%) Diarrhea: 1. 41 (13%) 2. 65 (20%) 3. 74 (22%) 4. 44 (4%) Vomiting: 1. 16 (5%) 2. 27 (8%) 3. 29 (9%) 4. 16 (2%) Hypoglycemia (less than or equal to 70 mg/dL): 1. 30 (8%) 2. 49 (14%) 3. 51 (14%) 4. 170 (48%) DC due to adverse events: 1. 37 (11%) 2. 28 (9%) 3. 36 (11%) 4. 54 (5%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Patients were randomized 1:1:1:3 using an interactive web-response system to receive tirzepatide or glargine. Baseline characteristics were well matched. Performance Bias: (High) Study was open-label due to different medication dosing frequencies which predisposes results to bias. Detection Bias: (Low) Data was stored via locked database. Analysis was done by manufacturer. Attrition Bias: (High) Attrition was high in 2 of the 4 groups. Missing data was handled by the mixed model for repeated measures. Reporting Bias: (Low) There were changes to the protocol to allow for in-home visits due to COVID and primary endpoint window was widened to 50 to 60 weeks if needed. Other Bias: Manufacturer was involved in funding, study design, data collection, data review, data analysis, and drafting of report. **Applicability**: Patient: Studied in patients with increased CV risk and a history of multiple AHA use. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Insulin glargine is an appropriate comparator (see dosing above in Table 4). Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes. Setting: 187 sites and 14 countries: Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania,

		- history of ketoacidosis - eGFR ≤30 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2 for patients taking metformin - history of pancreatitis - hepatitis - - use of other antihyperglycemic medications in 3 months prior to screening		Tirzepatide 10 mg vs. degludec: ETD -11.4 kg (95% CI, -12.1 to -10.6); P<0.0001 Tirzepatide 15 mg vs. degludec: ETD -13.5 kg (95% CI, -14.3 to -12.8); P<0.0001	NA NA			Russia, Slovakia, Spain, Taiwan, and the U.S. (number of sites not described).
5. Dahl, et al[21] SURPASS-5 Phase 3, DB, MC, PG, RCT	1. Tirzepatide 5 mg* SC once weekly 2. Tirzepatide 10 mg* SC once weekly 3. Tirzepatide 15 mg * SC once weekly 4. Placebo SC once weekly Duration: 40 weeks Background therapy: basal insulin glargine with or without metformin	Demographics: Female: 44% Age: 61 years White: 80.4% Baseline A1C: 8.3% Weight: 95.2 kg Metformin use: 83% Key Inclusion Criteria: - Age ≥18 years - T2DM - A1C 7.0% to 10.5% - Receiving insulin glargine (>20 units/day or >0.25IU/kg/day) - Metformin (minimum dose of 1500 mg/day) - BMI ≥23 kg/m^2 Key Exclusion Criteria: - T1DM - eGFR ≤30 mL/min/1.73 m^2 or <45 mL/min/1.73	mITT: 1. 116 2. 119 3. 120 4. 120 PP: 1. 109 2. 115 3. 110 4. 117 Attrition: 1. 7 (6%) 2. 4 (3%) 3. 10 (8.3%) 4. 3 (2.5%)	Primary Endpoint: Change in A1C level from baseline at 40 weeks: 1. -2.11% 2. -2.40% 3. -2.34% 4. -0.86 Tirzepatide 5 mg vs. placebo: MTD -1.24% (95% CI, -1.48 to -1.01); P<0.001 Tirzepatide 10 mg vs. placebo: MTD -1.53% (95% CI, -1.77 to -1.30); P<0.001 Tirzepatide 15 mg vs. placebo: MTD -1.47% (95% CI, -1.7 to -1.23); P<0.001 Secondary Endpoints: Patient met A1C target of <7%: 1. 101 (87%) 2. 106 (90%) 3. 100 (85%) 4. 41 (35%) Tirzepatide 5 mg vs. placebo: OR 14.7 (95% CI, 7.0 to 30.6); P<0.001 Tirzepatide 10 mg vs. placebo: OR 19.5 (95% CI, 9.2 to 41.3); P<0.001	NA NA NA ARR 52 NNT 2 ARR 55 NNT 2	Nausea: 1. 1 (0.9%) 2. 2 (1.7%) 3. 4 (3.3%) 4. 0 (0%) Diarrhea: 1. 1 (0.9%) 2. 2 (1.7%) 3. 4 (3.3%) 4. 0 (0%) Vomiting: 1. 1 (0.9%) 2. 2 (1.7%) 3. 4 (3.3%) 4. 0 (0.6%) Hypoglycemia (blood glucose less than 70 mg/dL): 1. 70 (60.3%) 2. 75 (63.0%) 3. 72 (60.0%) 4. 73 (60.8%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Patients were randomized 1:1:1:1 via a computer-generated random sequence using an interactive web response system. There were more women randomized to the tirzepatide 10 mg group. Performance Bias: (Low) All patients, providers and sponsors blinded to treatment assignment. Detection Bias: (Low) External independent adjudication committee members blinded to treatment. Attrition Bias: (Low) Assessment was done on FAS population and missing values were imputed using the method of multiple imputation. Attrition was low (less than 10%). Reporting Bias: (Low) Study protocol was followed as detailed in the methods. Other Bias: (High) Study was funded by manufacturer. **Applicability**: Patient: Studied in patients with T2DM inadequately controlled with insulin glargine with or without metformin. Results most applicable to patients who

		m^2 for patients taking metformin - history of pancreatitis - hepatitis - proliferative diabetic retinopathy requiring urgent treatment or diabetic maculopathy - use of other antihyperglycemic medications in 3 months prior to screening		Tirzepatide 15 mg vs. placebo: OR 11.5 (95% CI, 5.6 to 23.3); P<0.001 <u>Changes in body weight from baseline to week 40</u> 1. -5.4 kg 2. -7.5 kg 3. -8.8 kg 4. 1.6 kg Tirzepatide 5 mg vs. placebo: -7.1 kg (95% CI, -8.7 to -5.4); P<0.001 Tirzepatide 10 mg vs. placebo: -9.1 kg (95% CI, -10.7 to -7.5); P<0.001 Tirzepatide 15 mg vs. placebo: -10.5 kg (95% CI, -12.1 to -8.8); P<0.001	ARR 50 NNT 2 NA NA NA	<u>DC due to adverse events:</u> 1. 7 (6%) 2. 10 (8.4%) 3. 13 (10.8%) 4. 3 (2.5%)		are white with a history of AHA use. Other ethnicities were under represented compared to Oregon and National statistics. <u>Intervention</u>: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. <u>Comparator</u>: Placebo appropriate to determine efficacy. <u>Outcomes</u>: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes. <u>Setting</u>: Forty-five treatment centers in 7 countries: Czech Republic, Germany, Japan, Poland, Slovakia, Spain, and U.S.

<u>Key:</u> * CI not reported, ‡ Defined as known coronary, peripheral arterial or cerebrovascular disease or aged 50 years or older with either a history of chronic kidney disease and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2 or history of congestive heart failure (New York Heart Association Class II or III).
<u>Abbreviations</u>: A1C = glycated hemoglobin level; AHA = antihyperglycemic agent; ARR = absolute risk reduction; BMI = body-mass index; CI = confidence interval; CV = cardiovascular risk; DC = discontinuation; eGFR = estimated glomerular filtration rate; ETD = estimated treatment difference; TT = intention to treat; 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; NYHA = New York Heart Association; OL – open label; OR = odds ratio; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous; SGLT-2 = sodium glucose cotransporter; SU = sulfonylurea; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; U.S. = United States

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Appendix 1: Current Preferred Drug List

GLP-1 Receptor Agonists

Generic	Brand	Form	Route	PDL
dulaglutide	TRULICITY	PEN INJCTR	SQ	Y
exenatide	BYETTA	PEN INJCTR	SQ	Y
liraglutide	VICTOZA 2-PAK	PEN INJCTR	SQ	Y
liraglutide	VICTOZA 3-PAK	PEN INJCTR	SQ	Y
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	SQ	N
exenatide microspheres	BYDUREON PEN	PEN INJCTR	SQ	N
lixisenatide	ADLYXIN	PEN INJCTR	SQ	N
semaglutide	OZEMPIC	PEN INJCTR	SQ	N
semaglutide	RYBELSUS	TABLET	PO	N
tirzepatide	MOUNJARO	PEN INJCTR	SQ	N

SGLT-2 Inhibitors

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	STEGLUJAN	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Anker SD, Gerasimos Filippatos, João P Ferreira, Edimar Bocchi, Michael Böhm, Hans-Peter Brunner-La Rocca, Dong-Ju Choi, Vijay Chopra, Eduardo Chuquiure-Valenzuela, Nadia Giannetti, Juan Esteban Gomez-Mesa, Stefan Janssens, James L Januzzi, Jose R Gonzalez-Juanatey, Bela Merkely, Stephen J Nicholls, Sergio V Perrone, Ileana L Piña, Piotr Ponikowski, Michele Senni, David Sim, Jindrich Spinar, Iain Squire, Stefano Taddei, Hiroyuki Tsutsui, Subodh Verma, Dragos Vinereanu, Jian Zhang, Peter Carson, Carolyn Su Ping Lam, Nikolaus Marx, Cordula Zeller, Naveed Sattar, Waheed Jamal, Sven Schnaidt, Janet M Schnee, Martina Brueckmann, Stuart J Pocock, Faiez Zannad, Milton Packer, EMPEROR-Preserved Trial Investigators

Abstract

Background: Sodium-glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

Methods: In this double-blind trial, we randomly assigned 5988 patients with class II-IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

Results: Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

Conclusions: Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

Christopher P Cannon, Richard Pratley, Samuel Dagogo-Jack, James Mancuso, Susan Huyck, Urszula Masiukiewicz, Bernard Charbonnel, Robert Frederich, Silvina Gallo, Francesco Cosentino, Weichung J Shih, Ira Gantz, Steven G Terra, David Z I Cherney, Darren K McGuire, VERTIS CV Investigators

Abstract

Background: The cardiovascular effects of ertugliflozin, an inhibitor of sodium-glucose cotransporter 2, have not been established.

Methods: In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper boundary of a 95.6% confidence interval for the hazard ratio [ertugliflozin vs. placebo] for major adverse cardiovascular events). The first key secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

Results: A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients

(11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P = 0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.
Conclusions: Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.).

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J L Heerspink [1], Bergur V Stefánsson [1], Ricardo Correa-Rotter [1], Glenn M Chertow [1], Tom Greene [1], Fan-Fan Hou [1], Johannes F E Mann [1], John J V McMurray [1], Magnus Lindberg [1], Peter Rossing [1], C David Sjöström [1], Roberto D Toto [1], Anna-Maria Langkilde [1], David C Wheeler [1], DAPA-CKD Trial Committees and Investigators

Abstract

Background: Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.
Methods: We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.
Results: The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P = 0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P = 0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.
Conclusions: Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.).

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer [1], Stefan D Anker [1], Javed Butler [1], Gerasimos Filippatos [1], Stuart J Pocock [1], Peter Carson [1], James Januzzi [1], Subodh Verma [1], Hiroyuki Tsutsui [1], Martina Brueckmann [1], Waheed Jamal [1], Karen Kimura [1], Janet Schnee [1], Cordula Zeller [1], Daniel Cotton [1], Edimar Bocchi [1], Michael Böhm [1], Dong-Ju Choi [1], Vijay Chopra [1], Eduardo Chuquiure [1], Nadia Giannetti [1], Stefan Janssens [1], Jian Zhang [1], Jose R Gonzalez Juanatey [1], Sanjay Kaul [1], Hans-Peter Brunner-La Rocca [1], Bela Merkely [1], Stephen J Nicholls [1], Sergio Perrone [1], Ileana Pina [1], Piotr Ponikowski [1], Naveed Sattar [1], Michele Senni [1], Marie-France Seronde [1], Jindrich Spinar [1], Iain Squire [1], Stefano Taddei [1], Christoph Wanner [1], Faiez Zannad [1], EMPEROR-Reduced Trial Investigators

Abstract
Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.
Methods: In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.
Results: During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (-0.55 vs. -2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.
Conclusions: Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.).

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial

Rosenstock J , Carol Wysham, Juan P Frías, Shizuka Kaneko, Clare J Lee, Laura Fernández Landó, Huzhang Mao, Xuewei Cui, Chrisanthi A Karanikas, Vivian T Thieu

Background: Despite advancements in care, many people with type 2 diabetes do not meet treatment goals; thus, development of new therapies is needed. We aimed to assess efficacy, safety, and tolerability of novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist tirzepatide monotherapy versus placebo in people with type 2 diabetes inadequately controlled by diet and exercise alone.
Methods: We did a 40-week, double-blind, randomised, placebo-controlled, phase 3 trial (SURPASS-1), at 52 medical research centres and hospitals in India, Japan, Mexico, and the USA. Adult participants (≥18 years) were included if they had type 2 diabetes inadequately controlled by diet and exercise alone and if they were naive to injectable diabetes therapy. Participants were randomly assigned (1:1:1:1) via computer-generated random sequence to once a week tirzepatide (5, 10, or 15 mg), or placebo. All participants, investigators, and the sponsor were masked to treatment assignment. The primary endpoint was the mean change in glycated haemoglobin (HbA_{1c}) from baseline at 40 weeks. This study is registered with ClinicalTrials.gov, NCT03954834.
Findings: From June 3, 2019, to Oct 28, 2020, of 705 individuals assessed for eligibility, 478 (mean baseline HbA_{1c} 7·9% [63 mmol/mol], age 54·1 years [SD 11·9], 231 [48%] women, diabetes duration 4·7 years, and body-mass index 31·9 kg/m^2) were randomly assigned to tirzepatide 5 mg (n=121 [25%]), tirzepatide 10 mg (n=121 [25%]), tirzepatide 15 mg (n=121 [25%]), or placebo (n=115 [24%]). 66 (14%) participants discontinued the study drug and 50 (10%) discontinued the study prematurely. At 40 weeks, all tirzepatide doses were superior to placebo for changes from baseline in HbA_{1c}, fasting serum glucose, bodyweight, and HbA_{1c} targets of less than 7·0% (<53 mmol/mol) and less than 5·7% (<39 mmol/mol). Mean HbA_{1c} decreased from baseline by 1·87% (20 mmol/mol) with tirzepatide 5 mg, 1·89% (21 mmol/mol) with tirzepatide 10 mg, and 2·07% (23 mmol/mol) with tirzepatide 15 mg versus +0·04% with placebo (+0·4 mmol/mol), resulting in estimated treatment differences versus placebo of -1·91% (-21 mmol/mol) with tirzepatide 5 mg, -1·93% (-21 mmol/mol) with tirzepatide 10 mg, and -2·11% (-23 mmol/mol) with tirzepatide 15 mg (all p<0·0001). More participants on tirzepatide than on placebo met HbA_{1c} targets of less than 7·0% (<53

mmol/mol; 87-92% vs 20%) and 6·5% or less (≤48 mmol/mol; 81-86% vs 10%) and 31-52% of patients on tirzepatide versus 1% on placebo reached an HbA_{1c} of less than 5·7% (<39 mmol/mol). Tirzepatide induced a dose-dependent bodyweight loss ranging from 7·0 to 9·5 kg. The most frequent adverse events with tirzepatide were mild to moderate and transient gastrointestinal events, including nausea (12-18% vs 6%), diarrhoea (12-14% vs 8%), and vomiting (2-6% vs 2%). No clinically significant (<54 mg/dL [<3 mmol/L]) or severe hypoglycaemia were reported with tirzepatide. One death occurred in the placebo group.
Interpretation: Tirzepatide showed robust improvements in glycaemic control and bodyweight, without increased risk of hypoglycaemia. The safety profile was consistent with GLP-1 receptor agonists, indicating a potential monotherapy use of tirzepatide for type 2 diabetes treatment.

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes
Juan P Frías, Melanie J Davies, Julio Rosenstock, Federico C Pérez Manghi, Laura Fernández Landó, Brandon K Bergman, Bing Liu, Xuewei Cui, Katelyn Brown, SURPASS-2 Investigators
Background: Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist that is under development for the treatment of type 2 diabetes. The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown.
Methods: In an open-label, 40-week, phase 3 trial, we randomly assigned 1879 patients, in a 1:1:1:1 ratio, to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg. At baseline, the mean glycated hemoglobin level was 8.28%, the mean age 56.6 years, and the mean weight 93.7 kg. The primary end point was the change in the glycated hemoglobin level from baseline to 40 weeks.
Results: The estimated mean change from baseline in the glycated hemoglobin level was -2.01 percentage points, -2.24 percentage points, and -2.30 percentage points with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and -1.86 percentage points with semaglutide; the estimated differences between the 5-mg, 10-mg, and 15-mg tirzepatide groups and the semaglutide group were -0.15 percentage points (95% confidence interval [CI], -0.28 to -0.03; P = 0.02), -0.39 percentage points (95% CI, -0.51 to -0.26; P<0.001), and -0.45 percentage points (95% CI, -0.57 to -0.32; P<0.001), respectively. Tirzepatide at all doses was noninferior and superior to semaglutide. Reductions in body weight were greater with tirzepatide than with semaglutide (least-squares mean estimated treatment difference, -1.9 kg, -3.6 kg, and -5.5 kg, respectively; P<0.001 for all comparisons). The most common adverse events were gastrointestinal and were primarily mild to moderate in severity in the tirzepatide and semaglutide groups (nausea, 17 to 22% and 18%; diarrhea, 13 to 16% and 12%; and vomiting, 6 to 10% and 8%, respectively). Of the patients who received tirzepatide, hypoglycemia (blood glucose level, <54 mg per deciliter) was reported in 0.6% (5-mg group), 0.2% (10-mg group), and 1.7% (15-mg group); hypoglycemia was reported in 0.4% of those who received semaglutide. Serious adverse events were reported in 5 to 7% of the patients who received tirzepatide and in 3% of those who received semaglutide.
Conclusions: In patients with type 2 diabetes, tirzepatide was noninferior and superior to semaglutide with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks. (Funded by Eli Lilly; SURPASS-2 ClinicalTrials.gov number, NCT03987919.).

Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial
Bernhard Ludvik, Francesco Giorgino, Esteban Jódar, Juan P Frias, Laura Fernández Landó, Katelyn Brown, Ross Bray, Ángel Rodríguez
Background: Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist under development for the treatment of type 2 diabetes. We aimed to assess the efficacy and safety of tirzepatide versus titrated insulin degludec in people with type 2 diabetes inadequately controlled by metformin with or without SGLT2 inhibitors.
Methods: In this open-label, parallel-group, multicentre (122 sites), multinational (13 countries), phase 3 study, eligible participants (aged ≥18 years) had a baseline glycated haemoglobin (HbA_{1c}) of 7·0-10·5%, body-mass index of at least 25 kg/m^2, stable weight, and were insulin-naive and treated with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months before screening. Participants were randomly assigned (1:1:1:1), using an interactive web-

response system, to once-weekly subcutaneous injection of tirzepatide (5, 10, or 15 mg) or once-daily subcutaneous injection of titrated insulin degludec, and were stratified by country, HbA_{1c}, and concomitant use of oral antihyperglycaemic medications. Tirzepatide was initially given at 2·5 mg and the dose was escalated by 2·5 mg every 4 weeks until the assigned dose was reached. Insulin degludec was initially given at 10 U per day and was titrated once weekly to a fasting self-monitored blood glucose of less than 5·0 mmol/L (<90 mg/dL), following a treat-to-target algorithm, for 52 weeks. The primary efficacy endpoint was non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus insulin degludec in mean change from baseline in HbA_{1c} at week 52. Key secondary efficacy endpoints were non-inferiority of tirzepatide 5 mg versus insulin degludec in mean change from baseline in HbA_{1c} at week 52, superiority of all doses of tirzepatide versus insulin degludec in mean change from baseline in HbA_{1c} and bodyweight, and the proportion of participants achieving HbA_{1c} of less than 7·0% (<53 mmol/mol) at week 52. We used a boundary of 0·3% to establish non-inferiority in HbA_{1c} difference between treatments. Efficacy and safety analyses were assessed in the modified intention-to-treat population (all participants who received at least one dose of study drug). This trial is registered with ClinicalTrials.gov, number NCT03882970, and is complete.

Findings: Between April 1 and Nov 15, 2019, we assessed 1947 participants for eligibility, 1444 of whom were randomly assigned to treatment. The modified intention-to-treat population was 1437 participants from the tirzepatide 5 mg (n=358), tirzepatide 10 mg (n=360), tirzepatide 15 mg (n=359), and insulin degludec (n=360) groups. From a mean baseline HbA_{1c} of 8·17% (SD 0·91), the reductions in HbA_{1c} at week 52 were 1·93% (SE 0·05) for tirzepatide 5 mg, 2·20% (0·05) for tirzepatide 10 mg, and 2·37% (0·05) for tirzepatide 15 mg, and 1·34% (0·05) for insulin degludec. The non-inferiority margin of 0·3% was met. The estimated treatment difference (ETD) versus insulin degludec ranged from -0·59% to -1·04% for tirzepatide (p<0·0001 for all tirzepatide doses). The proportion of participants achieving a HbA_{1c} of less than 7·0% (<53 mmol/mol) at week 52 was greater (p<0·0001) in all three tirzepatide groups (82%-93%) versus insulin degludec (61%). At week 52, from a baseline of 94·3 kg (SD 20·1), all three tirzepatide doses decreased bodyweight (-7·5 kg to -12·9 kg), whereas insulin degludec increased bodyweight by 2·3 kg. The ETD versus insulin degludec ranged from -9·8 kg to -15·2 kg for tirzepatide (p<0·0001 for all tirzepatide doses). The most common adverse events in tirzepatide-treated participants were mild to moderate gastrointestinal events that decreased over time. A higher incidence of nausea (12-24%), diarrhoea (15-17%), decreased appetite (6-12%), and vomiting (6-10%) was reported in participants treated with tirzepatide than in those treated with insulin degludec (2%, 4%, 1%, and 1%, respectively). Hypoglycaemia (<54 mg/dL or severe) was reported in five (1%), four (1%), and eight (2%) participants on tirzepatide 5, 10, and 15 mg, respectively, versus 26 (7%) on insulin degludec. Treatment discontinuation due to an adverse event was more common in the tirzepatide groups than in the insulin degludec group. Five participants died during the study; none of the deaths were considered by the investigators to be related to the study treatment.

Interpretation: In patients with type 2 diabetes, tirzepatide (5, 10, and 15 mg) was superior to titrated insulin degludec, with greater reductions in HbA_{1c} and bodyweight at week 52 and a lower risk of hypoglycaemia. Tirzepatide showed a similar safety profile to that of GLP-1 receptor agonists.

Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial

Stefano Del Prato, Steven E Kahn, Imre Pavo, Govinda J Weerakkody, Zhengyu Yang, John Doupis, Diego Aizenberg, Alan G Wynne, Jeffrey S Riesmeyer, Robert J Heine, Russell J Wiese, SURPASS-4 Investigators

Background: We aimed to assess efficacy and safety, with a special focus on cardiovascular safety, of the novel dual GIP and GLP-1 receptor agonist tirzepatide versus insulin glargine in adults with type 2 diabetes and high cardiovascular risk inadequately controlled on oral glucose-lowering medications.

Methods: This open-label, parallel-group, phase 3 study was done in 187 sites in 14 countries on five continents. Eligible participants, aged 18 years or older, had type 2 diabetes treated with any combination of metformin, sulfonylurea, or sodium-glucose co-transporter-2 inhibitor, a baseline glycated haemoglobin (HbA_{1c}) of 7·5-10·5% (58-91 mmol/mol), body-mass index of 25 kg/m^2 or greater, and established cardiovascular disease or a high risk of cardiovascular events. Participants were randomly assigned (1:1:1:3) via an interactive web-response system to subcutaneous injection of either once-per-week tirzepatide (5 mg, 10 mg, or 15 mg) or glargine (100 U/mL), titrated to reach fasting blood glucose of less than 100 mg/dL. The primary endpoint was non-inferiority (0·3% non-

inferiority boundary) of tirzepatide 10 mg or 15 mg, or both, versus glargine in HbA_{1c} change from baseline to 52 weeks. All participants were treated for at least 52 weeks, with treatment continued for a maximum of 104 weeks or until study completion to collect and adjudicate major adverse cardiovascular events (MACE). Safety measures were assessed over the full study period. This study was registered with ClinicalTrials.gov, NCT03730662.
Findings: Patients were recruited between Nov 20, 2018, and Dec 30, 2019. 3045 participants were screened, with 2002 participants randomly assigned to tirzepatide or glargine. 1995 received at least one dose of tirzepatide 5 mg (n=329, 17%), 10 mg (n=328, 16%), or 15 mg (n=338, 17%), or glargine (n=1000, 50%), and were included in the modified intention-to-treat population. At 52 weeks, mean HbA_{1c} changes with tirzepatide were -2·43% (SD 0·05) with 10 mg and -2·58% (0·05) with 15 mg, versus -1·44% (0·03) with glargine. The estimated treatment difference versus glargine was -0·99% (multiplicity adjusted 97·5% CI -1·13 to -0·86) for tirzepatide 10 mg and -1·14% (-1·28 to -1·00) for 15 mg, and the non-inferiority margin of 0·3% was met for both doses. Nausea (12-23%), diarrhoea (13-22%), decreased appetite (9-11%), and vomiting (5-9%) were more frequent with tirzepatide than glargine (nausea 2%, diarrhoea 4%, decreased appetite <1%, and vomiting 2%, respectively); most cases were mild to moderate and occurred during the dose-escalation phase. The percentage of participants with hypoglycaemia (glucose <54 mg/dL or severe) was lower with tirzepatide (6-9%) versus glargine (19%), particularly in participants not on sulfonylureas (tirzepatide 1-3% vs glargine 16%). Adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina) occurred in 109 participants and were not increased on tirzepatide compared with glargine (hazard ratio 0·74, 95% CI 0·51-1·08). 60 deaths (n=25 [3%] tirzepatide; n=35 [4%] glargine) occurred during the study.
Interpretation: In people with type 2 diabetes and elevated cardiovascular risk, tirzepatide, compared with glargine, demonstrated greater and clinically meaningful HbA_{1c} reduction with a lower incidence of hypoglycaemia at week 52. Tirzepatide treatment was not associated with excess cardiovascular risk.

Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial
Dominik Dahl, Yukiko Onishi, Paul Norwood, Ruth Huh, Ross Bray, Hiren Patel, Ángel Rodríguez

Importance: The effects of tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, as an addition to insulin glargine for treatment of type 2 diabetes have not been described.
Objective: To assess the efficacy and safety of tirzepatide added to insulin glargine in patients with type 2 diabetes with inadequate glycemic control.
Design, setting, and participants: Randomized phase 3 clinical trial conducted at 45 medical research centers and hospitals in 8 countries (enrollment from August 30, 2019, to March 20, 2020; follow-up completed January 13, 2021) in 475 adults with type 2 diabetes and inadequate glycemic control while treated with once-daily insulin glargine with or without metformin.
Interventions: Patients were randomized in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of 5-mg (n = 116), 10-mg (n = 119), or 15-mg (n = 120) tirzepatide or volume-matched placebo (n = 120) over 40 weeks. Tirzepatide was initiated at 2.5 mg/week and escalated by 2.5 mg every 4 weeks until the assigned dose was achieved.
Main outcomes and measures: The primary end point was mean change from baseline in glycated hemoglobin A1c (HbA1c) at week 40. The 5 key secondary end points included mean change in body weight and percentage of patients achieving prespecified HbA1c levels.
Results: Among 475 randomized participants (211 [44%] women; mean [SD] age, 60.6 [9.9] years; mean [SD] HbA1c, 8.31% [0.85%]), 451 (94.9%) completed the trial. Treatment was prematurely discontinued by 10% of participants in the 5-mg tirzepatide group, 12% in the 10-mg tirzepatide group, 18% in the 15-mg tirzepatide group, and 3% in the placebo group. At week 40, mean HbA1c change from baseline was -2.40% with 10-mg tirzepatide and -2.34% with 15-mg tirzepatide vs -0.86% with placebo (10 mg: difference vs placebo, -1.53% [97.5% CI, -1.80% to -1.27%]; 15 mg: difference vs placebo, -1.47% [97.5% CI, -1.75% to -1.20%]; P < .001 for both). Mean HbA1c change from baseline was -2.11% with 5-mg tirzepatide (difference vs placebo, -1.24% [95% CI, -1.48% to -1.01%]; P < .001]). Mean body weight change from baseline was -5.4 kg with 5-mg tirzepatide, -7.5 kg with 10-mg tirzepatide, -8.8 kg with 15-mg tirzepatide and 1.6 kg with

placebo (5 mg: difference, -7.1 kg [95% CI, -8.7 to -5.4]; 10 mg: difference, -9.1 kg [95% CI, -10.7 to -7.5]; 15 mg: difference, -10.5 kg [95% CI, -12.1 to -8.8]; P < .001 for all). Higher percentages of patients treated with tirzepatide vs those treated with placebo had HbA1c less than 7% (85%-90% vs 34%; P < .001 for all). The most common treatment-emergent adverse events in the tirzepatide groups vs placebo group were diarrhea (12%-21% vs 10%) and nausea (13%-18% vs 3%).

Conclusions and relevance: Among patients with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine, the addition of subcutaneous tirzepatide, compared with placebo, to titrated insulin glargine resulted in statistically significant improvements in glycemic control after 40 weeks.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 08, 2022
Search Strategy:

#	Searches	Results
1	dulaglutide.mp.	605
2	exenatide.mp. or Exenatide/	3671
3	liraglutide.mp. or Liraglutide/	3702
4	lixisenatide.mp.	542
5	semaglutide.mp.	886
6	tirzepatide.mp.	106
7	dapagliflozin.mp.	2191
8	canagliflozin.mp. or Canagliflozin/	1592
9	empagliflozin.mp.	2279
10	ertugliflozin.mp.	221
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	12176
12	limit 11 to (english language and humans)	7486
13	limit 12 to (yr="2020 -Current" and (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review"))	263

Appendix 4: Prescribing Information Highlights

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

MOUNJARO™ (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

INDICATIONS AND USAGE

MOUNJARO™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis (1, 5.2)
- Is not indicated for use in patients with type 1 diabetes mellitus (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly (2.1)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly (2.1)
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage is 15 mg subcutaneously once weekly (2.1).
- Administer once weekly at any time of day, with or without meals. (2.2)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2)
- Rotate injection sites with each dose.

DOSAGE FORMS AND STRENGTHS

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen (3)

CONTRAINDICATIONS

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1)
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO (4, 5.4)

WARNINGS AND PRECAUTIONS

- *Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. (5.2)
- *Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:* Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary. (5.3)
- *Hypersensitivity Reactions:* Hypersensitivity reactions have been reported. Discontinue MOUNJARO if suspected. (5.4)
- *Acute Kidney Injury:* Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- *Severe Gastrointestinal Disease:* Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.6)
- *Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy:* Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.7)
- *Acute Gallbladder Disease:* Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated. (5.8)

ADVERSE REACTIONS

The most common adverse reactions, reported in ≥5% of patients treated with MOUNJARO are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

MOUNJARO delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Based on animal study, may cause fetal harm. (8.1)
- *Females of Reproductive Potential:* Advise females using oral contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (7.2, 8.3, 12.3)

Appendix 5: Key Inclusion Criteria

Population	Patients with type 2 diabetes mellitus
Intervention	GLP-1 RAs, SGLT-2 inhibitors or tirzepatide
Comparator	Placebo or active control (e.g., antihyperglycemic medications)
Outcomes	HbA1c lowering, cardiovascular events, death, hospitalization
Setting	Outpatient

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and GLP-1 Receptor + Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist

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:
- All non-preferred GLP-1 receptor agonists and GLP-1 receptor + GIP receptor agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

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 Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed metformin or have contraindications to metformin? (document contraindication, if any)	**Yes:** Approve for up to 12 months ~~Go to #5~~	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin. See below for metformin titration schedule.

~~5. Is the request for semaglutide or dulaglutide?~~	~~**Yes:** Approve for up to 12 months~~	~~**No:** Go to #6~~
~~5. Is the patient currently taking prandial insulin?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~ ~~The safety and efficacy of other insulin formations with GLP-1 agonists have not been studied.~~	~~**No:** Approve for up to 12 months~~

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. 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: *10/22 (KS), 8/20 (KS), 6/20), 3/19, 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *TBD; 9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*

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:
- All SGLT-2 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/

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 and HFrEF
Canagliflozin	X	X			
Dapagliflozin			X	X	X
Empagliflozin	X				X
Ertugliflozin					

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

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	

Approval Criteria		
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
4. Does the patient have T2D and failed, or have contraindications to, metformin or is requesting a SGLT2 inhibitor to be used in combination with metformin? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend trial of metformin. See below for metformin titration schedule.
5. 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 and eGFR 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

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

5.	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.
6.	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).
7.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
8.	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: *10/22 (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; 9/1/20; 8/15/18; 10/13/16; 2/3/15; 1/1/14*

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

Prior Authorization Criteria Update: Dupilumab (Dupixent®)
(Targeted Immune Modulators for Severe Asthma and Severe Atopic Dermatitis)

PLAIN LANGUAGE SUMMARY:

- This review was written because a medicine called Dupixent (dupilumab) was approved by the U.S. Food and Drug Administration to be used for a disorder called eosinophilic esophagitis. This disorder makes it difficult and painful to swallow food, or even cause people to vomit and have chest pain.
- Dupilumab was studied in one trial that lasted 24 weeks. The trial studied both adults and children older than 12 years who had eosinophilic esophagitis.
- Patients who took dupilumab in the trial had better improvement in tissue taken from the esophagus when viewed under a microscope. More importantly, patients tended to feel better on dupilumab because they could swallow food better.
- The side effects seen in patients who took dupilumab were not different than in patients who did not take dupilumab. We do not know if other side effects could come up if this drug is used for a long time.
- Dupilumab may be a treatment option in patients older than 12 years who are on the Oregon Health Plan and have a diagnosis of eosinophilic esophagitis.

Purpose of Update:

Dupilumab was recently reviewed by the Pharmacy and Therapeutics (P & T) Committee at the June 2022 meeting has part of the atopic dermatitis and severe asthma class updates. The literature search for the review was conducted through February, 2022. The P & T Committee approved recommendations to amend prior authorization (PA) criteria for targeted immune modulators approved to treat severe asthma and severe atopic dermatitis, including dupilumab. In May 2022, the Food and Drug Administration (FDA) approved an expanded indication for dupilumab to treat eosinophilic esophagitis in adults and pediatric patients 12 years and older weighing at least 40 kg.[1] In June 2022, the FDA expanded the approved age for the use of dupilumab in atopic dermatitis to pediatric patients aged 6 months and older.[1] This update reviews the evidence for the use of dupilumab in treating eosinophilic esophagitis.

Recommendation:

Revise clinical prior authorization (PA) criteria to:

- Provide coverage for treatment of eosinophilic esophagitis with dupilumab in patients aged 12 years of age and older who weigh at least 40 kg.
- Provide coverage for treatment of moderate-to-severe atopic dermatitis with dupilumab in patients who are not adequately controlled with topical prescription therapies or in patients aged 6 months or older in whom those topical therapies are not advisable.

Background:

Dupilumab is FDA-approved for 4 indications: 1) treatment of patients aged 6 months and older with moderate-to-severe atopic dermatitis; 2) as an add-on maintenance treatment of patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral

corticosteroid dependent asthma; 3) as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis; and 4) treatment of patients aged 12 years and older with eosinophilic esophagitis who weigh at least 40 kg.[1]

Eosinophilic esophagitis is a chronic immune-mediated disorder in which eosinophils are found in esophageal mucosa in response to various stimuli or antigens.[2] Assessment of esophageal tissues from patients with eosinophilic esophagitis has revealed a pattern of dilated interepithelial spaces, altered epithelial barrier function, and down-regulation of proteins associated with barrier function.[3] Altered epithelial permeability can lead to an environment that enhances antigen presentation, which in turn leads to recruitment of eosinophils.[3] In a recent study, 63.5% of patients with eosinophilic esophagitis also had a diagnosis of either asthma, allergic rhinitis, atopic dermatitis, or food allergies, with 3% having all 4 diagnoses.[4] Type 2 inflammation underpins the pathophysiology of these conditions, which are characterized by the release of cytokines such as interleukin (IL)-4, IL-13, and IL-5, resulting in tissue infiltration by eosinophils, epithelial hyperplasia, and tissue remodeling.[5]

Eosinophilic esophagitis is one of the most prevalent esophageal diseases after gastroesophageal reflux disease.[2] The incidence of eosinophilic esophagitis in industrialized countries has increased in the last 2 decades and currently varies from 1 to 20 new cases per 100,000 inhabitants per year.[2] Prevalence rates range between 13 and 49 cases per 100,000 inhabitants.[2] There is a predominance in males with a male-to-female ratio of 3:1.[6] In the Oregon Medicaid population, 784 patients (combined Coordinated Care Organizations and Fee-For-Service populations) were diagnosed with eosinophilic esophagitis in 2021.

In older children and adults with eosinophilic esophagitis, the most commonly reported symptoms are solid food dysphagia, food impaction, and non-swallowing associated chest pain.[2] In younger children and infants, the most frequently reported symptoms are reflux, vomiting, abdominal pain, food refusal, and failure to thrive.[2] Diagnosis is determined by biopsies obtained from different esophageal locations, focusing on areas with endoscopic mucosal abnormalities.[2] Because inflammatory changes in eosinophilic esophagitis are frequently patchy and may not be present in all biopsies, it is recommended that at least 6 biopsies should be obtained from at least 2 different locations, typically in both the distal and proximal halves of the esophagus.[2] The accepted threshold for eosinophil density for the diagnosis of eosinophilic esophagitis is 15 or more eosinophils per high power field (eos/hpf) in esophageal mucosa, taken as the peak concentration in the examined specimens.[2]

The patient-reported Dysphagia Symptom Questionnaire (DSQ) is a 3-question daily diary that has been validated for the measurement of dysphagia frequency and severity in patients with eosinophilic esophagitis.[7,8] Three questions ask whether solid food has been eaten; whether food has gone down slowly or become stuck; and what, if any, measures have been taken to achieve relief.[8] Scores can range from 0 to 84, with higher values indicating more frequent and severe dysphagia.[8] A DSQ score of 0 represents an absence of dysphagia symptoms.[8] The minimal clinically important difference (MCID) has been estimated as a change of 6.5 points in the DSQ score.[8]

No drugs were approved by the FDA for the treatment of eosinophilic esophagitis prior to the approval of dupilumab for this indication.[9] Current therapies for eosinophilic esophagitis include off-label use of proton pump inhibitors (PPIs), off-label use of locally applied corticosteroid preparations, dietary therapy with amino acid formula or empiric food elimination, and endoscopic dilation.[10] While high quality studies are not available to determine the best course of therapy for eosinophilic esophagitis, PPI therapy is usually initiated based on expert consensus, cost, ease of therapy.[11] A systematic review with meta-analysis, including 33 studies involving 619 patients with eosinophilic esophagitis, showed that PPIs led to histological remission (defined as less than 15 eos/hpf) in 50.5% of patients and symptomatic improvement in 60.8% of patients, irrespective of patient age, study design or type of PPI evaluated.[12] Omeprazole 20–40 mg twice daily or PPI equivalent is recommended in adults; in children, 1–2 mg/kg of omeprazole daily or PPI equivalent is recommended.[11] In patients with eosinophilic esophagitis who have an initial response to PPI therapy, the drug should be used long-term to maintain disease remission because discontinuation of therapy leads to symptomatic and/or histological relapse.[11] The long-term strategy is to use the minimal effective PPI dose to maintain remission.[11] There are no published data on long-term safety of PPIs in patients with eosinophilic esophagitis.[11] The 2020 American Gastroenterological Association (AGA) and the Joint

Task Force (JTF) on Allergy-Immunology Practice Parameters clinical guideline for the management of eosinophilic esophagitis suggests the use of PPIs over no treatment as a conditional recommendation based on very low-quality evidence.[13] Based on their longstanding safety profile and ease of administration, patients may prefer to start with PPI therapy and dietary restrictions before initiating a corticosteroid.[13]

When PPI therapy is not effective, inhaled corticosteroid preparations administered locally to the esophagus have been prescribed.[9] Although it has not been approved by the FDA, fluticasone administered locally as a spray from a metered-dose inhaler or a viscous preparation of budesonide (e.g., Pulmicort Respules for inhalation) are primarily used for treatment of eosinophilic esophagitis.[14-17] The efficacy of these medications applied locally to the esophagus in improving symptoms and histologic abnormalities after 2 to 12 weeks of use ranges from 53% to 95%.[15,17] Locally administered viscous budesonide and fluticasone inhaler were directly compared for initial treatment of eosinophilic esophagitis in a small, double-blind randomized clinical trial (RCT).[18] Patients were randomized to receive budesonide twice daily plus placebo (n=56) or fluticasone twice daily plus placebo (n=55).[18] Between baseline and week 8, the mean peak eosinophil count decreased from 73 to 15 eos/hpf and from 77 to 21 eos/hpf in the budesonide and fluticasone groups, respectively (p=0.31).[18] Similarly, there was no significant between-group difference with respect to the change in the DSQ score: the mean DSQ score decreased from 11 to 5 in the budesonide group and from 8 to 4 in the fluticasone group (p = 0.70).[18] Esophageal candidiasis developed in 12% of patients who received budesonide and 16% who received fluticasone; oral thrush was observed in 3% and 2%, respectively.[18] Based on the results of this trial, either corticosteroid is a potential treatment for eosinophilic esophagitis.[18]

The AGA/JTF guideline strongly recommends locally applied corticosteroids over no treatment based on moderate-quality evidence.[13] In short-term studies of 3 months or less, no increased risk of adverse events was observed in patients treated with topically applied corticosteroids compared with placebo (RR, 1; 95% CI, 0.85–1.19), although local viral and fungal infections and very limited description of adrenal suppression have been described in certain populations.[13] A conditional recommendation based on moderate-quality evidence suggests locally applied corticosteroids are preferred over systemic administration of oral corticosteroids, due to the increased risk of adverse events observed with systemic corticosteroid therapy.[13]

Efficacy and Safety:
The efficacy and safety of dupilumab in eosinophilic esophagitis were studied in a double-blind, parallel-group, multicenter, phase 3 RCT conducted over 24 weeks in 240 adults and adolescents aged 12 to 17 years of age, weighing at least 40 kg.[1,19] This study has not been published as of June 2022. Dupilumab prescribing information, clinicaltrials.gov, and the recent FDA dupilumab review were consulted for study details.[1,19,20] Because of the brevity of detail, an evidence table could not be constructed. Eligible subjects had 15 or more eos/hpf following a treatment course of a PPI and symptoms of dysphagia as measured by the DSQ.[1] Participants were allocated to 2 treatment groups: Group A with 81 participants (61 adults and 20 pediatric patients) and Group B with 159 participants (107 adults and 52 pediatric patients).[1] Group A evaluated one active dupilumab treatment group of 300 mg once weekly, while Group B had 2 different dosing arms of dupilumab, 300 mg once a week and 300 mg every 2 weeks.[20] At baseline, the groups had similar demographics. Forty-three percent of patients in Group A and 37% of patients in Group B had a history of prior esophageal dilations.[1] The mean baseline DSQ score was 33.6 in Group A and 37.2 in Group B.[1] The co-primary endpoints were: 1) the proportion of patients who achieved peak esophageal interepithelial count of 6 or less eos/hpf at week 24 and 2) the reduction in dysphagia symptoms as measured by a change in the patient-reported DSQ score from baseline to week 24.[19]

In Group A of the trial, 59.5% (n=25) of patients who received dupilumab 300 mg once a week achieved the pre-determined level of reduced eosinophils (≤ 6 eos/hpf) in the esophagus compared to 5.1% (n=2) of the patients who received placebo at 24 weeks (difference: 57; 95% confidence interval (CI), 40.9 to 73.1; p<0.0001).[20] Patients in Group A who received dupilumab experienced an average least square mean (LSM) change of -21.9 points in their 14-day DSQ score at week 24 compared to -9.6 points in patients who received placebo (difference: -12.3; 95% CI, -19.1 to -5.5; p=0.004).[20] In Group B, 58.8% (n=47) of patients who received dupilumab 300 mg once a week achieved the pre-determined level of reduced eosinophils (≤ 6 eos/hpf) in the esophagus compared to 5 (6.3%) of

patients who received placebo (difference: 53.5; 95% CI, 41.2 to 65.8; p<0.0001).[20] Patients in Group B who received dupilumab 300 mg once a week experienced an average LSM change of -23.8 points in their DSQ score compared to -13.9 points in patients who received placebo (difference: -9.9; 95% CI, -14.8 to -5.0; p<0.0001).[20] Patients in Group B who received dupilumab 300 mg every 2 weeks did not demonstrate significant symptom improvement compared with placebo by week 24 (change in DSQ total score: -14.4 vs. -13.9, respectively; treatment difference of -0.5; 95% CI -5.4 to 4.4; p = 0.84).[20] The proportion of patients who discontinued treatment due to adverse events was 2% in both the dupilumab and placebo groups.[1] The most frequently reported adverse events in patients who received dupilumab were injection site reactions (38%), upper respiratory tract infections (18%), arthralgia (2%), and herpes viral infections (2%).[1]

References:

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Appendix 1. Proposed Prior Authorization

Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Restrict use of targeted immune modulators to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Table 1. Maximum Adult Doses for Inhaled Corticosteroids

High Dose Corticosteroids:	Maximum Dose

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

Table 2. FDA-approved Indications and Ages

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate to Severe Allergic Asthma	Difficult To Treat, Severe Asthma*	Hypereosinophilic Syndrome (HES)	Eosinophilic Granulomatosis with Polyangiitis (EGPA)	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Eosinophilic Esophagitis	Atopic Dermatitis (AD)
Abrocitinib CIBINQO								≥18 years
Benralizumab FASENRA	≥12 years							
Dupilumab DUPIXENT	≥6 years (or with oral corticosteroid dependent asthma)					≥18 years	≥12 years and weighing at least 40 kilograms	≥6 months
Mepolizumab NUCALA	≥6 years			≥ 12 years	≥18 years	≥18 years		
Omalizumab XOLAIR		≥6 years				≥18 years		
Reslizumab CINQAIR	≥18 years							
Tezepelumab TEZSPIRE			≥ 12 years					
Tralokinumab ADBRY								≥18 years
Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS).								

Table 3. Abrocitinib Dosing Adjustments for Atopic Dermatitis

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

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

Generic Name	Brand Name	Asthma Indication	Initial Dose and Administration Route	Maintenance Dose and Administration Route

Benralizumab	FASENRA	Severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks for the first 3 doses	30 mg SC every 8 weeks
Dupilumab	DUPIXENT	Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Pediatrics (6 to 11 yo)**:** An initial loading dose is not necessary Adults and Adolescents ≥ 12 yo : 400 mg to 600 mg SC x 1 dose	Ages 6 – 11 yo (weight 15 to 30 kg) 100 mg SC every 2 weeks OR 300 mg SC every 4 weeks Adults and Adolescents ≥ 12 yo: 200 to 300 mg SC every 2 weeks
Mepolizumab	NUCALA	Severe asthma with an eosinophilic phenotype	N/A	Ages ≥ 6 – 11 yo: 40 mg SC every 4 weeks Ages ≥ 12 yo: 100 mg SC every 4 weeks
Omalizumab	XOLAIR	Moderate to severe persistent asthma and positive allergy testing	N/A	75 to 375 mg SC every 2 to 4 weeks based on weight and serum IgE levels
Reslizumab	CINQAIR	Severe asthma with an eosinophilic phenotype	N/A	3 mg/kg IV infusion every 4 weeks
Tezepelumab	TEZSPIRE	Severe asthma	N/A	210 mg SC every 4 weeks
Abbreviations: IgE = immunoglobulin E; IV = intravenous; kg = kilogram; mg = milligram; N/A = Not Applicable; SC = subcutaneous; yo = years old				

Table 5. Dupilumab Dosing by Indication

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for an FDA-approved indication and indications (**Table 2**)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for dupilumab?	**Yes:** Go to # 5	**No:** Go to #6
5. If the request is for dupilumab, is the dose appropriate for the indication (**Table 5**)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7
7. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		

8. Is the diagnosis Severe Atopic Dermatitis (AD)?
 	
Severe disease is defined as:[1]
 	
• Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:
  ○ At least 10% body surface area involved, or
  ○ Hand, foot, face, or mucous membrane involvement
	Yes: Go to #9	**No:** Go to #17

9. Is the medication being prescribed by or in consultation with a dermatologist, allergist, or a provider who specializes in care of atopic dermatitis?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for abrocitinib?	**Yes:** Go to #11	**No:** Go to #16
11. Are baseline labs (platelets, lymphocytes, lipids) documented? *Note: Abrocitinib therapy should not be initiated if platelet count is < 150,000/mm^3, absolute lymphocyte count is < 500/mm^3, absolute neutrophil count is < 1,000/mm^3, or hemoglobin is < 8 g/dL	**Yes:** Go to #12 Document Lab and Date Obtained: Platelets:_____ Lymphocytes:_____ Lipids:_____ Hemoglobin:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is the patient currently taking other targeted immune modulators or oral immunosuppressants?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. If the patient has renal or hepatic impairment has the dose been adjusted as described in Table 3?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Is the patient taking a strong CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2C9 inducer, CYP2C19 inducer, or antiplatelet inhibitor?	**Yes:** Go to # 15	**No:** Go to # 16
15. If the patient is taking a strong CYP2C19 inhibitor (e.g., fluvoxamine, fluoxetine), or CYP2C9 inhibitor (e.g., fluconazole, amiodarone), or CYP2C9 inducer (e.g., rifampin, phenobarbital), or CYP2C19 inducer (carbamazepine), or antiplatelet agent has the abrocitinib dose been adjusted in Table 3 or has the interacting drug been discontinued if necessary? *Note: agents with antiplatelet properties (NSAIDs, SSRIs, etc.) should not be used during the first 3 months of abrocitinib therapy. Do not use aspirin at doses ≥ 81 mg/day with abrocitinib during the first 3 months of therapy.	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
16. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
17. Is the request for eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #18
18. Is the request for the treatment of a patient with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #19
19. Is the request for treatment of nasal polyps?	**Yes:** Go to #20	**No:** Go to #22

Approval Criteria		
20. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to #21	**No:** Pass to RPh. Deny; medical appropriateness
21. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
22. Is the request for treatment of severe asthma?	**Yes:** Go to #23	**No:** Go to #30
23. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #24	**No:** Pass to RPh. Deny; medical appropriateness
24. Has the patient experienced one of the following: • at least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR • taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR • at least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #25 Document number asthma exacerbations over the previous 12 months or oral corticosteroid dose over the previous 6 months or number of hospitalizations or ED visits in the past 12 months _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
25. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #26	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
26. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, tezepelumab etc.)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #27
27. Is the request for tezepelumab?	**Yes:** Approve for up to 12 months.	No: Go to #28
28. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #29
29. If the request is for asthma with an eosinophilic phenotype, can the prescriber provide documentation of one of the following biomarkers: • severe eosinophilic asthma, confirmed by blood eosinophil count ≥150 cells/µL OR • fractional exhaled nitric oxide (FeNO) ≥25 ppb in the past 12 months?	**Yes:** Approve up to 12 months, based on dosing outlined in **Table 4**. Document eosinophil count (or FeNO date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
30. Is the request for treatment of eosinophilic esophagitis?	**Yes:** Go to #31	**No:** Pass to RPh. Deny; medical appropriateness.
31. Does the patient have a documented contraindication or failed trial of the following treatments: • Proton pump therapy for at least 8 weeks OR • Corticosteroid therapy with local administration of fluticasone inhaler	**Yes**: Document drug and dates trialed and intolerances (if applicable): _____ (dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness

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

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports.* *http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed March 1, 2022.*
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.
3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021

4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

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

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 Literature Scan: ADHD Drugs

Date of Review: October 2022

Date of Last Review: June 2022
Literature Search: 05/01/20 – 07/05/22

Plain Language Summary: Should the Oregon Health Authority change the current policy for medicines that treat attention deficit/hyperactivity disorder (ADHD) based on new evidence?

- The Food and Drug Administration (FDA) has already approved many medicines to treat attention deficit/hyperactivity disorder (ADHD). Since the last time the Pharmacy and Therapetuics Committee reviewed these medicines, the FDA has approved 2 new medicines for ADHD and approved 2 older medicines for new age groups. Evidence does not show that these new medicines are any better at improving ADHD symptoms than older medicines.
- The FDA has updated safety information for ADHD medicines since the last review:
    - Strattera™ (atomoxetine) now has a stronger warning for risk of worsening behaviors.
    - All amphetamine products may reduce blood supply to the gut.
- The Drug Use Research Management program does not recommend any policy changes to preferred products based on this new evidence.

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

Conclusions:

- No new high-quality systematic reviews or guidelines were published since the last ADHD class update.
- The Food and Drug Administration (FDA) approved a new formulation of amphetamine extended-release (ER) tablets (Dyanavel XR™) for the treatment of ADHD in patients 6 years of age and older.[1] Prior to this approval, Dynavel XR™ was only available as a 2.5 mg/mL ER oral suspension.[1]
- The FDA approved Xelstrym™ (dextroamphetamine transdermal system) for the treatment of ADHD in patients 6 years of age and older.[2] This is the first amphetamine-based medication formulated as a transdermal product for once daily use.[2-4]
- Evekeo ODT™ (amphetamine sulfate) received expanded FDA approval for the treatment of ADHD in children 3 to 5 years of age.[5] Previously it was approved for patients 6 to 17 years old.[5]
- Qelbree™ (viloxazine ER capsules) received expanded FDA approval for the treatment of ADHD in patients 18 years of age and older.[6] Previously it was approved for pediatric patients 6 to 17 years of age. [6]
- Two new FDA safety alerts have been identified since the last review. The medication guide labeling was updated to reflect a stronger warning for Strattera™ (atomoxetine) use and its association between risks of aggression and manic symptoms in all age groups (new psychotic/manic symptoms), increased risk in bipolar patients, and risk of aggressive behavior and hostility.[8] There was also an update to the labeling for all amphetamine products to include intestinal ischemia among documented adverse reactions.[9]

Author: Dave Engen, PharmD

Recommendations:

- Current evidence does not support changes to the Preferred Drug List (PDL).
- Revise prior authorization (PA) criteria to reflect maximum age and dose limits as specified in product labeling or supported compendia (see **Appendix 6**). To avoid disruption in care, patients initiated on an ADHD medication as a child should be excluded from PA if they age into a maximum age limit.
- Review comparative costs in the executive session.

Summary of Prior Reviews and Current Policy

Prior reviews have found evidence to support that stimulant and non-stimulant pharmacologic agents are beneficial in ADHD treatment compared to placebo. Comparisons between different formulations (immediate-release [IR] vs. ER) within this class have not demonstrated consistent differences. In addition, there is insufficient evidence to directly compare differences in efficacy or safety outcomes for different ADHD drugs in children or adults. The most frequent adverse effects from stimulants are appetite loss, abdominal pain, headache and sleep disturbance; only low-quality evidence suggests any differences in harms between various ADHD agents. There is insufficient evidence that one ADHD drug is more effective or associated with fewer adverse events in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities.

To ensure safe and appropriate use within the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all medications within the ADHD class have limits based on patient age and quantity prescribed. Safety edits are in place to ensure that medication use reflects best practices. Any request for a non-preferred agent or for an agent that exceeds the age or quantity limit requires consultation with a specialist prescriber such as a psychiatrist or other mental health specialist. Preferred agents within the ADHD class are listed in **Appendix 1**. Note that three agents in **Appendix 1** are part of the mental health carve-out and are exempt from traditional PA requirements.

Methods:

A Medline literature search for new systematic reviews, evidence-based guidelines, and randomized controlled trials (RCTs) assessing clinically relevant outcomes was conducted. 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.

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.

New Systematic Reviews:

No new high-quality systematic reviews were identified. Ten systematic reviews were excluded due to poor quality, wrong study design of included trials, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10-19]

New Guidelines:

No new high-quality guidelines were identified.

Additional Guidelines for Clinical Context:

Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit/Hyperactivity Disorder

The Society for Developmental and Behavioral Pediatrics (SDBP) created guidelines to assist primary care in the integrated interprofessional management of children and adolescents with complex ADHD, defined by the presence of coexisting conditions, moderate to severe functional impairment, diagnostic uncertainty, or inadequate response to treatment.[20] These guidelines were intended to complement general practice guidelines for ADHD management already published by the American Academy of Pediatrics (AAP).[20] The guideline did not report whether a systematic search of the literature had been performed but noted that literature was assembled and examined based on previously published evidence reviews and expert opinion. Each published study was organized into an evidence table under a key action statement (KAS) then evaluated/graded by 2 volunteer reviewers associated with SDBP and ADHD guideline panels.[20] Authors reported that evidence was graded based on the similar methods described in the 2011 AAP ADHD practice guideline, where classification was defined by level of policy (strong recommendation (S), recommendation (R), or option (O)) and based on the following levels of aggregate evidence quality: A (systematic review of RCTs), B (RCTs or observational studies with overwhelmingly consistent evidence), C (observational studies), and D (case reports or expert opinion).[20] Harm was assessed by a clear majority of benefit or a relative balance of benefits and harms.[20] There was also a category for recommendation under exceptional situations (X) in which evidence could not be obtained but clear benefits or harm are evident.[20] Treatment algorithms were based on consensus expert opinion of the Panel. There was no risk of bias assessment used as inclusion criteria for publications used for guideline development.[20] Other limitations to the guideline include the absence of the following: clearly defined target users, criteria specifics for evidence selection, diversity in representation from professional groups, patient and public input, external review by experts in the field, unambiguous and specific recommendations, and discussion on resource implications/barriers of recommendations.[20] Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL.[20]

The following description summarizes each of the KAS presented in the guideline[20]:

KAS 1: The clinician with specialized training or expertise should initiate a comprehensive assessment and develop an interprofessional, multimodal treatment plan for any child or adolescent through age 18 years with suspected or diagnosed complex attention-deficit/hyperactivity disorder (ADHD) upon referral from a primary care clinician.
(Strong Recommendation (S); Evidence Level B)

KAS 2: In the evaluation of a child or adolescent with complex ADHD, the clinician should verify any previous diagnoses and assess for coexisting conditions, employing an evidence-based approach that is developmentally appropriate, culturally sensitive, and inclusive of data from multiple settings and sources (home, school, community). The evaluation should include an appropriate, comprehensive medical history and physical examination, and psychological assessment based on the child's presenting problems and their severity, functional impairments, cognitive/developmental level, and the judgment of the treating clinician.
(Strong Recommendation (S); Evidence Level B)

KAS 3: Psychoeducation about ADHD and its coexisting conditions and evidence-based behavioral and educational interventions are foundational for the treatment of complex ADHD and should be implemented at the outset of treatment whenever possible. Evidence-based behavioral and educational interventions (e.g., behavioral parent training, behavioral classroom management, behavioral peer interventions, and, for older children, organizational skills training) should be provided to all children and adolescents with complex ADHD. These approaches address key functional domains (behavioral, educational, social) in home, school, and peer settings that are associated with long-term outcomes.
(Strong Recommendation (S); Evidence Level B)

KAS 4: Treatment of complex ADHD should include evidence-based approaches that address ADHD and account for coexisting conditions while respecting family background and preferences. It is often necessary to combine these approaches with pharmacological treatments. Treatment should focus on areas of functional impairment, not just symptom reduction, by incorporating developmentally appropriate strategies for self-management, skill building, and prevention of adverse outcomes (e.g., substance use, conduct problems, depression/anxiety, suicidal ideation, educational failure).
(Recommendation (R); Evidence Level C-B)

KAS 5: Treatment of complex ADHD should include ongoing, scheduled monitoring of patients throughout the lifespan, commensurate with the individual patient's needs and profile, with particular emphasis on preparing for key developmental transitions (preschool to school, elementary to middle school, middle to high school, and high school to postsecondary education or employment).
(Strong Recommendation (S); Evidence Level B)

New Formulations:
In November 2021, the FDA approved a new formulation of Dyanavel XR® (amphetamine ER; Schedule II) tablets for the treatment of ADHD in patients 6 years of age and older.[1] Tablets are supplied 5 mg, 10 mg, 15 mg, and 20 mg strengths and taken once daily.[1] The FDA initially approved Dynavel XR® as a 2.5 mg/mL ER oral suspension in 2015.[1] Tablet and oral suspension formulations can be converted on a mg-per-mg basis; however, it should not be substituted for other amphetamine products on a mg-per-mg basis because of different amphetamine salt compositions and pharmacokinetic profiles.[1]

In March 2022, the FDA approved Xelstrym™ (dextroamphetamine transdermal system; Schedule II) for the treatment of ADHD in patients 6 years of age and older.[2] This is the first amphetamine-based transdermal product for once daily use.[2,3] Xelstrym™ is available as 4.5 mg, 9 mg, 13.5 mg, and 18 mg patches to be worn during a 9-hour period.[2] Xelstrym™ should not be substituted for other amphetamine products on a mg-per-mg basis, because of different amphetamine salt compositions and pharmacokinetic profiles.[2,3]

Approval of Xelstrym™ was based on a single phase 2, multi-center, modified analog classroom study in 106 pediatric patients aged 6 to 17 years with ADHD.[2-4] The study had a 4-week screening period followed by a 5-week, open-label, dose-optimization phase and a 2-week double-blind, randomized, placebo-controlled crossover treatment period with weekly classroom assessments and telephone-based safety follow-up 7-10 days after last dose of the study drug.[2-4] Patients were randomized by interactive response system in a 1:1 ratio to either their optimized dose of Xelstrym™ or placebo.[2-4] Patients at baseline must have had an ADHD-Rating Sacle (ADHD-RS-IV) total score 90% or greater of the general population of children by age and gender.[2-4] The ADHD-RS is an 18-item scale (range 0 to 54 points) that assesses symptoms of inattentiveness, hyperactivity, and impulsivity with higher scores indicative of more severe symptoms.[21] Patients were excluded if they had hypertension or a body mass index (BMI) outside of 95th percentile for age/gender, cardiovascular disease, history of substance use disorder (SUD), seizure history, other psychiatric disorder, or were a known non-responder to amphetamine treatment.[3,4] The demographics of the study participants were as follows: mean age 10.5 years; 69% male; 76% White, 14% Black or African American, 6% mixed race, 3% Asian, and 1% Caribbean Islander.[3,4]

The primary outcome measure was change from baseline in Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) total score.[2-4] The SKAMP total score assesses 13 items including attention, quality of work, deportment and compliance.[21] Each item is assessed on a 0 to 6-point scale with total score ranging from 0 to 78 and higher scores associated with more severe impairment.[21] A minimal clinically important difference (MCID) for ADHD outcomes related to the SKAMP scale is not well defined. Over the 12-hour assessment period, treatment with Xelstrym™ resulted in a least-squares mean difference (LSMD) in SKAMP total score of -4.7 (95% CI, -8.0 to −1.4) compared to placebo.[2-4] No serious treatment-emergent adverse events were reported.[3] Adverse reactions with incidence of 5% or

greater that occurred during the dose-optimization phase of the clinical study included decreased appetite (54%), insomnia (32%), headache (21%), irritability (16%), abdominal pain (16%) affect lability (16%), application site pain (13%), nausea (9%), application site pruritus (7%), and fatigue (5%).[2,3] In the double-blind, placebo-controlled phase of the clinical study, adverse reactions that occurred in 5% or greater of Xelstrym™ patients and at least twice the rate of placebo, respectively, were decreased appetite (10% vs. 1%), insomnia (8% vs. 4%), and headache (6% vs. 2%).[2,3]

New Indications:
In April 2021, the FDA expanded the approval for Evekeo ODT® (amphetamine sulfate oral disintegrating tablets; Schedule II) to include patients 3 to 5 years of age for the treatment of ADHD.[5] Prior to the change, the labeled indication was for patients 6 to 17 years of age.[5]

Amphetamine sulfate oral disintegrating tablets contains a 1:1 racemic mixture of dextroamphetamine sulfate and levoamphetamine sulfate.[5] The expanded approval was based on amendments to the originally submitted study with amphetamine sulfate IR tablets (Evekeo®) for the treatment of ADHD in patients 6 years of age and older.[5] Evekeo ODT® should not be substituted with other amphetamine sulfate products due to different salt compositions and pharmacokinetic profiles.[5] Evekeo ODT® is supplied in 2.5 mg tablets for use in 3 to 5-year-old patients which may be titrated in 2.5 mg increments at weekly intervals.[5] Evekeo ODT® is also available as 5 mg, 10 mg, 15 mg, and 20 mg tablets in 30-count blister cards.[5]

In May 2022, the FDA granted expanded approval for Qelbree® (viloxazine ER capsules) for the treatment of ADHD in patients 18 years of age and older.[6] Viloxazine, a selective norepinephrine reuptake inhibitor, which was initially approved in April in pediatric patients 6 to 17 years of age. It was the first novel, non-stimulant medication for ADHD approved by the FDA since 2002.[6] The maximum dose for the adults is 600 mg per day.[6]

Expanded approval for adults with ADHD was based on one multicenter, randomized, double-blind, placebo-controlled, flexible-dose, parallel-group monotherapy trial in 374 patients aged 18 to 65 years.[6] The patients were randomized to receive either dose-adjusted viloxazine ER capsules (n=175) or placebo (n=179) once daily for 6 weeks.[6] The viloxazine group was given 200 mg once daily in Week 1, followed by 400 mg once daily in Week 2, then individually adjusted by 200 mg per day once a week (range 200mg to 600 mg once per day).[6] Eligible patients had an adult ADHD Investigator Symptom Rating Scale (AISRS) total score of 26 or higher at baseline and a BMI classified as normal or overweight (18 to 35 kg/m^2).[6] Patients were excluded if they had a history of moderate or severe head trauma or other neurological disorder (e.g. seizures, encephalopathy, etc.), SUD, Hamilton Anxiety Rating Scale (HAM-A) score of > 21, organic mental disorder, a known or self-identified current habitual/chronic cannabis user, any clinically significant medical condition (including, but not limited to cardiovascular, metabolic, endocrine, gastrointestinal, hepatic, infectious, hematological, immunological or dermatological disorders), or history or risk of suicide.[6] The ADHD population treated with viloxazine ER was 56% male, 81% White, 12% Black, 3% Asian, 3% other races and 1% multiracial.[6]

The primary endpoint for the study was the change from baseline in the adult AISRS total score at Week 6.[6] The AISRS is an 18-item scale that corresponds to the 18 DSM-IV symptoms of ADHD where 9 inattentive items alternate with 9 hyperactive-impulsive items.[6] Each item has 4 numerical values and is scored as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe); the maximum total score for the scale is 54 points, with 27 points for each subscale.[6] The AISRS total score is the sum of the inattentive and hyperactive-impulsive subscales.[6] A higher AISRS score correlates with more severe symptoms.[6] A MCID related to the AISRS score is not defined. At week 6, the AISRS was reported to result in a LSMD from baseline of -15.5 points for the viloxazine ER group compared to a -11.7-point decline from baseline for placebo patients (LSMD -3.7; 95% CI, -6.2 to -1.2; P=0.004).[6] Seventeen out of 189 (9%) of patients receiving viloxazine ER discontinued treatment due to an adverse reaction.[6] The most commonly reported adverse reactions associated with discontinuation of viloxazine ER were fatigue (n=4), insomnia (n=3), constipation (n=3), and headache (n=2).[6] The most common adverse reactions occurring in 5% or more of viloxazine ER-treated patients and at

least twice the rate of placebo, respectively, were insomnia (23% vs. 7%), headache (17% vs. 7%), nausea (12% vs. 3%), fatigue (12% vs. 3%), decreased appetite (10% vs. 3%), dry mouth (10% vs. 2%), somnolence (6% vs. 2%) and constipation (6% vs. 1%).[6]

New FDA Safety Alerts:

Table 1. FDA Drug Safety-related Labeling Changes[7-9]

Generic Name	Brand Name	Month/Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
Atomoxetine[8]	Strattera™	January 2022	Warning	**Emergence of New Psychotic or Manic Symptoms** Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania can be caused by STRATTERA at usual doses. If such symptoms occur, consider discontinuing STRATTERA. **Screening Patients for Bipolar Disorder** Patients with bipolar disorder or risk factors for bipolar disorder may be at increased risk of developing mania or mixed episodes during treatment with STRATTERA. It may not be possible to determine whether a manic or mixed episode that appears during treatment with STRATTERA is due to an adverse reaction to STRATTERA or a patient's underlying bipolar disorder. Before initiating treatment with STRATTERA, patients should be adequately screened for risk factors for bipolar disorder such as a personal or family history of mania and depression. **Aggressive Behavior or Hostility** Patients beginning treatment with STRATTERA should be monitored for the appearance or worsening of aggressive behavior or hostility. There is evidence that STRATTERA may cause the emergence or worsening of aggressive behavior or hostility. ADHD and other mental illnesses can be associated with irritability, which can make it difficult to determine if the drug or the underlying psychiatric condition is causing the emergence or worsening of aggressive behavior or hostility in specific patients. If such symptoms occur during treatment, consider a possible causal role of STRATTERA.
Amphetamine products (all)[7,9]	Adderall™ Adzenys ER™ Adzenys XR-ODT™ Desoxyn™ Dexedrine™ Dynavel XR™	February 2022	Adverse Reactions	Gastrointestinal: intestinal ischemia

	Evekeo ODT™ Mydayis™ Vyvanse™			

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Appendix 1: Current Preferred Drug List

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

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

Appendix 2: New Comparative Clinical Trials

A total of 89 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).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to July 05, 2022

1	*serdexmethylphenidate.mp.*	*5*
2	*methylphenidate hydrochloride.mp. or Methylphenidate/*	*7681*
3	*Amphetamine sulfate.mp. or Amphetamine/*	*13078*
4	*mixed amphetamine salts.mp.*	*150*
5	*lisdexamfetamine.mp. or Lisdexamfetamine Dimesylate/*	*479*
6	*dexmethylphenidate.mp. or Dexmethylphenidate Hydrochloride/*	*99*
7	*viloxazine.mp. or Viloxazine/*	*366*
8	*clonidine.mp. or Clonidine/*	*18643*
9	*Guanfacine/ or guanfacine.mp.*	*1147*
10	*atomoxetine.mp. or Atomoxetine Hydrochloride/*	*1977*
11	*attention deficit disorder.mp. or Attention Deficit Disorder with Hyperactivity/*	*33939*
12	*adhd.mp.*	*29597*
13	*1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10*	*41512*
14	*10 or 11 or 12*	*41928*
15	*13 and 14*	*6507*
16	*limit 15 to (english language and humans and yr="2020 -Current" and (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 review"))*	*151*
17	*limit 16 to yr="2021 -Current"*	*89*

Appendix 5: Key Inclusion Criteria

Population	Adult and pediatric patients with attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)
Intervention	Drugs in ADHD class (Appendix 1)
Comparator	Drugs in ADHD class (Appendix 1) or placebo if clinically important safety outcomes
Outcomes	Efficacy: symptom improvement, functional capacity, quality of life, time to onset of effectiveness, duration of effectiveness. Safety: withdrawals due to adverse events, serious and long-term (>12 months) adverse events, misuse/diversion
Timing	Literature from 05/01/20 – 07/05/22
Setting	Outpatient

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

Drug Use Evaluation: Dose Limits for ADHD Drugs

Plain Language Summary: Do Oregon Health Plan providers recommend doses of attention deficit hyperactivity disorder (ADHD) medicines that are based on the evidence?

- Most providers prescribe doses of ADHD medicine that are approved by the Food and Drug Administration (FDA). Providers prescribe doses higher than the FDA approved dose in 1.9% of people. Adderall and Adderall XR (dextroamphetamine/amphetamine salts) were the most common medicines recommended at doses higher than the FDA labeled dose.
- About half of people who take ADHD drugs see a provider who has training in mental or behavioral health.
- If providers prescribe doses higher than recommended by current guidelines, providers must send information to the Oregon Health Plan (OHP) before OHP will pay for the drug. This process is called prior authorization.
- We recommend updating the current prior authorization criteria to clarify maximum doses for ADHD medicines.

Research Questions:

- What proportion of patients are prescribed ADHD drugs above the maximum FDA-labeled dose?
- What proportion of patients with high doses have prescriptions written from a behavioral health specialist?

Conclusions:

- Of patients with paid FFS prescriptions for ADHD drugs (n=10,834) during the study period, only 1.9% (n=207) had a prescription above the FDA approved maximum dose for their age. The most common ADHD drug prescribed above the FDA-approved maximum dose was dextroamphetamine/amphetamine salts (n=158, 76%).
- About half of prescriptions were written by behavioral health specialists. The proportion of patients with prescriptions written by a behavioral health specialist was similar for subgroups based on age, drug, or dose. The most common prescribing provider types were psychiatric/mental health nurse practitioners, family medicine physicians, and pediatric physicians.

Recommendations:

- Update current prior authorization criteria to clarify recommended ages and doses for each drug.
- Revise prior authorization (PA) criteria to reflect maximum age and dose limits as specified in product labeling or supported compendia (see **Appendix 2**). To avoid disruption in care, patients initiated on an ADHD medication as a child should be excluded from PA if they age into a maximum age limit.

Background

There are many drugs which are used for treatment of ADHD. These include broadly, stimulants (such as amphetamine and methylphenidate derivatives) and non-stimulants (including atomoxetine, clonidine, guanfacine and viloxazine). Stimulants are available in both immediate-release and extended-release formulations, and not all agents share the same FDA-approved ages or doses. Current guidelines and available literature support off-label dosing in certain

circumstances. An example of variation in dosing recommendations for mixed amphetamine salts is shown in **Table 1**. Most guidelines note that effective dose of ADHD treatment varies among patients and should be individualized based on symptoms and adverse effects.[1-3] Adverse events of ADHD drugs can include decreased appetite, tics, sexual dysfunction, new or worsening seizures, cardiovascular events, and changes in sleep.[3] Recommended monitoring includes changes in weight and/or height, blood pressure and heart rate, potential for stimulant diversion, and assessment of adverse events.[3] Efficacy for reduced symptoms, positive behavior change, and improvements in education, employment and relationships should also be reassessed frequently during dose titration and periodically during maintenance treatment.[3]

Table 1. Example of variations in dosing recommendations for mixed amphetamine salts.

	FDA-approved max doses	Guideline-recommended max doses
Amphetamine/dextroamphetamine IR	Adderall: 40 mg for ≥ 3 years[4]	AACAP: 60 mg for > 50 kg[5]
Amphetamine/dextroamphetamine XR	Adderall XR: 30 mg for 6-12 years[6] 20 mg for ≥ 13 years[6] Mydayis: 25 mg for 13-17 years[7] 50 mg for ≥18 years[7]	AACAP: 60 mg for > 50 kg[5] CADDRA: 30 mg for <18 years[2] 50 mg for ≥18 years[2]

Abbreviations: AACAP = American Academy of Child and Adolescent Psychiatry; CADDRA = Canadian ADHD Resource Alliance; IR = immediate-release; XR = extended-release

Preferred medications are available for FFS patients without prior authorization if they are within usual doses and age limits typically used in clinical practice. Medications prescribed outside usual dose, age limits, or guideline-directed combinations for ADHD require prior authorization and documentation of consultation or review by a mental health provider. Stimulant medications are paid for by both FFS and coordinated care organizations (CCOs) and are subject to the PDL in addition to age and dose limits. Non-stimulant ADHD medications are also subject to appropriate age and dose limits, but these drugs are carved-out of CCOs and are designated as preferred or voluntary non-preferred.

This review evaluates the incidence of prescribing above the maximum FDA-approved dose in the OHP FFS population.

Methods:

Patients were included in the analysis if they had paid FFS claims for drugs in the ADHD Drugs PDL class during the study period from 4/1/2021 to 3/31/2022. Patients were excluded if they had other insurance, Medicare, or OHP with limited drug benefit during the study period because data from these patients are likely to be incomplete. Patients with Medicare or limited drug benefits were identified based on the following benefit packages:

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

The index event (IE) for each patient was defined as the claim with the largest daily dose during the study period. If multiple claims were identified with the same daily dose, then the first claim in the study period with the largest dose was used as the IE. Baseline demographics were evaluated at the time of the IE.

The following definitions were used for the analysis:

- Daily dose was calculated for each claim using the following formula: drug strength per unit*units dispensed/days' supply.
- The dose for IEs was categorized as above or below the FDA max labeled dose according to the drug, daily dose, and age identified on the claim. **Table A1** lists maximum FDA labeled doses for various products and ages.
- Behavioral health specialists were defined according to taxonomies in **Table A2.**

Results:

Of patients with paid FFS prescriptions for ADHD drugs (n=10,834) during the study period, only 1.9% (n=207) had a prescription higher than the FDA labeled dose for their age (**Table 2**). Patients with high doses were more commonly adults over 17 years of age. Most patients included in this study were documented as White or Unknown race on their OHP profile. **Table 3** further describes subgroups based on age, prescriber type, and doses above or below the FDA labeled dose. Regardless of age or dose, about half of patients had prescriptions written from a behavioral health specialist. The most common drugs prescribed higher than the FDA-labeled dose are listed in **Table 4**. Of patients with high-dose prescriptions (n=207), the most common entity prescribed was dextroamphetamine/ amphetamine salts (n=158, 76%). Use of other agents higher than the FDA-labeled dose was infrequent.

There were no major trends in prescribing provider type when evaluating patients with claims above or below the FDA-labeled dose. The most common prescribing provider types for ADHD drugs were psychiatric/mental health nurse practitioners, family medicine physicians, and pediatric physicians (**Table 5**). These prescribers were the most common regardless of the dose prescribed. Psychiatrists, family nurse practitioners, and physician assistants were also common prescribers of ADHD drugs.

Table 2. Demographics

	IE above max FDA dose		IE at or below max FDA dose	
N=	**207**	**1.9%**	**10,627**	**98.1%**
Age				
≤12	23	11.1%	3,859	36.3%
13-17	30	14.5%	2,230	21.0%
≥18	154	74.4%	4,538	42.7%
Female	104	50.2%	4,570	43.0%
Behavioral health specialist				
Y	100	48.3%	4,882	45.9%
N	107	51.7%	5,745	54.1%
Race				
White	76	36.7%	4,953	46.6%
Unknown	62	30.0%	3,940	37.1%
HNA	53	25.6%	1,002	9.4%
Other	16	7.7%	732	6.9%

Current PDL status				
Y	181	87.4%	5,877	55.3%
N	6	2.9%	62	0.6%
V	20	9.7%	4,688	44.1%

Table 3. Dosing by age and prescriber type

	Specialist		Non-Specialist	
N=	**4,982**	**%**	**5,852**	**%**
IE above max FDA dose				
≤12	16	0.3%	7	0.1%
13-17	13	0.3%	17	0.3%
≥ 18	71	1.4%	83	1.4%
IE at or below max FDA dose				
≤12	1,668	33.5%	2,191	37.4%
13-17	1,153	23.1%	1,077	18.4%
≥ 18	2,061	41.4%	2,477	42.3%

Table 4. Most common drugs prescribed above max FDA dose (by molecular entity)

	Specialist		Non-Specialist	
N=	**4,982**	**%**	**5,852**	**%**
IE above max FDA dose				
Carve-out drugs				
clonidine HCl	12	0.2%	2	0.0%
guanfacine HCl	6	0.1%	0	0.0%
Physical health drugs				
dextroamphetamine/amphetamine	61	1.2%	97	1.7%
amphetamine	13	0.3%	2	0.0%
methylphenidate HCl	4	0.1%	3	0.1%
dexmethylphenidate HCl	2	0.0%	1	0.0%
dextroamphetamine sulfate	2	0.0%	2	0.0%

IE at or below max FDA dose				
Carve-out drugs				
atomoxetine HCl	2,058	41.3%	2,732	46.7%
guanfacine HCl	1,901	38.2%	2,007	34.3%
clonidine HCl	476	9.6%	268	4.6%
viloxazine HCl	30	0.6%	6	0.1%
Physical health drugs				
dextroamphetamine/amphetamine	186	3.7%	365	6.2%
methylphenidate HCl	135	2.7%	273	4.7%
lisdexamfetamine dimesylate	80	1.6%	68	1.2%
dexmethylphenidate HCl	14	0.3%	22	0.4%
dextroamphetamine sulfate	1	0.0%	3	0.1%
methylphenidate	1	0.0%	1	0.0%

Table 5. Top 10 common prescriber taxonomies

	IE above max FDA dose		
		207	**%**
1	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	62	30.0%
2	PHYSICIAN-FAMILY MEDICINE	41	19.8%
3	PHYSICIAN-PEDIATRICS	17	8.2%
4	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	16	7.7%
5	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	15	7.2%
6	NURSE PRACTITIONER - FAMILY	9	4.3%
7	PHYSICIAN-INTERNAL MEDICINE	9	4.3%
8	PHYSICIAN ASSISTANT	9	4.3%
9	STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	7	3.4%
10	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH	4	1.9%

	IE at or below max FDA dose		
		10,627	**%**
1	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	2,616	24.6%
2	PHYSICIAN-PEDIATRICS	1,786	16.8%
3	PHYSICIAN-FAMILY MEDICINE	1,221	11.5%
4	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	1,102	10.4%
5	NURSE PRACTITIONER - FAMILY	814	7.7%
6	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	806	7.6%
7	PHYSICIAN ASSISTANT	441	4.1%
8	NURSE PRACTITIONER - PEDIATRICS: PEDIATRICS	264	2.5%
9	PHYSICIAN-INTERNAL MEDICINE	230	2.2%
10	NATUROPATH	215	2.0%

Limitations:

- Diagnostic data were not included in this evaluation. In some cases, drugs for ADHD are also approved by the FDA for other indications, including narcolepsy at higher doses than doses recommended for treatment of ADHD. It is unclear based on this current study if drugs were prescribed for ADHD or sleep-wake disorders.
- Use of highest dose claim as the IE may overestimate number of patients with high-dose utilization. Daily dose was calculated based on information submitted by the pharmacy and cannot account for adherence, drug holidays, or the average dose actually taken by the patient. Patients were included even if utilization appeared to be off-label for a given age. If max dose was unavailable for a given age, maximum doses were estimated based available information for other ages for the same product. Some doses are weight based which cannot be easily captured in claims data. In these circumstances, a single threshold was chosen as the max dose and used to categorize claims.
- Patients were categorized based on a single IE, and patients who had claims for multiple different doses or drugs would be identified according to the highest strength dose. A recent drug use evaluation conducted in the OHP population estimated that about 7.2% of patients had claims for multiple agents.[8]
- Prescriber specialty was identified using the primary prescriber taxonomy which may be incomplete or not accurately reflect the prescriber specialty. This study also only evaluated prescriber type associated with IE. It would not capture patients who may have previously transitioned care from a specialist to a general practitioner. Additionally, this study would not identify scenarios where general practitioners consult with a behavioral health specialist prior to prescribing off-label dosing.

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Appendix 1: Drug Coding

Table A1. Unit doses and max daily FDA approved doses for various age for ADHD drugs

GSN	Brand Name	Generic Name	Form	Drug Strength	Strength Calculated	Max Pediatric Dose	Max Pediatric Age	Max Adult Dose	Min Adult Age
77736	ADZENYS ER	amphetamine	SUS BP 24H	1.25 mg/mL	1.25	18.8	12	12.5	13
75549	ADZENYS XR-ODT	amphetamine	TAB RAP BP	18.8 mg	18.8	18.8	12	12.5	13
75548	ADZENYS XR-ODT	amphetamine	TAB RAP BP	15.7 mg	15.7	18.8	12	12.5	13
75547	ADZENYS XR-ODT	amphetamine	TAB RAP BP	12.5 mg	12.5	18.8	12	12.5	13
75546	ADZENYS XR-ODT	amphetamine	TAB RAP BP	9.4 mg	9.4	18.8	12	12.5	13
75545	ADZENYS XR-ODT	amphetamine	TAB RAP BP	6.3 mg	6.3	18.8	12	12.5	13
75544	ADZENYS XR-ODT	amphetamine	TAB RAP BP	3.1 mg	3.1	18.8	12	12.5	13
75025	DYANAVEL XR	amphetamine	SUS BP 24H	2.5 mg/mL	2.5	20			
79482	EVEKEO ODT	amphetamine sulfate	TAB RAPDIS	20 mg	20	40			
79481	EVEKEO ODT	amphetamine sulfate	TAB RAPDIS	15 mg	15	40			
79480	EVEKEO ODT	amphetamine sulfate	TAB RAPDIS	10 mg	10	40			
79479	EVEKEO ODT	amphetamine sulfate	TAB RAPDIS	5 mg	5	40			
5003	EVEKEO	amphetamine sulfate	TABLET	5 mg	5	40			
5002	EVEKEO	amphetamine sulfate	TABLET	10 mg	10	40			
60391	STRATTERA	atomoxetine HCl	CAPSULE	100 mg	100	100			
60390	STRATTERA	atomoxetine HCl	CAPSULE	80 mg	80	100			
51493	STRATTERA	atomoxetine HCl	CAPSULE	60 mg	60	100			
51492	STRATTERA	atomoxetine HCl	CAPSULE	40 mg	40	100			
51491	STRATTERA	atomoxetine HCl	CAPSULE	25 mg	25	100			
51490	STRATTERA	atomoxetine HCl	CAPSULE	18 mg	18	100			
51489	STRATTERA	atomoxetine HCl	CAPSULE	10 mg	10	100			
66895	KAPVAY	clonidine HCl	TAB ER 12H	0.1 mg	0.1	0.4			
67693	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	35 mg	35	30	17	40	18
67692	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	25 mg	25	30	17	40	18
66611	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	40 mg	40	30	17	40	18
65909	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	30 mg	30	30	17	40	18
61317	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	15 mg	15	30	17	40	18
59192	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	20 mg	20	30	17	40	18
59191	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	10 mg	10	30	17	40	18
59190	FOCALIN XR	dexmethylphenidate HCl	CPBP 50-50	5 mg	5	30	17	40	18
48984	FOCALIN	dexmethylphenidate HCl	TABLET	10 mg	10	20			
48983	FOCALIN	dexmethylphenidate HCl	TABLET	5 mg	5	20			
48982	FOCALIN	dexmethylphenidate HCl	TABLET	2.5 mg	2.5	20			
72314	ZENZEDI	dextroamphetamine sulfate	TABLET	30 mg	30	40			
72313	ZENZEDI	dextroamphetamine sulfate	TABLET	20 mg	20	40			
71049	ZENZEDI	dextroamphetamine sulfate	TABLET	7.5 mg	7.5	40			

71048	ZENZEDI	dextroamphetamine sulfate	TABLET	2.5 mg	2.5	40			
64090	PROCENTRA	dextroamphetamine sulfate	SOLUTION	5 mg/5 mL	1	40			
5011	DEXEDRINE	dextroamphetamine sulfate	TABLET	5 mg	5	40			
5010	ZENZEDI	dextroamphetamine sulfate	TABLET	15 mg	15	40			
5009	ZENZEDI	dextroamphetamine sulfate	TABLET	10 mg	10	40			
5007	DEXEDRINE	dextroamphetamine sulfate	CAPSULE ER	5 mg	5	40			
5006	DEXEDRINE	dextroamphetamine sulfate	CAPSULE ER	15 mg	15	40			
5005	DEXEDRINE	dextroamphetamine sulfate	CAPSULE ER	10 mg	10	40			
77501	MYDAYIS	dextroamphetamine/amphetamine	CPTP 24HR	50 mg	50	25	17	50	18
77500	MYDAYIS	dextroamphetamine/amphetamine	CPTP 24HR	37.5 mg	37.5	25	17	50	18
77499	MYDAYIS	dextroamphetamine/amphetamine	CPTP 24HR	25 mg	25	25	17	50	18
77498	MYDAYIS	dextroamphetamine/amphetamine	CPTP 24HR	12.5 mg	12.5	25	17	50	18
50430	ADDERALL XR	dextroamphetamine/amphetamine	CAP ER 24H	25 mg	25	30	12	20	13
50429	ADDERALL XR	dextroamphetamine/amphetamine	CAP ER 24H	15 mg	15	30	12	20	13
50428	ADDERALL XR	dextroamphetamine/amphetamine	CAP ER 24H	5 mg	5	30	12	20	13
48703	ADDERALL XR	dextroamphetamine/amphetamine	CAP ER 24H	30 mg	30	30	12	20	13
48702	ADDERALL XR	dextroamphetamine/amphetamine	CAP ER 24H	20 mg	20	30	12	20	13
48701	ADDERALL XR	dextroamphetamine/amphetamine	CAP ER 24H	10 mg	10	30	12	20	13
47133	ADDERALL	dextroamphetamine/amphetamine	TABLET	15 mg	15	40			
47132	ADDERALL	dextroamphetamine/amphetamine	TABLET	12.5 mg	12.5	40			
47131	ADDERALL	dextroamphetamine/amphetamine	TABLET	7.5 mg	7.5	40			
34359	ADDERALL	dextroamphetamine/amphetamine	TABLET	30 mg	30	40			
5001	ADDERALL	dextroamphetamine/amphetamine	TABLET	20 mg	20	40			
5000	ADDERALL	dextroamphetamine/amphetamine	TABLET	10 mg	10	40			
4999	ADDERALL	dextroamphetamine/amphetamine	TABLET	5 mg	5	40			
65574	INTUNIV	guanfacine HCl	TAB ER 24H	4 mg	4	4	12	7	13
65573	INTUNIV	guanfacine HCl	TAB ER 24H	3 mg	3	4	12	7	13
65572	INTUNIV	guanfacine HCl	TAB ER 24H	2 mg	2	4	12	7	13
65570	INTUNIV	guanfacine HCl	TAB ER 24H	1 mg	1	4	12	7	13
77146	VYVANSE	lisdexamfetamine dimesylate	TAB CHEW	60 mg	60	70			
77145	VYVANSE	lisdexamfetamine dimesylate	TAB CHEW	50 mg	50	70			
77144	VYVANSE	lisdexamfetamine dimesylate	TAB CHEW	40 mg	40	70			
77143	VYVANSE	lisdexamfetamine dimesylate	TAB CHEW	30 mg	30	70			
77142	VYVANSE	lisdexamfetamine dimesylate	TAB CHEW	20 mg	20	70			
77083	VYVANSE	lisdexamfetamine dimesylate	TAB CHEW	10 mg	10	70			
73292	VYVANSE	lisdexamfetamine dimesylate	CAPSULE	10 mg	10	70			
63647	VYVANSE	lisdexamfetamine dimesylate	CAPSULE	60 mg	60	70			
63646	VYVANSE	lisdexamfetamine dimesylate	CAPSULE	40 mg	40	70			
63645	VYVANSE	lisdexamfetamine dimesylate	CAPSULE	20 mg	20	70			
62285	VYVANSE	lisdexamfetamine dimesylate	CAPSULE	70 mg	70	70			
62284	VYVANSE	lisdexamfetamine dimesylate	CAPSULE	50 mg	50	70			

62283	VYVANSE	lisdexamfetamine dimesylate	CAPSULE	30 mg	30	70			
5014	DESOXYN	methamphetamine HCl	TABLET	5 mg	5	25			
77496	COTEMPLA XR-ODT	methylphenidate	TAB RAP BP	25.9 mg	25.9	51.8			
77495	COTEMPLA XR-ODT	methylphenidate	TAB RAP BP	17.3 mg	17.3	51.8			
77494	COTEMPLA XR-ODT	methylphenidate	TAB RAP BP	8.6 mg	8.6	51.8			
60618	DAYTRANA	methylphenidate	PATCH TD24	30 mg/9 hour	30	30			
60617	DAYTRANA	methylphenidate	PATCH TD24	20 mg/9 hour	20	30			
60616	DAYTRANA	methylphenidate	PATCH TD24	15 mg/9 hour	15	30			
60615	DAYTRANA	methylphenidate	PATCH TD24	10 mg/9 hour	10	30			
78728	JORNAY PM	methylphenidate HCl	CPDR ER SP	100 mg	100	100			
78727	JORNAY PM	methylphenidate HCl	CPDR ER SP	80 mg	80	100			
78726	JORNAY PM	methylphenidate HCl	CPDR ER SP	60 mg	60	100			
78725	JORNAY PM	methylphenidate HCl	CPDR ER SP	40 mg	40	100			
78724	JORNAY PM	methylphenidate HCl	CPDR ER SP	20 mg	20	100			
78099	ADHANSIA XR	methylphenidate HCl	CPBP 20-80	85 mg	85	85	17	100	18
78098	ADHANSIA XR	methylphenidate HCl	CPBP 20-80	70 mg	70	85	17	100	18
78097	ADHANSIA XR	methylphenidate HCl	CPBP 20-80	55 mg	55	85	17	100	18
78096	ADHANSIA XR	methylphenidate HCl	CPBP 20-80	45 mg	45	85	17	100	18
78095	ADHANSIA XR	methylphenidate HCl	CPBP 20-80	35 mg	35	85	17	100	18
78094	ADHANSIA XR	methylphenidate HCl	CPBP 20-80	25 mg	25	85	17	100	18
78038	RELEXXII	methylphenidate HCl	TAB ER 24	72 mg	72	54	12	72	13
75265	QUILLICHEW ER	methylphenidate HCl	TAB CBP24H	40 mg	40	60			
75264	QUILLICHEW ER	methylphenidate HCl	TAB CBP24H	30 mg	30	60			
75263	QUILLICHEW ER	methylphenidate HCl	TAB CBP24H	20 mg	20	60			
72092	METHYLPHENIDATE LA	methylphenidate HCl	CPBP 50-50	60 mg	60	60			
70374	QUILLIVANT XR	methylphenidate HCl	SU ER RC24	5 mg/mL (25 mg/5 mL)	5	60			
61449	APTENSIO XR	methylphenidate HCl	CSBP 40-60	60 mg	60	60			
61448	APTENSIO XR	methylphenidate HCl	CSBP 40-60	50 mg	50	60			
61447	APTENSIO XR	methylphenidate HCl	CSBP 40-60	40 mg	40	60			
61446	APTENSIO XR	methylphenidate HCl	CSBP 40-60	30 mg	30	60			
61445	APTENSIO XR	methylphenidate HCl	CSBP 40-60	20 mg	20	60			
61444	APTENSIO XR	methylphenidate HCl	CSBP 40-60	15 mg	15	60			
61443	APTENSIO XR	methylphenidate HCl	CSBP 40-60	10 mg	10	60			
60547	METHYLPHENIDATE HCL CD	methylphenidate HCl	CPBP 30-70	60 mg	60	60			
60546	METHYLPHENIDATE HCL CD	methylphenidate HCl	CPBP 30-70	50 mg	50	60			
60545	METHYLPHENIDATE HCL CD	methylphenidate HCl	CPBP 30-70	40 mg	40	60			
54680	METHYLIN	methylphenidate HCl	SOLUTION	10 mg/5 mL	2	60			
54679	METHYLIN	methylphenidate HCl	SOLUTION	5 mg/5 mL	1	60			
54678	METHYLPHENIDATE HCL	methylphenidate HCl	TAB CHEW	10 mg	10	60			
54677	METHYLPHENIDATE HCL	methylphenidate HCl	TAB CHEW	5 mg	5	60			

54676	METHYLPHENIDATE HCL	methylphenidate HCl	TAB CHEW	2.5 mg	2.5	60			
53974	RITALIN LA	methylphenidate HCl	CPBP 50-50	10 mg	10	60			
53061	RITALIN LA	methylphenidate HCl	CPBP 50-50	40 mg	40	60			
53060	RITALIN LA	methylphenidate HCl	CPBP 50-50	30 mg	30	60			
53059	RITALIN LA	methylphenidate HCl	CPBP 50-50	20 mg	20	60			
53058	METHYLPHENIDATE HCL CD	methylphenidate HCl	CPBP 30-70	30 mg	30	60			
53057	METHYLPHENIDATE HCL CD	methylphenidate HCl	CPBP 30-70	20 mg	20	60			
53056	METHYLPHENIDATE HCL CD	methylphenidate HCl	CPBP 30-70	10 mg	10	60			
50172	CONCERTA	methylphenidate HCl	TAB ER 24	27 mg	27	54	12	72	13
47318	CONCERTA	methylphenidate HCl	TAB ER 24	54 mg	54	54	12	72	13
45982	CONCERTA	methylphenidate HCl	TAB ER 24	36 mg	36	54	12	72	13
45981	CONCERTA	methylphenidate HCl	TAB ER 24	18 mg	18	54	12	72	13
44072	METHYLPHENIDATE ER	methylphenidate HCl	TABLET ER	10 mg	10	60			
4029	METHYLPHENIDATE ER	methylphenidate HCl	TABLET ER	20 mg	20	60			
4028	RITALIN	methylphenidate HCl	TABLET	5 mg	5	60			
4027	RITALIN	methylphenidate HCl	TABLET	20 mg	20	60			
4026	RITALIN	methylphenidate HCl	TABLET	10 mg	10	60			
82024	AZSTARYS	serdexmethylphen/dexmethylphen	CAPSULE	52.3 mg-10.4 mg	52.3	52.3			
82023	AZSTARYS	serdexmethylphen/dexmethylphen	CAPSULE	39.2 mg-7.8 mg	39.2	52.3			
82022	AZSTARYS	serdexmethylphen/dexmethylphen	CAPSULE	26.1 mg-5.2 mg	26.1	52.3			
82135	QELBREE	viloxazine HCl	CAP ER 24H	200 mg	200	400	17	600	18
82134	QELBREE	viloxazine HCl	CAP ER 24H	150 mg	150	400	17	600	18
82132	QELBREE	viloxazine HCl	CAP ER 24H	100 mg	100	400	17	600	18

Table A2. Taxonomy codes associated with behavioral health or psychiatric specialists

Taxonomy	Taxonomy Description
163WP0807X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH
163WP0808X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH
163WP0809X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH
167G00000X	NURSING SERVICE - LICENSED PSYCHIATRIC TECHNICIAN
1835P1300X	PHARMACIST - PSYCHIATRIC
2080P0006X	PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS
2080P0008X	PHYSICIAN-PEDIATRICS-NEURODEVELOPMENTAL DISABILITIES
2084A0401X	PSYCHIATRY & NEUROLOGY, ADDICTION MEDICINE
2084B0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-BARIATRIC MEDICINE
2084B0040X	BEHAVIORAL NEUROLOGY & NEUROPSYCHIATRY
2084D0003X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-DIAGNOSTIC NEUROIMAGING
2084F0202X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-FORENSIC PSYCHIATRY
2084H0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-HOSPICE AND PALLIATIVE MEDICINE
2084N0008X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROMUSCULAR MEDICINE

2084N0400X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY
2084N0402X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY WITH SPECIAL QUAL IN CHILD NEUROLO
2084N0600X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-CLINICAL NEUROPHYSIOLOGY
2084P0005X	PHYSICIAN-PSYCHIATRY&NERUOLOGY-NEURODEVELOPMENTAL DISABILITIES
2084P0015X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHOSOMATIC MEDICINE
2084P0800X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY
2084P0802X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-ADDICTION PSYCHIATRY
2084P0804X	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY
2084P0805X	PHYSICIAN-PSYCHIATRY&NEUROLGY-GERIATRIC PSYCHIATRY
2084P2900X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PAIN MEDICINE
2084S0010X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SPORTS MEDICINE
2084S0012X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SLEEP MEDICINE
2084V0102X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-VASCULAR NEUROLOGY
273R00000X	PSYCHIATRIC UNIT
283Q00000X	HOSPITALS: PSYCHIATRIC HOSPITAL
323P00000X	PSYCHIATRIC RESIDENTIAL TREATMENT FACILITY
363LP0808X	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH
364SP0807X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0808X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0809X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0810X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0811X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0812X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0813X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover medications used for ADHD and narcolepsy if diagnosis is funded by the OHP, and medication use is consistent with best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best practices.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Table 1. Age Range and Maximum Daily Doses for Drugs Approved for ADHD.

Drug	Brand Name (or generic equivalents)	Min Age	Max Age	Max Daily Dose
STIMULANTS				
Amphetamine IR	Evekeo (tab)	3	NA	40 mg
	Evekeo ODT (dist tab)	3	NA	40 mg
Amphetamine ER	Adsensys ER (susp) and XR-ODT (tab)	6	12	18.8
		13	NA	12.5 mg
	Dyanavel XR (susp, tab)	6	NA	20 mg
Dextroamphetamine IR	ProCentra (sol)	3	16	40 mg
	Zenzedi (tab)	3	16	40 mg
Dextroamphetamine ER	Dexedrine Spansule (cap)	6	16	40 mg
	Xelstrym (transdermal patch)	6	NA	18 mg/9 hr

Dextroamphetamine/ amphetamine salts IR	Adderall (tab)	3	NA	40 mg
Dextroamphetamine/ amphetamine salts ER	Adderall XR (cap)	6	12	30 mg
		13	NA	60 mg
	Mydayis (cap)	13	17	25 mg
		18	55	50 mg
Dexmethylphenidate IR	Focalin (tab)	6	17	20 mg
Dexmethylphenidate ER	Focalin XR (cap)	6	17	30 mg
		18	NA	40 mg
Lisdexamfetamine	Vyvanse (cap; chew tab)	6	NA	70 mg
Methamphetamine IR	Desoxyn (tab)	6	17	25 mg
Methylphenidate IR	Methylin (sol)	6	NA	60 mg
	Ritalin (tab)	6	NA	60 mg
Methylphenidate ER	Adhansia XR (cap)	6	17	85 mg
		18	NA	100 mg
	Aptensio XR (cap)	6	NA	60 mg
	Concerta (tab)	6	12	54 mg
		13	65	72 mg
	Cotempla XR-ODT (tab)	6	17	51.8 mg
	Daytrana (transdermal patch)	6	17	30 mg/9 hr
	Jornay PM (cap)	6	NA	100 mg
	Metadate CD (tab)	6	NA	60 mg
	QuilliChew ER (chew tab)	6	NA	60 mg
	Quillivant XR (susp)	6	NA	60 mg
	Relexxi (tab)	6	12	54 mg
		13	65	72 mg
	Ritalin LA (cap)	6	NA	60 mg
Serdexmethylphenidate/ dexmethylphenidate	Azstarys (cap)	6	NA	52.3 mg/ 10.4 mg
NON-STIMULANTS				
Atomoxetine	Strattera (cap)	6	17	≤70 kg: lesser of 1.4 mg/kg or 100 mg >70 kg: 100 mg
		18	NA	100 mg
Clonidine ER	Kapvay (tab)	6	17	0.4 mg
Guanfacine ER	Intuniv (tab)	6	12	4 mg

		13	17	7 mg
Viloxazine ER	Qelbree (cap)	6	17	400 mg
		18	NA	600 mg
Abbreviations: cap = capsule; chew = chewable; dist = disintegrating; ER = extended-release formulation; IR = immediate-release formulation; NA = not applicable; sol = solution; susp = suspension; tab = tablet.				

Table 2. Age Range and Maximum Daily Doses for Drugs Approved for Narcolepsy.

Drug	Brand Name (or generic equivalents)	Min Age	Max Age	Max Daily Dose
STIMULANTS				
Amphetamine IR	Evekeo (tab)	6	12	40 mg
		13	NA	60 mg
Dextroamphetamine IR	ProCentra (sol)	3	17	40 mg
		18	NA	60 mg
	Zenzedi (tab)	3	17	40 mg
		18	NA	60 mg
Dextroamphetamine ER	Dexedrine (cap)	6	17	40 mg
		18	NA	60 mg
Dextroamphetamine/amphetamine salts IR	Adderall (tab)	6	17	40 mg
		18	NA	60 mg
Methylphenidate IR	Methylin (sol)	6	NA	60 mg
	Ritalin (tab)	6	NA	60 mg
Methylphenidate ER	Ritalin LA (cap)	6	12	60 mg
Abbreviations: cap = capsule; ER = extended-release formulation; IR = immediate-release formulation; NA = not applicable; sol = solution; tab = tablet.				

Table 3. Standard Combination Therapy for ADHD

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

Abbreviations: ER = extended-release; IR = immediate-release formulation.

* Recommended by the American Academy of Pediatrics. Wolraich ML, Hagan JF, Jr., Allan C, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4).
**Identified by: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2015.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Preferred drugs reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an ADHD diagnosis?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #7	**No:** Go to #11
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen a standard combination therapy, as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #11
9. Is the request for a narcolepsy diagnosis?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Approve for up to 12 months	**No:** Go to #11
11. Was the drug regimen developed by or in consultation with a mental health specialist (e.g., psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist)?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Go to #12

Approval Criteria		
12. Was the current drug regimen *initiated* at doses and ages recommended in Tables 1-3 and has the provider assessed ongoing need for treatment in the past year?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Ages or doses exceeding defined limits, or non-recommended multi-drug regimens, are only approved when prescribed by or in consultation with a mental health specialist. Specialist consultation is not required if patients age into a maximum age limit. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *10/22 (DE);6/22; 8/20; 5/19; 9/18; 5/16; 3/16; 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*
Implementation: *11/1/2018; 10/13/16; 7/1/16; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*

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

Drug Use Evaluation: Lumateperone

Plain Language Summary: How is lumateperone prescribed for people on Oregon Medicaid compared to similar medicines?

- Lumateperone is a medicine that providers can recommend for schizophrenia. Studies do not show that lumateperone improves behavior or thought patterns more than other medicines in people with schizophrenia.
- Providers who live in rural counties are the ones who usually recommend lumateperone. People taking lumateperone had higher health costs than people who were taking similar medicines.
- The Drug Use Research Management program recommends reaching out to providers to identify why they recommend this medicine. Educate providers on the cost of lumateperone compared to other medicines that have similar benefits and risks.

Research Questions:

1. Which potential indications are present on or prior to initiation of lumateperone or MHCAG recommended first line, second generation antipsychotics for schizophrenia in Oregon Medicaid patients.
2. Which provider specialties initiate lumateperone or MHCAG recommended first line, second generation antipsychotics in Oregon Medicaid patients?
3. How are lumateperone and MHCAG recommended first line, second generation antipsychotics used in conjunction with other psychotropic medications in Oregon Medicaid patients?
4. What are the impacts on healthcare resource utilization (HRU) for Oregon Medicaid patients starting lumateperone or MHCAG recommended antipsychotics?

Conclusions:

1. Lumateperone had a significantly higher rate of patients with schizophrenia compared to MHCAG agents (56.86% vs. 19.83%; $p<0.0001$) and a significantly lower rate of bipolar disorder (29.41% vs. 49.16%; $p=0.0064$).
2. Prescribers in Douglas County accounted for 16.43% of patients receiving lumateperone compared to only 3.75% of patients in the MHCAG agent group. Several other rural counties had higher rates of lumateperone use (e.g., Lincoln 9.29% vs. 1.37%, Polk 6.43% vs. 2.93%, Columbia 2.86% vs. 0.68%). Prescriber specialties also varied significantly with “Nurse Practitioner – Psychiatric/Mental Health” accounting for 72.86% of lumateperone initial prescriptions vs. 33.23% of MHCAG initial prescriptions ($p<0.0001$).
3. Concurrent use of psychotherapeutic regimens was common, with lumateperone patients having a higher rate of other antipsychotic use compared to MHCAG patients (74.51% vs. 53.63%; $p=0.0038$). Concurrent antidepressant use was lower in the lumateperone group compared to the MHCAG group (50.98% vs. 64.80%; $p=0.0471$).
4. The time to discontinuation of the index antipsychotic was similar for lumateperone vs. MHCAG patients. Lumateperone patients had significant increases in costs for inpatient services, pharmacy services, and total cost of care. The lumateperone group had significantly lower baseline inpatient

HRU and significantly higher follow up HRU compared to the MHCAG group, suggestive of treatment patterns beyond the direct effects of lumateperone use.

Recommendations:

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

Background

In August 2020, the Drug Use Research and Management program reviewed lumateperone as part of the antipsychotic drug class update and new drug evaluation.[1] Low quality evidence shows that lumateperone 42mg once daily may reduce Positive and Negative Syndrome Scale (PANSS) scores compared to placebo in patients with schizophrenia who were treatment experienced, but not treatment resistant.[2–4] The failure to demonstrate a dose-response and a lack of consistent statistical differences between placebo and treatment arms for the primary study endpoints makes interpretation of the available evidence challenging. In December 2021, the FDA approved lumateperone for the treatment of bipolar depression.[5] Beginning in April of 2020, the Oregon Fee For Service (FFS) Medicaid program began seeing claims for lumateperone treatment.

The objective of this study was to determine how lumateperone is used compared to other antipsychotics medications used to treat schizophrenia in treatment-experienced patients. In particular, this study evaluated which indications were present and likely targets for lumateperone treatment, which prescribers initiated lumateperone treatment, how lumateperone was used in combination with other antipsychotics, and finally how the use of lumateperone impacted the overall cost of care.

Methods:

The Oregon Medicaid Decision Support and Surveillance Utilization Review System (DSSURS) data warehouse was the data source for this retrospective observational study. DSSURS contains all medical and pharmacy administrative calls for all fee-for-service (FFS) and coordinated care organization (CCO) paid claims from the Oregon Medicaid Management Information System (MMIS).[7] The claim evaluation window was from 4/1/2019 to 12/31/2021. For patients with at least one claim for lumateperone, the index event was the first claim for lumateperone. For all other included patients, the index event was the first claim for any MHCAG antipsychotic. The Mental Health Clinical Advisory Group (MHCAG), a subcommittee of the Pharmacy and Therapeutics Committee, has developed treatment algorithms for patients with schizophrenia. [6] The MHCAG algorithm suggests the use of aripiprazole, risperidone, or paliperidone as starting antipsychotics for the treatment of schizophrenia. The index date was the date of service of the index event. The index antipsychotic was the antipsychotic associated with the index event. The baseline period was the 365 days prior to the index date (excluding the index date). The follow-up period was the 365 days following the index date (inclusive of the index date). SAS software version 9.4 was used to perform all data analysis and statistical operations. (Copyright ©2021 SAS Institute Inc.) Continuous outcomes were compared using Student T-Tests while categorical variables were compared using Chi Squared tests.

Inclusion Criteria:

1. At least one paid FFS claim for either lumateperone or a MHCAG antipsychotic (**Table 7**) during the claim evaluation window

Exclusion Criteria:

1. Patients under 18 years old
2. Patients with non-Medicaid primary insurance coverage (TPL) effective during either the baseline or follow up period

3. Heritage Native American All Inclusive Rate (HNA AIR) claims during the baseline or follow up period
4. Claims for benefit plans other than OHP Plus (BMH) during either the baseline or follow up period
5. Patient without a history of antipsychotic pharmacy claims
6. Less than 75% of days OHP Plus (BMH) benefit plan eligibility during the 365 day baseline period
7. Less than 75% of days OHP Plus (BMH) benefit plan eligibility during the 365 day follow up period

Cohorts:

Patients with an index antipsychotic of lumateperone were assigned to the lumateperone group. Patients with any other index antipsychotic were assigned to the MHCAG group.

Definitions:

Patients were considered antipsychotic experienced if there were any claims during the claims evaluation window for any antipsychotic medication for more than 42 days (**Table 7, Table 8**). Age was calculated based on the index date. Patients were categorized based on their enrollment in a CCO, FFS or both during both the baseline and follow up periods. Concurrent psychotropic regimens were defined by the presence of medications defined in **Table 7** and **Table 8**. The index medication was excluded from the concurrent psychotropic regimen definitions. Persistence to antipsychotic therapy was measured by the time from the index date to the last date covered by the index medication (time to discontinuation). Costs were calculated based on the amount paid and averaged over the entire study population. Inpatients days were cumulative across all hospitalizations.

Supplemental Analysis:

For the supplemental analysis, all patients meeting inclusion criteria and not meeting any exclusion criteria 1-4 were evaluated for geographic distribution and provider specialty.

Results:

Of the 12,452 patients meeting inclusion criteria, 767 were included in the final study population (**Table 1**). There were no statistically significant differences in baseline demographics of age, gender, or CCO enrollment (**Table 2**). **Table 3** shows lumateperone had a significantly higher rate of patients with schizophrenia compared to MHCAG agents (56.86% vs. 19.83%; p<0.0001) and a significantly lower rate of bipolar disorder (29.41% vs. 49.16%; p=0.0064). Concurrent use of psychotherapeutic regimens was common (**Table 4**), with lumateperone patients having a higher rate of other antipsychotic use compared to MHCAG patients (74.51% vs. 53.63%; p=0.0038). Concurrent antidepressant use was lower in the lumateperone group compared to the MHCAG group (50.98% vs. 64.80%; p=0.0471). As illustrated in **Figure 1**, the time to discontinuation of the index antipsychotic was similar between the groups. The lumateperone group had lower mean baseline HRU for emergency department ($414 vs. $728; p=0.0113) and inpatients services ($2,224 vs. $5,707; p=0.0004) and higher baseline pharmacy utilization ($6,969 vs. $2,879; p=0.0026), though baseline total costs were similar between the 2 groups (p=0.6518). The lumateperone group had an increase in inpatient HRU from baseline to follow up, while the MHCAG group had a reduction in inpatient HRU ($1,920 vs. -$2,031; p=0.0212). The lumateperone group

had a significantly larger increase in pharmacy costs as well ($3,681 vs. $726; p=0.0429). Lumateperone had an overall increase in costs of $8,081 compared to the reduction in overall costs in the MHCAG group of -$692 (p=0.0192).

The supplemental analysis revealed significant differences in prescriber location between the groups (p<0.0001). In particular, prescribers in Douglas County accounted for 16.43% of patients receiving lumateperone compared to only 3.75% of patients in the MHCAG group. Several other rural counties had similarly higher rates of lumateperone use (e.g., Lincoln 9.29% vs. 1.37%, Polk 6.43% vs. 2.93%, Columbia 2.86% vs. 0.68%). Prescriber specialties also varied significantly with "Nurse Practitioner – Psychiatric/Mental Health" accounting for 72.86% of lumateperone initial prescriptions vs. 33.23% of MHCAG initial prescriptions (p<0.0001).

Table 1. Attrition Table

Exclusion Criteria	Lumateperone		MHCAG	
00-Available patients	147		12,305	
01-Patients under 18 years old	0	0%	1,752	14%
02-Baseline TPL Coverage	4	3%	681	5%
03-Followup TPL Coverage	3	2%	85	1%
04-Has Baseline or Follow up HNA Air Claims	0	0%	46	0%
05-Has claims Benefit Plan other than BMH during baseline	0	0%	15	0%
06-Has claims Benefit Plan other than BMH during followup	0	0%	44	0%
07-Not treatment experienced	25	17%	8,020	64%
08-Less than 25% baseline eligibility	0	0%	25	0%
09-Less than 25% follow up eligibility	25	17%	328	3%
10-Less than 50% baseline eligibility	4	3%	65	1%
11-Less than 50% follow up eligibility	13	9%	237	2%
12-Less than 75% baseline eligibility	3	2%	72	1%
13-Less than 75% follow up eligibility	19	13%	219	2%
Patient Remaining	**51**	**35%**	**716**	**6%**

Abbreviations: BMH: Oregon Health Plan plus benefit package; HNA AIR = Heritage Native American All Inclusive Rate; TPL = third party liability (e.g., other primary insurance)

Table 2. Baseline Demographics

		Lumateperone (n=51)	MHCAG (n=716)	
		n(%)	n(%)	p
Age (Years)	Mean (Median)[Standard Deviation]	39.4 (36.0) [12.1]	37.4 (36.0) [11.5]	0.2408
	18-29	12 (23.53%)	207 (28.91%)	0.6653
	30-39	15 (29.41%)	224 (31.28%)	
	40-49	12 (23.53%)	156 (21.79%)	
	50-59	11 (21.57%)	105 (14.66%)	
	60 and over	1 (1.96%)	24 (3.35%)	
Gender	Female	26 (50.98%)	447 (62.43%)	0.1042
	Male	25 (49.02%)	269 (37.57%)	
Plan	CCO	45 (88.24%)	530 (74.02%)	0.0552
	CCO+FFS	5 (9.80%)	176 (24.58%)	
	FFS	1 (1.96%)	10 (1.40%)	

Table 3. Baseline Comorbidities

	Lumateperone (n=51)	MHCAG (n=716)	
	n(%)	n(%)	p
Bipolar	**15 (29.41%)**	**352 (49.16%)**	**0.0064**
Schizophrenia	**29 (56.86%)**	**142 (19.83%)**	**<0.0001**

Table 4. Concurrent Psychotherapeutic Regimens

	Lumateperone (n=51)	MHCAG (n=716)	
	n(%)	n(%)	p
Antidepressants	**26 (50.98%)**	**464 (64.80%)**	**0.0471**
Anxiolytics	12 (23.53%)	113 (15.78%)	0.1478
Mood Stabilizer	10 (19.61%)	192 (26.82%)	0.2588
Other Antipsychotics	**38 (74.51%)**	**384 (53.63%)**	**0.0038**

Figure 1. Time to Index Antipsychotic Discontinuation

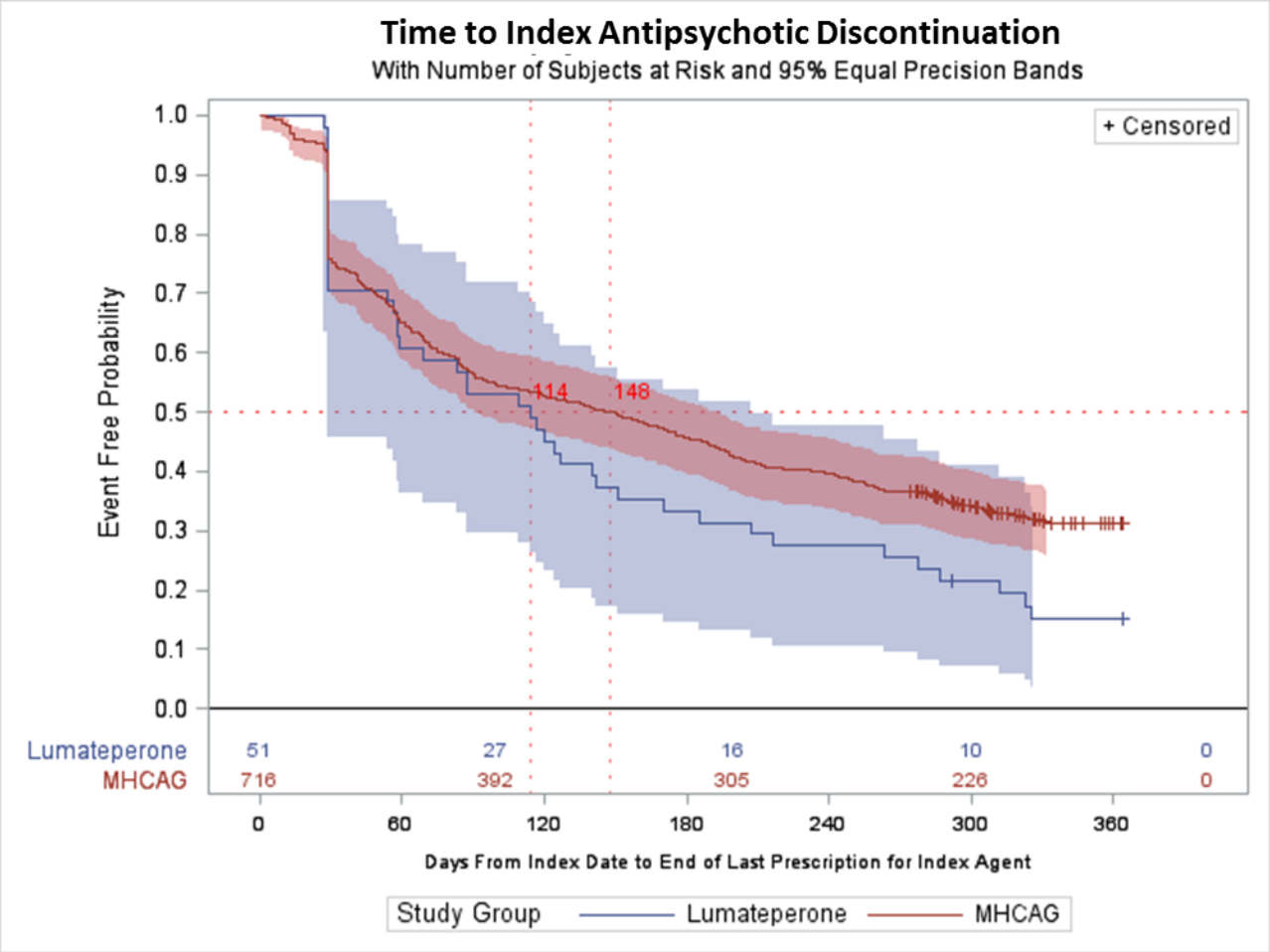

Table 5. Health Resource Utilization (US Dollars)

		Lumateperone (n=51)	MHCAG (n=716)	
		Mean(Median)[SD]	Mean(Median)[SD]	p
Baseline	**Emergency Department**	**414 (87) [776]**	**728 (246) [1,436]**	**0.0113**
	Inpatient	**2,224 (0) [4,983]**	**5,707 (0) [17,921]**	**0.0004**
	Outpatient	7,738 (3,641) [14,273]	9,281 (5,349) [14,285]	0.4564
	Pharmacy	**6,969 (3,091) [9,112]**	**2,879 (471) [5,377]**	**0.0026**
	Total	17,346 (13,970) [18,414]	18,595 (11,025) [26,050]	0.6518
Follow up	**Emergency Department**	**357 (0) [769]**	**711 (134) [1,806]**	**0.0065**
	Inpatient	4,144 (0) [12,769]	3,676 (0) [12,606]	0.7978
	Outpatient	10,275 (3,722) [20,747]	9,912 (4,938) [17,207]	0.9032
	Pharmacy	**10,650 (8,164) [9,027]**	**3,605 (549) [7,500]**	**<0.0001**
	Total	25,427 (16,255) [30,702]	17,903 (8,870) [26,675]	0.0545
Change From Baseline to Follow up	Emergency Department	-56.2 (0.0) [404.8]	-17.6 (0.0) [1,471.2]	0.6256
	Inpatient	**1,920 (0) [10,787]**	**-2,031 (0) [19,659]**	**0.0212**
	Outpatient	2,537 (315) [18,135]	631 (-74) [13,514]	0.4647
	Pharmacy	**3,681 (3,439) [9,992]**	**726 (41) [7,241]**	**0.0429**
	Total	**8,081 (4,198) [25,330]**	**-692 (-592) [25,829]**	**0.0192**

Table 6. Inpatient Days

	Lumateperone (n=51)	MHCAG (n=716)	
Inpatient Days	Mean(Median)[SD]	Mean(Median)[SD]	p
Baseline	**1.86 (0.00) [4.50]**	**4.84 (0.00) [15.14]**	**0.0006**
Follow up	4.14 (0.00) [12.71]	2.58 (0.00) [8.04]	0.3915
Change from Baseline to Follow up	**2.27 (0.00) [10.06]**	**-2.26 (0.00) [15.32]**	**0.0039**

Discussion:

Patients receiving lumateperone had significantly higher increases in total costs, pharmacy costs, and inpatient costs compared to MHCAG patients. The difference in pharmacy cost was not unexpected, given that most MHCAG formulations have generic versions. The differences in inpatient costs raises a number of questions. The higher baseline inpatient costs in the MHCAG group suggests the possibility that the initiation of MHCAG prescriptions may be triggered by an inpatient encounter. The higher follow up inpatient costs may suggest that lumateperone may have been initiated in an attempt to prevent inpatient hospitalizations. These inpatient findings, combined with generally higher rates of lumateperone use in more rural counties (e.g., Douglas, Lincoln, Polk, and Columbia) also raise questions about access to acute mental health services.

Limitations:
All retrospective administrative claims studies have inherent limitations. Such studies cannot determine causality and results should be interpreted with caution. Study groups were selected based on the initiation of either lumateperone or an MHCAG antipsychotic. Antipsychotic in general, and MHCAG recommended agents in particular, have indications beyond schizophrenia, which may affect the presence of other psychotropic agents (**Table 4**).Although there were no significant differences in baseline demographics between the groups, no propensity matching was performed, so there may be undetected differences between the groups. The geographical distribution of patients receiving lumateperone was significantly different compared to the MHCAG group. These geographic differences may contribute to differences in access to mental health services, further complicating interpretation of the results. The exclusion of patients with incomplete or peculiar administrative claims data (i.e., TPL coverage, less than 75% eligibility, HNA AIR) reduced the sample size substantially and therefore may not represent utilization across the entire Medicaid population.

References:

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2. Lieberman JA, Davis RE, Correll CU, et al. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. *Biol Psychiatry*. 2016;79(12):952-961. doi:10.1016/j.biopsych.2015.08.026

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5. FDA Approves New Treatment for Bipolar Depression. Accessed July 30, 2022. https://www.psychiatrictimes.com/view/fda-approves-new-treatment-for-bipolar-depression

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7. Medicaid Management Information System | Medicaid. Accessed April 30, 2022. https://www.medicaid.gov/medicaid/data-systems/medicaid-management-information-system/index.html

Appendix 1: Drug Coding

Table 7 Included Antipsychotics

HSN	Drug Name
008721	Risperidone
025509	Risperidone microspheres
024551	Aripiprazole
042595	Aripiprazole lauroxil
045050	Aripiprazole lauroxil, submicr
034343	Paliperidone
036479	Paliperidone
046280	Lumateperone

Table 8 Other Drug Codes

Code Type	Code Value	Drug Name	Route
HIC	H7O, H7P, H7T, H7U, H7X (Excluding drugs in Table 1)	Other antipsychotics	Any
HSN	001669, 001670, 007378	Mood stabilizers	Any
HIC	H24, H2H, H2S, H2U, H7B, H7C, H7D, H7E, H7J, H7Z, H8P, H8T, H8Z	Antidepressants	Any
HIC	J2B, H20, H8K, H2X, H4A	Anxiolytics	Any

Table 9 Diagnosis Codes

ICD 10 codes	Description
F20.x	Schizophrenia
F31.x	Bipolar Disorder

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

Prior Authorization Criteria Update: ethinyl estradiol/segesterone (Annovera®)

Purpose of Update:

Hormonal birth control vaginal rings are available in both yearly[1] and monthly formulations. A quantity limit for the yearly product is proposed to limit waste associated with confusion between the formulations.

Recommendation:

- Implement coding audit for minimum of 300 days* at the pharmacy point of sale for all prescriptions of ethinyl estradiol/segesterone yearly vaginal ring.
- Require pharmacy point of sale override for any 1st refill of ethinyl estradiol/segesterone yearly vaginal ring in fewer than 300 days from previous prescription fill.
- Require quantity limit **(Appendix 1)** for any patient requesting 2nd refill within a 12-month time period.

*Will update to a minimum days supply once system change allows to prevent pharmacy-of-sale entry for shorter than one year

References:

1. **Annovera (segesterone acetate and ethinyl estradiol vaginal system) package insert. Boca Raton, FL: TherapeuticsMD, Inc.; Jan 2020.**

Annovera® (segesterone acetate and ethinyl estradiol yearly vaginal system)

Goal(s):

- To reduce waste associated with confusion between monthly and yearly vaginal birth control ring systems.

Length of Authorization:

- Up to 11 months

Requires PA:

- Any 2nd refill request (3rd total request) within any 12 month time period at pharmacy point of sale.

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. Has the provider attested that the patient has been counseled on the appropriate use, storage, and duration of use of this product since the most recent prescription fill? (include date of counseling) Note: Product should be used continuously for 21 days followed by a 7 day ring free interval. One ring is effective for 13 total 28-day cycles (1 year).	**Yes**: Approve single ring for 11 months. Previous fill date_____ Date of new counseling_____	**No:** Pass to RPh. Deny; medical appropriateness