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, November 29, 2018 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302
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 as required by 414.325(9).

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	T. Klein (Chair)
	D. Department Update	T. Douglass (OHA)
	E. Legislative Update	T. Douglass (OHA)
1:10 PM	II. CONSENT AGENDA TOPICS	T. Klein (Chair)

A. Long-Acting Insulins DERP Summary
B. Humira® (adalimumab) Indication Review for Hidradenitis Suppurativa
C. Quarterly Utilization Reports
   1. Public Comment

III. DUR ACTIVITIES

1:15 PM	A. ProDUR Report	R. Holsapple (DXC)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Reviews	K. Sentena (OSU)

1. Update on Treatment Options for Moderate to Severe Atopic Dermatitis
2. Management Strategies for Patients with Prediabetes

IV. PREFERRED DRUG LIST NEW BUSINESS

1:30 PM	A. Severe Acne Class Review	J. Page (OSU)

1. Class Review/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

1:50 PM	B. Hepatitis C Direct Acting Antivirals Policy Discussion 1. Public Health Response to HCV in Oregon: Need for Screening and Treatment 2. Prior Authorization Criteria 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	A. Thomas (OHA)
2:20 PM	C. Orilissa™ (elagolix) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
	V. DUR OLD BUSINESS	
2:35 PM	A. Nusinersen: OHA SMARTEN Participation 1. OHA SMARTEN Participation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	J. Page (OSU)
2:55 PM	B. Growth Hormone Prior Authorization Criteria Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:05 PM	BREAK	
3:15 PM	C. Testosterone Prior Authorization Criteria Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
	VI. DUR NEW BUSINESS	
3:15 PM	A. Substance Use Disorder Class Update/Drug Use Evaluation 1. Class Update/Prior Authorization Criteria 2. Lucemyra™ (lofexidine hydrochloride) New Drug Evaluation 3. Drug Use Evaluation 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU) S. Servid (OSU)
3:55 PM	VII. EXECUTIVE SESSION	
4:50 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS	
	IX. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2020
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2020
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2020
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2020
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Corvallis	December 2019
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2018
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2018
Rich Clark, M.D., M.P.H.	Physician	Anesthesiologist	Salem	December 2018
Walter Hardin, D.O., M.B.A.	Physician	Medical Director	Hillsboro	December 2018

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 27, 2018
1:00 p.m. – 5:00 p.m.
DXC Building, 4070 27th Ct
Salem, OR 97301

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 as required by 414.325(9).

Members Present: Kelley Burnett, D.O.; Tracy Klein, PhD, FNP; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD; James Slater, PharmD; Cathy Zehrung, RPh

Members Present by Phone: Dave Pass, MD

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Trevor Douglass, DC, MPH; Sarah Servid, PharmD; Dee Weston; Julia Page, PharmD; Jonnaliz Corbett; David Engen, PharmD

Staff Present by Phone: Megan Herink, PharmD

Audience: Rick Frees, Vertex; Steve Nemiron, Kartini Clinic*; Lisa Allen, Vertex*, Jake Mazzola, AllCare; Keri Smith, ViiV; Steve Kimball, Actellion; Allen Hammagren, AbbVie; Nik Seiffer, Sunovion*; Deron Groth, Teva; Jeana Colabiachi, Sunovion; Margaret Olmon, AbbVie*; Jason Way; Emily Shephard; Danielle Shannon, WFP Health Authority; Sylvia Churchill, Amgen*; Camille Kerr, Amgen; Valerie Ng, Indivior; Tim McFerror, Alkermes; Paul Thompson, Allkermes; Randy Blom, MD, Grane Ronde Clinic*; Stuart O'Briochta, Gilead*; Mary Kemhus, Novartis; Marine Schmitt, CareOregon; Kali Schweitler, CareOregon; Laura Jeffcoat, AbbVie; Robin Traver, Umpqua Health Alliance; Amy Burns, AllCare; Lisa Talbott, Gilead; Lorren Sandt, Caring Ambassadors*; Kurt Jensen, Caring Ambassadors*; Kent Benner, The Oregon Clinic*; Andrew Seamen, MD, Oregon Health Sciences University*; BJ Cavnor, One in Four*

(*) Provided verbal testimony

Written testimony provided: Posted to OSU Website

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff. No new conflict of interests were declared.
B. Dr. Douglass provided a department update and legislative update.
C. Approval of Agenda and Minutes

II. CONSENT AGENDA TOPICS

A. Approval of agenda and July minutes

B. Overactive Bladder DERP Summary
Recommendation:
No further review or research needed at this time
Evaluate comparative costs in executive session

C. Oral and Parenternal Antipsychotics Literature Scan
Recommendation:
No changes to the PDL are recommended based on efficacy or safety data
Evaluate comparative costs in executive session

D. Pancreatic Enzymes Literature Scan
Recommendation:
No changes to the PDL are recommended based on efficacy or safety data
Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd, All in Favor

III. PREFERRED DRUG LIST NEW BUSINESS

A. Pulmonary Arterial Hypertension Class Update
Dr. Servid presented the proposal to update the prior authorization (PA) criteria to include contraindications for riociguat in patients with idiopathic interstitial pneumonias and evaluate comparative costs in executive session.
ACTION: Motion to approve, 2nd, all in favor

B. Attention Deficit Hyperactivity Disorder Literature Scan
Dr. Page presented the proposal to update the guanfacine extended-release dosing in Table 2 in the PA criteria to clarify FDA-recommended maximum daily doses for monotherapy versus adjunctive therapy and to evaluate comparative costs in executive session.
ACTION: Motion to approve, 2nd, all in favor

C. Vaginal Antibiotics Drug Class Review

Dr. Sentena presented the class review and recommendation to add the class to the PMPDP and make at least one metronidazole and one clindamycin formulation preferred and to evaluate comparative drug costs in executive session.
ACTION: Motion to approve, 2nd, all in favor

D. Aimovig (erenumab-aooe) New Drug Evaluation
Dr. Engen presented the NDE and recommendation to add the class to the PMPDP and implement the proposed PA criteria for CGRP antagonists.
ACTION: Modify question #6 to specify migraine prophylaxis classes rather than specific agents; change required specialists to a neurologist or headache specialist; add a question to assess medication overuse assessment in initial approval and renewal criteria.
Motion to approve, 2nd, all in favor

E. Palynziq (pegvaliase-pqpz) New Drug Evaluation
Dr. Page presented the NDE and proposal to implement PA criteria for pegvaliase.
ACTION: Add a question to ensure epinephrine is prescribed concurrently
Motion to approve, 2nd, all in favor

F. Hepatitis C Direct Acting Antivirals Class Update
Dr. Herink presented the class update and recommendation to remove the treatment requirements for those with substance use disorder, alcohol abuse and illicit injective drug use and incorporate the necessary support into case management programs and to evaluate comparative costs in executive session.
ACTION: Designate a specific meeting in October to discuss expanding HCV coverage
Motion to approve, 2nd, one opposed, motion passed

IV. DUR NEW BUSINESS

A. Benzodiazepine Policy Evaluation and DERP Report
Dr. Servid presented the proposal to update the PA criteria to: limit use for treatment of PTSD, allow patients receiving long-term therapy time to taper the dose when appropriate, and require prescribers to provide supporting medical literature and/or appropriate rationale for long-term benzodiazepine use.
ACTION: add requirement to approval and renewal criteria that providers assess PDMP
Motion to approve, 2nd, all in favor

V. DUR OLD BUSINESS

A. Cystic Fibrosis
Dr. Herink presented the proposal to update the PA criteria to reflect updated FDA labeling based on approved indications.
ACTION: Motion to approve, 2nd, all in favor

B. Botulinum Toxins Prior to Authorization Update
Dr. Page presented the proposal to update the PA criteria to reflect current guidelines in the OHA Prioritized List of Health Services.

ACTION: modify step therapy to specify migraine prophylaxis classes rather than specific agents.
Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Present in room: Kelley Burnett, D.O.; Tracy Klein, PhD, FNP; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD; James Slater, PharmD; Cathy Zehrung, RPh; Richard Holsapple, RPh; Roger Citron, RPh; Trevor Douglass, DC, MPH; Sarah Servid, PharmD; Dee Weston; Julia Page, PharmD; Jonnaliz Corbett; David Engen, PharmD

VII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Overactive Bladder DERP Summary
   Recommendation: no changes to the PMPDP
B. Antipsychotics Literature Scan
   Recommendation: Make Vraylar®, Aristada® Initio™, Invega® Sustenna® and Trinza® syringes, and Perseris™ preferred agents on the PMPDP.
C. Pancreatic Enzymes Literature Scan
   Recommendation: Make Zenpep® preferred on the PMPDP.
D. Pulmonary Arterial Hypertension Class Update
   Recommendation: No changes to the PMPDP.
E. Attention Deficit Hyperactivity Disorder Literature Scan
   Recommendation: No changes to the PMPDP.
F. Vaginal Antibiotics Drug Class Review
   Recommendation: Make clindamycin phosphate cream with applicator, clindamycin phosphate vaginal suppositories, and metronidazole gel preferred and to designate all other agents non-preferred on the PMPDP.
G. Hepatitis C Direct Acting Antiviral (DAA) Class Update
   Recommendation: Limit Vosevi use to genotypes where there are no other treatment options available.

   ACTION ON ITEMS A-G: **Motion to approve, 2nd, all in favor**

H. Request from the Oregon Health Authority for the Committee to make a Hep C DAA secondary recommendation for expanding coverage. The Committee requested more time to deliberate on the criteria and requested a meeting by the end of October.
   ACTION: **Motion to approve, 2nd, all in favor**

VIII. ADJOURN

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OHSU Drug Effectiveness Review Project Summary Report – Long-Acting Insulins

Date of Review: November 2018

Date of Last Review: September 2017
Literature Search: 08/17/18

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

Research Questions:
1. Is there any new comparative evidence for long-acting insulins based on surrogate efficacy outcomes (e.g., hemoglobin A1c [HbA1c]) or long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new comparative evidence for long-acting insulins based on harms outcomes (e.g., severe hypoglycemia, nocturnal hypoglycemia)?
3. Are there subpopulations of patients which specific long-acting insulins may be more effective or associated with less harm?

Conclusions:
- A significant amount of evidence identified by the Drug Effectiveness Review Project (DERP) report was of low or insufficient quality, and therefore, not included per evidence inclusion criteria.[1]
- Overall evidence of moderate to high quality found no clinically significant differences between long-acting insulins for a majority of comparisons.

Clinical Efficacy
- Moderate to high quality evidence found no differences in HbA1c lowering between the long-acting insulin products.[1]

Harms
- Moderate quality evidence found no difference between insulin degludec and insulin glargine in major adverse cardiovascular events (rate ratio [RR] 0.92; 95% confidence interval [CI], 0.80 to 1.06; absolute risk reduction [ARR] not provided).[1]
- Based on moderate quality of evidence, nocturnal hypoglycemia risk was lower for insulin degludec compared to insulin glargine in patients with type 1 diabetes mellitus (T1DM), RR 0.68 (95% CI, 0.56 to 0.81).[1]
- The incidence of severe hypoglycemia events was lower with insulin degludec compared to insulin glargine in patients with type 2 diabetes mellitus (T2DM) (3.3% vs. 5.1%) and also for nocturnal hypoglycemia RR 0.84 (95% CI, 0.71 to 1.0; ARR not provided) (moderate quality of evidence).[1]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended for the long-acting insulin based on review of efficacy and safety data provided by DERP.
- Evaluate comparative drug costs in executive session.

Summary of Prior Reviews and Current Policy

- Previous reviews have not identified clinically significant differences in efficacy or harms between the long-acting insulins. There is insufficient evidence on health outcomes (i.e., mortality) as well as cardiovascular comparisons to delineate preferred treatment options. The Oregon Health Plan (OHP) Fee-for-Service (FFS) policy includes the preferred long-acting insulins: detemir pens (requires prior authorization [PA]) and Lantus pens and vials are available without a PA (Basaglar pens and vials still require PA). A PA is required for non-preferred long-acting insulin pens and cartridges. For approval, the PA criteria requires that patients (or non-professional caregiver) have dexterity issues/vision impairment, comprehension difficulties, history of dosing errors, or is a child less than 18 years old. Policy was changed in September 2017 which removed maximum insulin utilization restrictions to allow access to concentrated insulin products if appropriate (PA dependent). There is 79% preferred drug utilization of insulin glargine followed by 8% utilization of the non-preferred insulin glargine formulation, Basaglar, which accounts for a majority of the class expenditures.

Methods:

The July 2018 drug class report on long-acting insulins by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

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

Summary Findings:

In July 2018 DERP reported on the evidence for use of long-acting insulins in adult and children with T1DM and T2DM.[1] Twelve new studies were added to the most recent update with seventy-one studies included overall. Studies ranged from 16 weeks to 2 years and 74% were graded as fair quality by DERP. Insulins included in the review are the following: three follow-on insulin glargine products (Semglee [not available in the United States], Lusduna Nexvue [tentatively approved by the FDA but not yet available], and Basaglar), insulin degludec (Tresiba), insulin degludec/insulin aspart (Ryzodeg 70/30), insulin glargine (Toujeo), insulin detemir (Levemir) and insulin glargine U100.[1] Placebo-controlled trials and pooled analyses combining selected studies without reproducible methods were excluded. Differences in concomitant antidiabetic therapy and/or dosing schedules of insulins resulted in the inability to pool results and/or produced evidence which lacked precision preventing strong conclusions for many of the analyses. Evidence on outcomes of moderate to high quality with applicable external validity to the Oregon Medicaid population are included in **Table 1**.

Table 1. Insulin Comparisons: Outcomes with Evidence of Moderate to High Quality[1]

Comparison	Outcome	Result	Strength of Evidence†
Type 1 DM			
Insulin degludec+ **Vs.**	HbA1c	Insulin degludec: 6.92% Insulin glargine: 6.78%	Moderate

Insulin glargine+		WMD 0.07% (95% CI, -0.05 to 0.19%) *No difference between treatments*	
	Nocturnal Hypoglycemia	RR 0.68 (95% CI, 0.56 to 0.81) ARRs not provided *Favored insulin degludec*	Moderate
Insulin glargine U300 **Vs.** **Insulin glargine U100**	Nocturnal hypoglycemia	RR 0.91 (95% CI, 0.80 to 1.05) ARRs not provided *No difference between treatments*	Moderate
Type 2 DM			
Once daily insulin degludec* **Vs.** **Once daily insulin glargine**	Percent of patients obtaining an HbA1c of ≤7%	RR 0.97 (95% CI, 0.91 to 1.03) ARRs not provided *No difference between treatments*	High
	Severe hypoglycemia episodes	Insulin degludec: 3.3% Insulin glargine: 5.1% RR 0.72 (95% 0.54 to 0.96) *Favored insulin degludec*	Moderate
	Nocturnal hypoglycemia episodes	RR 0.84 (95% CI, 0.71 to 1.0) ARRs not provided *Favored insulin degludec*	Moderate
	Major adverse cardiovascular events	RR 0.92 (95% CI, 0.80 to 1.06) ARRs not provided *No difference between treatments*	Moderate
FDCP Insulin Degludec/Aspart **Vs.** **Insulin glargine alone**	Patients with HbA1c <7%	Degludec/Aspart: 43% Glargine: 41% RR 1.04 (95% CI, 0.90 to 1.21) *No difference between treatments*	Moderate
Insulin glargine U300 **Vs.** **Insulin glargine U100**	Patients with HbA1c <7%	Insulin glargine U300: 35% Insulin glargine U100: 35% RR 1.0 (95% CI, 0.92 to 1.1) *No difference between treatments*	Moderate

	Nocturnal hypoglycemia	Insulin glargine U300: 37% Insulin glargine U100: 50% RR 0.74 (95% CI, 0.66 to 0.82) *Favored insulin glargine U300*	Moderate
Abbreviations: ARR – absolute risk reduction, CI – confidence interval, DM – diabetes mellitus, ETD – estimated treatment difference, FDCP – fixed dose combination product, HbA1c – hemoglobin A1c, RR – rate ratio; WMD – weighted mean difference **Key: † Evidence grades provided by DERP, * included fixed and flexible dosing, + in combination with bolus insulin aspart**			

Subgroup analysis

Severe hypoglycemia rates were lower in patients treated with insulin degludec, versus insulin glargine, in women who were not Hispanic or Latino, had history of cardiovascular (CV) disease, and were residing in the United States (US).

References

1. McDonagh M, Holmes R, Hsu F, et al. Long-acting insulins. Update 2 Final Report, prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health and Science University, Portland, Oregon, July 2018.

Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	PDL
insulin detemir	LEVEMIR FLEXTOUCH	INSULN PEN	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	INSULN PEN	Y
insulin glargine,hum.rec.anlog	LANTUS	VIAL	Y
insulin degludec	TRESIBA FLEXTOUCH U-100	INSULN PEN	N
insulin degludec	TRESIBA FLEXTOUCH U-200	INSULN PEN	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	INSULN PEN	N
insulin detemir	LEVEMIR	VIAL	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	INSULN PEN	N
insulin glargine/lixisenatide	SOLIQUA 100-33	INSULN PEN	N

Appendix 2: Search History

Database(s): **Ovid MEDLINE(R)** 1946 to August Week 2 2018

Search Strategy:

#	Searches	Results
1	degludec.mp.	296
2	detemir.mp.	767
3	glargine.mp. or Insulin Glargine/	2151
4	1 or 2 or 3	2610
5	limit 4 to (english language and humans and yr="2017 -Current")	224
6	limit 5 to (clinical trial, phase iii or guideline or meta analysis or systematic reviews)	44

Insulins

Goal:

- Restrict certain insulin products to specific patient populations to ensure appropriate use.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred insulin vials
- All pre-filled insulin pens, cartridges and syringes with the exception of insulin glargine (Lantus SoloSTAR®) or insulin aspart (Novolog Flexpen®)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is the request for an insulin pen or cartridge?	**Yes:** Go to #4	**No:** Go to #7
4. Is the request for either a short-acting or a long-acting insulin pen or cartridge?	**Yes:** Go to #5	**No:** Got to #6
5. Has the patient tried and failed or have contraindications to either: • Insulin aspart (Novolog®) if the request is for short-acting insulin OR • Insulin glargine (Lantus®) if the request is for long-acting insulin?	**Yes:** Go to #6	**No:** Pass to RPh: deny and recommend a trial of insulin glargine (Lantus Solostar®) or insulin aspart (Novolog Flexpen®)

Approval Criteria		
6. Will the insulin be administered by the patient or a non-professional caregiver **AND** do any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is a child less than 18 years of age?	**Yes:** Go to #7	**No:** Pass to RPh; deny for medical appropriateness
7. Will the provider consider a change to a preferred product? <u>Message:</u> • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Approve for up to 12 months

P&T / DUR Review: 11/18 (KS), 9/17 (KS), 3/16; 11/15; 9/10
Implementation: 11/1/17; 10/13/16; 1/1/11

Long-Acting Insulins for Type 1 and Type 2 Diabetes

Update 2 Final Report

Executive Summary

July 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaidagency and public agency partners.

This report updates the comparative evidence on long-acting insulins (LAIs). The prior DERP report (Update 1) was published in May, 2017.

Key Questions

- What is the evidence on the comparative effectiveness and harms of long-acting insulins in adults and children with diabetes mellitus?
  - Drug vs. drug
  - Follow-on vs originator drug
  - Pen vs. vial
  - More concentrated (300 or 200 units/mL) vs. less concentrated (100 units/mL)
- Is there evidence on whether effectiveness or harms vary in subgroups of patients?

Background

Thirty million people in the U.S. have diabetes, 1.25 million with Type 1 diabetes. Long-term consequences include cardiovascular disease, renal disease, and blindness. Long-acting insulins (LAIs) mimic basal physiologic insulin secretion, with durations of action from 8 to greater than 42 hours (degludec > glargine > detemir).

The percent glycated hemoglobin (HbA_{1c}) reflects mean blood glucose over previous 2 to 3 months, and is used to monitor control of diabetes. The American Diabetes Association suggests goal of HbA_{1c} < 7%. Hypoglycemia may occur with insulin treatment, and is the most common adverse event reported. Severe hypoglycemia, requiring assistance from others or admission to the emergency department or hospital is associated with loss of consciousness, injury, seizures, and mortality. Nocturnal hypoglycemia is typically defined as blood glucose < 70 mg/dL at night, and is concerning due to the potential to miss warning signs of severe hypoglycemia. Differences in pharmacokinetic profiles of the LAIs are thought to lead to variation in risk for severe or nocturnal hypoglycemia.

Glargine was the first LAI approved, as Lantus®, in 2000. More recently, follow-on versions have been approved or are under by the US Food and Drug Administration (Basaglar®, Lusduna, Semglee).

Inclusion Criteria for Systematic Review

Populations: Adults or children with Type 1 or Type 2 diabetes mellitus.

Drugs: Listed in Table below.

Comparators: Head to head including fixed-dose combinations), one formulation/device vs. same insulin in another formulation/device (e.g. vial/syringe versus pen).

Key Outcomes:

Cardiovascular (CV) events (microvascular and macrovascular), mortality, glycemic control (HbA1c at 2-3 months), nocturnal and severe hypoglycemia and adverse event withdrawals

SOE = Strength of Evidence (low, moderate, high or insufficient)

Table 1: Included Insulins

Drug	Forms	Frequency
Glargine		
Lantus®, U100 Toujeo®, U300 F-O insulin Semglee F-O insulin Lusduna Nexvue F-O insulin Basaglar®	Vial or pen Pen Pen Vial or pen Pen Pen	Once daily
Detemir		
Levemir®, U100	Vial or pen	Once or twice daily
Degludec		
Tresiba® U100, U200	Pen	Once daily
Ryzodeg® 70/30 Degludec/ aspart	Pen	Once or twice daily

F-O, Follow-on Insulin (patent infringement lawsuits have been filed against products with FDA approvals)

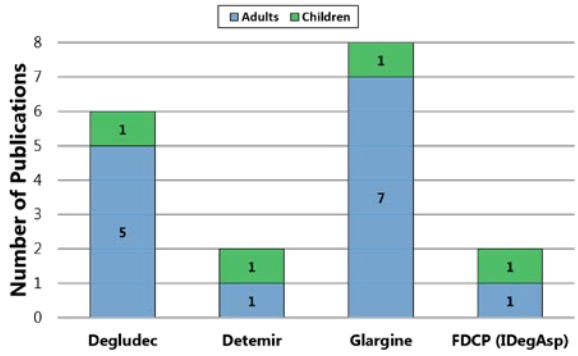
Overview of Included Evidence

For this update, we included 12 new studies (9 RCTs, 3 observational studies, and 8 extension studies or subgroup analyses). Cumulatively, there are 71 included studies of LAIs (Table 2). Trial sample sizes ranged from 615 to 7,637, and 6 were rated poor quality. The majority

of the RCTs were 8 to 12 weeks in duration, with 1 being 52 weeks. Most of the studies were funded by 1 of the included insulin's manufacturers.

Outcomes reported in RCTs are primarily glycemic control and adverse events. One new trial (DEVOTE) was designed to measure CV outcomes with degludec versus glargine in patients with Type 2 diabetes. Observational studies provided evidence on other harms, such as cancer and neonatal exposure to LAIs.

Figure 1. New Evidence by Insulin



Findings

Degludec

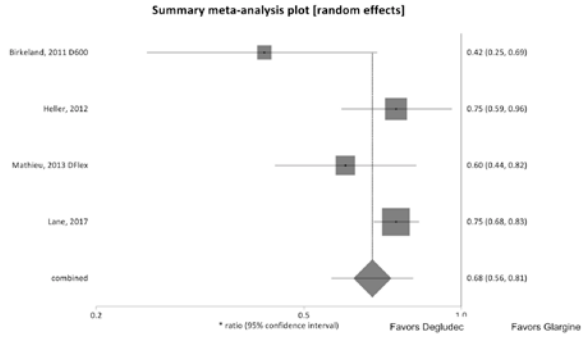
Versus Detemir

Type 1 DM: No significant difference in glycemic control (2 RCTs, SOE: Low). Evidence from a 52-week extension trial in adults did not change these findings.

Versus Glargine

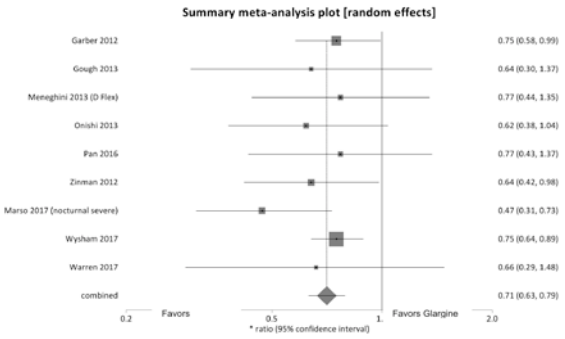
Type 1 DM: No significant difference in glycemic control at 16 to 52 weeks (4 RCTs, SOE: Moderate). Incidence of nocturnal hypoglycemia was **significantly lower** with degludec than with glargine (4 RCTs, pooled rate ratio 0.68, 95% CI 0.56 to 0.81) (SOE: Moderate)(Figure 2).

Figure 2. Nocturnal hypoglycemia: degludec versus glargine (adults with Type 1)



Type 2 DM: No significant differences in glycemic control (9 RCTs, SOE: High), or adverse event withdrawals (9 RCTs, SOE: Low, 16 weeks - 2 years). Hypoglycemia **significantly less** with degludec (nocturnal: 9 RCTs, pooled rate ratio 0.71, 95% CI 0.63 to 0.79 and severe: 9 RCTs, 3.3% vs. 5.1% of patients, RR 0.72, 95% CI 0.54 to 0.96; SOE: Moderate) (Figure 3).

Figure 3. Nocturnal hypoglycemia: degludec versus glargine (adults with Type 2)



DEVOTE Trial: A CV outcomes trial randomized 7,637 patients at high risk for CV events. Event-driven trial continued until > 600 adjudicated major adverse CV events (CV death, nonfatal MI, or nonfatal stroke) occurred. The FDA mandated the trial due to concerns over CV harms (based on a meta-analysis of earlier trials). Combined with other RCT evidence, there is no significant difference in CV events (4 RCTs), deaths (8 RCTs), and cancer (6 RCTs).

Detemir

Versus Glargine

Type 1 DM: No significant differences in glycemic control, severe hypoglycemic events or withdrawal due to adverse events at 26 or 52 weeks (2 RCTs, SOE: Low).

Type 2 DM: No significant differences in glycemic control (6 RCTs, 12 - 52 weeks), severe or nocturnal hypoglycemia (6 RCTs, 6 cohort studies; SOE: Low). Adverse event withdrawals **significantly greater** with detemir (6 RCTs, pooled RR 2.1; 95% CI, 1.4 to 3.3; SOE: Moderate). Evidence does not support a difference in risk of any cancer (4 studies) or breast cancer (3 studies; SOE: Low).

Glargine

Follow-On Glargine vs. Glargine

Type 1 and 2 DM: No significant difference in glycemic control (1 RCT each, SOE: Low).

Glargine U300 vs. Glargine U100

Type 1 DM: No significant differences in glycemic control, severe hypoglycemia, adverse event withdrawals (4 RCTs, N=871, 2, 6 and 12 months; SOE: Low) or nocturnal hypoglycemia (2- 12 months, SOE: Moderate).

Type 2 DM: No significant differences in glycemic control, severe hypoglycemia or adverse event withdrawals (4 RCTs, 6-12 months; SOE: Moderate, Low). Nocturnal hypoglycemia **significantly less frequent** with U300 (3 RCTs, pooled RR 0.74, 95% CI 0.66 to 0.82) at 2 to 6 months, not different at 12 months (SOE: Moderate).

Glargine U100 Pen vs. Glargine U100 Vial

Type 2 DM: Severe hypoglycemia significantly less frequent with pen than vial /syringe (pooled RR 0.72; 95% CI, 0.65 to 0.79, 7 cohort studies,) (SOE: Moderate).

FDCP: Degludec/Aspart 70/30 Comparisons

Versus Degludec (Type 2): Evidence was insufficient.

Versus Detemir (Type 1): Low-strength evidence (2 RCTs, 1 children, 1 adults) of no difference in glycemic control; 12-month extension in adults confirms these findings. Other outcomes had insufficient evidence.

Versus Glargine (Type 2): Moderate-strength evidence (2 RCTs) of no difference in glycemic control. Conflicting findings from 2 RCTs on risk of nocturnal hypoglycemia, possibly less frequent with FDCP but unclear. Other outcomes had insufficient evidence.

Conclusions

A total of 71 studies were included (90 publications), with 12 new studies this update and 5 new extension studies (12-months) of RCTs. Across the comparisons, there were no significant differences in glycemic control. Differences in adverse events were found in a few comparisons: degludec has lower risk of hypoglycemia than glargine (nocturnal hypoglycemia in Type 1 patients, and both nocturnal and severe hypoglycemia in Type 2 patients), adverse event withdrawals were greater with detemir than glargine in Type 2 patients, glargine U300 had lower risk of nocturnal hypoglycemia than U100 in the short-term (only), and glargine given via pen injector was associated with lower risk of severe hypoglycemia than via vial and syringe (observational evidence). Evidence on other harms (e.g. cancer, neonatal effects) or the

comparative harms of fixed-dose combination degludec/aspart 70/30 was insufficient to draw conclusions.

DERP Systematic Review Methods

We followed systematic review methodology and procedures developed specifically for the Drug Effectiveness Review Project (DERP) and that are in accordance with current guidance for systematic reviews; for example, using dual review for study inclusion, quality assessments, and data abstraction. We searched MEDLINE and the Cochrane randomized trial database through March 2018. We requested dossiers of study information from manufacturers of included drugs, but received none. We created evidence tables, strength of evidence tables, and updated meta-analyses found in systematic reviews with newer trial data, using random effects models in Stata. Additional details on our methods can be found in Appendix A of the full report.

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Indication Review: Humira® (adalimumab) for Hidradenitis Suppurativa

Date of Review: November 2018 **End Date of Literature Search:** 8/2/2018

Purpose for Indication Review: To evaluate evidence for Humira® (adalimumab) in the setting of hidradenitis suppurativa (HS) as requested by the Health Evidence Review Commission (HERC). Medical therapy for HS is currently not funded by the Oregon Health Authority (OHA).[1]

Research Questions:
1. What is the efficacy and effectiveness of adalimumab in treating HS?
2. What are the comparative harms of adalimumab in patients with HS?

Conclusions:
- Evidence for adalimumab in HS comes from two phase 3 trials[2] and a systematic review from the Cochrane Collaboration.[3] A technology appraisal of adalimumab in HS was also completed by the National Institute for Health and Care Excellence (NICE).[4] The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed.
- There is low quality evidence from 2 randomized controlled trials (RCT) that adalimumab 40 mg weekly improves the proportion of patients achieving a Hidradenitis Suppurativa Clinical Response (HiSCR), defined as at least a 50% reduction in total abscess and inflammatory nodule count from baseline with no increase in the abscess or draining-fistula count, compared to placebo at 12 weeks (41.8% vs. 26.0%, respectively, number needed to treat [NNT] 7; and 58.9% vs. 27.6%, NNT 4).[2]
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with a 0-2 total abscess and inflammatory-nodule count at week 12 for patients with Hurley stage 2 disease at baseline compared to placebo (28.9% vs. 28.6%, respectively, p=0.96; and 51.8% vs. 32.2%, respectively, p=0.01, NNT 6).[2] The Hurley staging system ranges from stage 1 (least severe) to stage 3 (most severe), with stage 2 indicating recurrent abscesses with tract formation and cicatrization, single or multiple, and widely separated lesions.[5]
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with at least 30% reduction and at least 1 unit reduction in pain score from baseline compared to placebo at week 12 (27.9% vs. 24.8%, respectively, p=0.63; and 45.7% vs. 20.7%, respectively, p<0.001, NNT 4).[2] Clinical significance of a 30% reduction is unclear and it has been suggested that a 50% reduction in baseline pain is considered clinically meaningful.[4]
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly improves the mean change in modified Sartorius score compared to placebo from baseline to week 12 (-24.4 points vs. -15.7 points, respectively, p=0.12; and -28.9 points vs. -9.5 points, respectively, p<0.001).[2] Points for this scale are assigned in categories which include anatomical regions involved (3 points per region involved), number and scores of lesions (2 points for nodules,

4 for fistulas, 1 for scars, and 1 for others), the longest distance between two relevant lesions (<5 cm, 2 points; <10 cm, 4 points; ≥10 cm, 8 points), and if all lesions are clearly separated by normal skin (for each region: yes, 0 points; no, 6 points).[6,7] There is no upper limit and a larger score indicates more severe disease, but the definition of a minimum clinically significant change is unclear.[8]

- Differences in efficacy outcome results between the two trials may be due to differences in baseline characteristics, antibiotic use, and geographic distribution of patients.[2] A greater benefit for several outcomes was seen in PIONEER 2, in which the patients had less severe disease and were able to continue on stable doses of tetracycline antibiotics.[2]
- There is moderate quality evidence that adalimumab 40 mg weekly improves the Dermatology Life Quality Index (DLQI) score compared to placebo in moderate to severe HS at week 12 and week 16. Evidence from 2 RCTs found decreases of 5.4 points and 5.1 points with adalimumab compared with decreases of 2.9 points and 2.3 points with placebo at 12 weeks.[2] The differences between placebo and adalimumab group changes do not meet the suggested minimum clinically significant difference of 4-5 points.[2,4] Additionally, another RCT assessed in the Cochrane review found a benefit with adalimumab compared to placebo at 16 weeks in DLQI score (mean difference 4 points; 95% confidence interval [CI], 6.5 to 1.5 points lower).[3,9] The DLQI questionnaire consists of 10 quality of life questions each ranked from 0 to 3, with a max score of 30 indicating the skin disease has a very large impact on the patient's quality of life.[10] A change of 0-1 points indicates no effect; 2-5 points a small effect; 6-10 points a moderate effect; 11-20 points a large effect; and 21-30 an extremely large effect.[11]
- There is insufficient evidence to determine the effect of adalimumab on the need for surgery from clinical trials. However, NICE guidance based on post-hoc analyses of draining fistulas and non-draining fistulas concludes there is a decreased need for some types of surgical procedures (likely minor surgeries such as narrow margin excisions and incision and drainage procedures).[4] No definite conclusions could be made on the effect of adalimumab on surgical-inpatient admissions.[4] The post hoc analysis assessed by NICE found that a greater proportion of patients treated with adalimumab as compared to placebo had improvement in draining fistulas (33% vs. 19%; p<0.001; NNT 8) and non-draining fistulas (15% vs. 9%; p=0.017; NNT 17).[4,12]
- There is low quality evidence that adalimumab 40 mg weekly and placebo have similar risks of serious adverse events [SAEs] (1.3%-1.8% vs. 1.3%-3.7%, respectively; RCT = 2), infections (24.8%-25.2% vs. 28.3%-32.5%, respectively; RCT = 2), and serious infections (0.6-0.7% vs. 0-1.2%, respectively; RCT = 2) through 12 weeks.[2]
- There is low quality of evidence from patients who remained continuously on the respective treatment that adalimumab-treated patients have a similar risk of SAE at 12-36 weeks of therapy compared to placebo (2.1-3.9% vs. 4.6%, respectively; RCT=2 for adalimumab and 1 for placebo).[2] Similarly, there is low quality of evidence in the same time frame that adalimumab- and placebo-treated patients have similar risk for serious infections (0-2.0% vs. 1.3%; RCT=2 for adalimumab and 1 for placebo).[2] This evidence is limited by a high rate of overall attrition (41.3% and 52.8% for the two RCTs).[2]
- Long-term safety data for adalimumab in HS is limited to 36 weeks in RCTs and an additional 60 weeks in a subsequent open-label extension study.[2,13] The safety profile of adalimumab dosed every other week for other conditions has been well characterized since the drug's initial U.S. approval in 2002.[14] Like other immunosuppressants, adalimumab has FDA boxed warnings for serious infections and malignancies.[14]
- NICE guidance recommend adalimumab as an option for treating active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[4] It is recommended to assess response to treatment after 12 weeks of treatment, and only continue treatment if there is a reduction of 25% or more in total abscess and inflammatory nodule count and no increase in abscesses and draining fistulas.[4]
- In October 2018, the indication for adalimumab in moderate to severe hidradenitis suppurativa was expanded to include patients age 12 years and older.[15]

Recommendations:

- No further review or research needed at this time.

Background:
Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease which has a prevalence of 1-4% worldwide and is 3 times more common in women than men.[7,16] The mean age of onset is 22 years.[16] It is characterized by inflamed nodules which occur most frequently in the axillary, inguinal, and anogenital regions of the body.[7,16] These nodules are painful, recurrent, and can result in abscesses, chronic draining sinus tracts, scarring, disfigurement, and disability.[16] Genetic predisposition, hormonal factors, immune factors, medications such as lithium and medroxyprogesterone acetate, obesity, and smoking all are potential contributors to the etiology.[16]

There are multiple staging systems that evaluate symptoms and severity of HS. The Hurley clinical staging system describes disease severity by 3 stages: stage 1 indicates abscess formation, single or multiple, without sinus tracts and cicatrization (scar formation); stage 2 indicates recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions; and stage 3 indicates diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.[5] About 69% of patients have stage 1 disease, while approximately 28% and 4% of patients have more severe stage 2 and 3 disease.[5] The minimum clinically significant change in Hurley staging is unclear.[17]

The modified Sartorius score is another method of determining severity in which individual nodules and fistulas are counted.[5] Points are assigned in categories which include anatomical regions involved (3 points per region involved), number and scores of lesions (2 points for nodules, 4 for fistulas, 1 for scars, and 1 for others), the longest distance between two relevant lesions (<5 cm, 2 points; <10 cm, 4 points; ≥10 cm, 8 points), and if all lesions are clearly separated by normal skin (for each region: yes, 0 points; no, 6 points).[6,7] There is no upper limit as scoring depends on the individual patient's lesions, and a larger score indicates more severe disease.[8] The definition of a minimum clinically important change in this score is unclear.[17]

The Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) is another scale utilized which stages severity as clear (no inflammatory or non-inflammatory nodules), minimal (only non-inflammatory nodules), mild (<5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules), moderate (<5 inflammatory nodules or one abscess or draining fistula and ≥1 inflammatory nodules or 2-5 abscesses or draining fistulas and <10 inflammatory nodules), severe (2-5 abscesses or draining fistulas and ≥10 inflammatory nodules), or very severe (more than 5 abscesses or draining fistulas).[5,18]

The Hidradenitis Suppurativa Clinical Response (HiSCR) measure incorporates the status of lesions: abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulas (sinus tracts, with communications to skin surface, draining purulent fluid).[19] A responder is identified as having a 50% or greater reduction in abscesses and inflammatory nodules, no increase in the number of abscesses, and no increase in the number of draining fistulas from baseline.[19] However, the minimum clinically important difference is unclear.[4] A 25% reduction in total abscess and inflammatory nodules may also reflect a partial response to treatment.[4]

The Dermatology Life Quality Index (DLQI) can be used to determine quality of life. The questionnaire consists of 10 quality of life questions, each ranked from 0 to 3, with a maximum score of 30 indicating the skin disease has a very large negative impact on the patient's quality of life.[10] A change of 0-1 points indicates no effect; 2-5 points a small effect; 6-10 points a moderate effect; 11-20 points a large effect; and 21-30 points an extremely large effect.[11] It has been suggested that a change of 4 or 5 points may be the minimum clinically important difference, but this scale may underestimate effects of treatment in patients who have developed coping mechanisms for the disease.[2,4] Patient-reported pain scales are also used to determine disease severity and effects of treatment, and a reduction of 50% from baseline in pain scores may be considered clinically meaningful.[4]

Nonpharmacological treatments for HS include local hygiene and cleansing, reducing heat, humidity, and friction in the area, weight loss to ideal weight, and smoking cessation.[16] Surgical treatment may also be an option for Hurley stage 2 and 3 patients.[16] Pharmacological treatments for HS include antibiotics, retinoids, corticosteroids, and immunosuppressive agents such as tumor necrosis factor (TNF)-alpha inhibitors.[5,16] However, the most commonly used treatments are topical and oral antibiotics.[4] Antibiotics can be used both for the acute treatment of an infected area as well as for maintenance treatment.[7,16,20] The most commonly used oral antibiotic treatments are tetracyclines.[4] The next most commonly utilized therapies are acitretin, isotretinoin, dapsone, and cyclosporine.[4]

TNF-alpha inhibitors are often reserved for patients with moderate to severe HS.[5,16] Guidance from NICE recommends the use of adalimumab for active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[4] Continuation of therapy beyond 12 weeks is recommended only if there is a reduction of 25% or more in the total abscess and inflammatory nodule count as well as no increase in abscesses or draining fistulas at that time.[4]

Adalimumab was approved for moderate to severe HS in September 2015 and is the only medication FDA-approved for this condition.[14] Adalimumab is administered with a loading dose of 160 mg subcutaneously followed by a second dose of 80 mg two weeks later (Day 15) and then 40 mg for the third (Day 29) and subsequent weekly doses.[14] In October 2018, the indication was expanded to include patients age 12 years and older, with varied dosing based on weight.[15] Medical therapy for HS currently appears in the unfunded region of the Oregon Health Authority's Prioritized List of Health Services.[1]

Randomized Controlled Trials:
A total of 26 citations were manually reviewed from the initial literature search for the HS indication review. After further review, 25 citations were excluded because of wrong study design (e.g., observational or phase 2 trial when phase 3 trials available), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or already being included in a systematic review within the indication review. The one included citation was the PIONEER 1 and PIONEER 2 study manuscript, described below.

Clinical Efficacy:
Clinical Trials
Adalimumab, a TNF-alpha inhibitor, is approved by the FDA for the treatment of moderate to severe HS.[14] Two phase 3 trials (PIONEER 1 and PIONEER 2) provide efficacy and safety data for adalimumab in HS compared to placebo.[2] Both trials were manufacturer-funded and the manufacturer participated in data collection, data analysis, data interpretation, and manuscript writing, review, and approval.[2] Additionally, all of the authors disclosed potential conflicts of interest including conflicts specific to the manufacturer (such as employment, consulting fees, grant support, honoraria, etc.).[2]

The methods and trial design for PIONEER 1 and PIONEER 2 were similar.[2] Both trials were composed of 2 periods which compared adalimumab to placebo. In the first period, adalimumab was dosed at 160 mg at week 0, 80 mg at week 2, and 40 mg weekly at 4 through 12 weeks.[2] In the second period, patients who had been randomized to adalimumab in the first period underwent re-randomization to either adalimumab weekly, adalimumab 40 mg every other week, or placebo.[2] Patients randomized to placebo in the first period were reassigned in a blinded fashion in period 2 to either adalimumab 160 mg at week 12, 80 mg at week 14, followed by 40 mg weekly starting at week 16 (in PIONEER 1) or placebo beginning at week 12 (in PIONEER 2).[2] The second period lasted for a duration of 24 weeks, resulting in a total study duration of 36 weeks for period 1 and period 2 combined.[2] However, the primary and secondary efficacy endpoints were

all determined at week 12 which marked the end of period 1.[2] Patients enrolled in both PIONEER 1 (n=307) and PIONEER 2 (n=326) had moderate to severe HS and a duration of disease of at least one year.[2]

The primary efficacy endpoint was the proportion of patients with a HiSCR response, defined as at least a 50% reduction from baseline in total abscess and inflammatory nodule count, with no increase in the abscess or draining-fistula count.[2] Three ranked secondary endpoints included the proportion of patients with a total abscess and inflammatory-nodule count of 0, 1, or 2 for patients with Hurley stage 2 disease at baseline, at least 30% reduction and at least 1-unit reduction from baseline in pain score, and the change from baseline in modified Sartorius score.[2]

In PIONEER 1, HiSCR response at week 12 was achieved by a statistically significant greater proportion of adalimumab-treated patients compared to placebo-treated patients (41.8% vs. 26%, respectively; ARR 15.8%; NNT 7; p=0.003).[2] However, no statistically significant results were seen in the three ranked secondary endpoints.[2] No statistically significant difference was found between the number of adalimumab-treated and placebo-treated patients in the proportion of patients with a total abscess and inflammatory nodule count of 0, 1, or 2 at week 12 (28.9% vs. 28.6%, respectively; ARR 0.3%; 95% CI -13.4 to 14.1; p=0.96).[2] Similarly, no statistically significant difference was found in the proportion of patients with at least 30% reduction and at least 1-unit reduction from baseline in pain score between adalimumab and placebo groups at week 12 (27.9% vs. 24.8%, respectively; ARR 3.1%; 95% CI -8.6 to 14.2; p=0.63).[2] Finally, no statistically significant difference was found for the change in mean score from baseline in modified Sartorius score for either adalimumab or placebo group at week 12 (-24.4 points vs. -15.7 points, respectively; mean difference: -8.7 points; 95% CI -19.7 to 2.4; p=0.12).[2]

In PIONEER 2, HiSCR response at week 12 was achieved by a statistically significant greater proportion of adalimumab-treated patients compared to placebo-treated patients (58.9% vs 27.6%, respectively; ARR 31.3%; NNT 4; p<0.001).[2] In contrast to PIONEER 1, a statistically significant benefit was seen with adalimumab compared to placebo in the three ranked secondary outcomes.[2] A statistically significant difference was also found in the proportion of adalimumab- and placebo-treated patients with a total abscess and inflammatory nodule count of 0, 1, or 2 at week 12 (51.8% vs. 32.2%, respectively; ARR 19.6%; 95% CI 4.7 to 34.2; p=0.01; NNT 6).[2] Similarly, a statistically significant difference was found in the proportion of patients with at least 30% reduction and at least 1 unit reduction from baseline in pain score between adalimumab and placebo groups at week 12 (45.7% vs. 20.7%, respectively; ARR 25.1%; 95% CI 12.7 to 37.6; p<0.001; NNT 4).[2] A statistically significant difference was also found for the change in mean score from baseline in modified Sartorius score for either adalimumab or placebo group at week 12 (-28.9 points vs. -9.5 points, respectively; mean difference: -19.4 points; 95% CI -28.6 to -10.1; p<0.001).[2]

Differences in the results of the three ranked secondary endpoints, all non-statistically significant in PIONEER 1 yet all statistically significant in PIONEER 2, may be due to differences in baseline characteristics, antibiotic use, and geographic distribution of patients.[2] Patients in PIONEER 1 had higher mean abscess count (2.75 vs. 2.2, respectively), inflammatory nodule count (11.55 vs. 9, respectively) and draining fistula count (4.2 vs. 3.35, respectively) as well as higher mean modified Sartorius scores (149.1 vs. 115.1 points, respectively) compared to patients in PIONEER 2.[2] While patients were required to stop oral antibiotic treatment in PIONEER 1, patients who were on stable doses of tetracycline antibiotics were allowed to continue them in PIONEER 2.[2] Concomitant oral antibiotics were used by 19% of patients in PIONEER 2.[2] Approximately 50% of patients in PIONEER 1 were from the U.S., while only 27% of patients in PIONEER 2 were from the U.S., which limits applicability to the Oregon Medicaid population.[2] Other countries of origin for patients in PIONEER 1 included Australia, Canada, Czech Republic, Germany, and Hungary.[2] Other countries of origin for patients in PIONEER 2 included Australia, Canada, Denmark, France, Greece, the Netherlands, Puerto Rico, Sweden, Switzerland, and Turkey.[2]

Quality of life, as assessed by DLQI, was a non-ranked secondary endpoint for both PIONEER 1 and PIONEER 2.[2] Patients treated with adalimumab experienced greater improvements in DLQI score compared to placebo in both PIONEER 1 (-5.4 vs. -2.9, respectively) and PIONEER 2 (-5.1 and -2.3, respectively).[2] The minimum clinically significant difference is suggested to be around 4-5 points.[2,4] Among patients with a baseline score of greater than or equal to 5 (>90% of patients in period 1), a decrease of 5 points was seen with a greater proportion of patients in the adalimumab groups compared to the placebo groups in both PIONEER 1 (50.7% vs. 33.8%, p=0.004, respectively) and PIONEER 2 (49% vs. 34%, p=0.011, respectively).[2]

Both PIONEER 1 and PIONEER 2 were rated as poor quality due to manufacturer involvement and attrition. There was low attrition in period 1 which encompassed the primary and ranked secondary endpoints (5.5% and 6.1%, respectively) but high attrition occurred with longer follow-up in period 2 (41.3% and 52.8%, respectively).[2] A majority of the attrition in period 2 for both trials was due to loss of response, worsening of symptoms, or absence of improvement.[2]

Systematic Reviews

A 2017 Cochrane review on treatments for HS evaluated RCTs through August 2015 for all interventions.[3] Five of the eleven authors disclosed conflicts of interest related to the manufacturer of adalimumab (including advisory fees, honorarium, or acting as an investigator for a manufacturer-funded study).[3] As the PIONEER 1 and PIONEER 2 trials discussed above were published in 2016, these were not included in this review.[2,3] The review found moderate quality evidence that adalimumab 40 mg weekly improved the DLQI score compared to placebo in moderate to severe HS (difference: 4 points; 95% CI 6.5 to 1.5 points lower; studies = 1).[3] However, the lower end of the 95% CI (1.5 points) may not be clinically significant and the overall effect (4 points) was small.[3] This study of weekly adalimumab dosing was limited by not being powered to detect rare or delayed AEs.[3] For adalimumab every other week dosing, a meta-analysis of two trials (n=124) found no difference between adalimumab and placebo in quality of life or secondary outcomes such as pain score, HS scoring systems, PGA, or duration of remission.[3] The review concluded that results from the PIONEER studies may improve confidence in the effect size and safety of weekly adalimumab therapy.[3]

Guidelines

National Institute for Health and Care Excellence

In June 2016, NICE published a technology appraisal guidance for adalimumab in treating moderate to severe HS.[4] This guidance evaluated both the clinical and cost effectiveness and provided recommendations for place in therapy.[4] Clinical effectiveness was determined from the PIONEER 1 and 2 trials (described above).[4] It was concluded that adalimumab provides a significant benefit for symptom improvement and quality of life compared to placebo in the short term, but have not been shown long term.[4] The recommendations for use of adalimumab in HS were as follows:

- Adalimumab is recommended as an option for treating active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[4]
- After 12 weeks of treatment, assess the response to adalimumab and only continue if there is clear evidence of response as defined as
  - a reduction of 25% or more in total abscess and inflammatory nodule count and
  - no increase in abscesses and draining fistulas.[4]

The definition of response in the recommendations based on a 25% or more reduction in total abscess and inflammatory nodule count differs from the 50% reduction in the PIONEER 1 and 2 primary endpoints.[2,4] However, the clinical experts determined that the 50% reduction threshold was too high, and instead

determined that a 25% reduction in total abscess and inflammatory nodule count with no increase in abscesses or draining fistulas would reflect a treatment response.[4]

While the recommendations do not specify which conventional systemic therapies must be tried, the most commonly used treatments are topical and oral antibiotics.[4] The most commonly used oral antibiotic is tetracycline, followed by a combination of clindamycin and rifampicin.[4] The next most commonly utilized conventional therapies are acitretin, isotretinoin, dapsone, and cyclosporine.[4]

In the cost effectiveness analysis, the cost of surgical-inpatient admissions was a key consideration.[4] However, there was a lack of data regarding surgeries in the PIONEER trials as surgery was not permitted in the trials per protocol.[4,12] In response to a request from the evidence review group for outcome data on surgical procedures, the manufacturer completed a post-hoc analysis of pooled PIONEER 1 and 2 data.[4,12] The post hoc analysis found that a greater proportion of patients treated with adalimumab as compared to placebo had improvement in draining fistulas (33% vs. 19%; p<0.001; NNT 8) and non-draining fistulas (15% vs. 9%; p=0.017; NNT 17).[4,12] These outcomes would likely be associated with minor surgeries, such as narrow margin excisions and incision and drainage procedures, and therefore, the committee concluded that adalimumab reduces the need for some types of surgical procedures.[4] However, based on the lack of robust evidence, no conclusions could be made on adalimumab's effect on surgical-inpatient admissions.[4]

Clinical Safety:
In PIONEER 1 and PIONEER 2 through week 12 (period 1), the proportions of patients with any adverse event (AE) were similar for adalimumab- and placebo-treated patients (50.3% vs. 58.6%, respectively in PIONEER 1; 57.1% vs. 63.2%, respectively in PIONEER 2).[2] The two AEs which occurred by week 12 in at least 10% of patients in either the adalimumab or placebo groups of either trial included headache (9.2% vs. 9.9%, respectively in PIONEER 1; 12.9% vs. 12.9%, respectively in PIONEER 2) and nasopharyngitis (5.9% vs. 10.5%, respectively in PIONEER 1; 5.5% vs. 6.1%, respectively in PIONEER 2).[2] SAEs reported by week 12 were similar or lower with adalimumab compared to placebo (1.3% vs. 1.3%, respectively for PIONEER 1; 1.8% vs. 3.7%, respectively for PIONEER 2).[2] Infections occurred at a lower rate by week 12 for adalimumab-treated patients compared to placebo-treated patients in both trials (24.8% vs. 28.3%, respectively for PIONEER 1; 25.2% vs. 32.5%, respectively for PIONEER 2) and rates of serious infections were also low and similar between groups (0.7% vs. 0%, respectively; 0.6% vs. 1.2%, respectively).[2]

Safety outcomes from period 2 (weeks 12-36) of PIONEER 1 and 2 are presented in **Table 1**.[2] For period 2 of both trials, high attrition was seen (41.3% and 52.8% for PIONEER 1 and PIONEER 2, respectively).[2]

Table 1: Selected Safety Outcomes in Period 2 (weeks 12-36) of PIONEER 1 and PIONEER 2.[2]

	PIONEER 1				PIONEER 2			
Safety Outcome	**Adalimumab Weekly (n=145; reassigned from placebo in Period 1)**	**Placebo (n=49)**	**Adalimumab Every Other Week (n=48)**	**Adalimumab Weekly (n=48)**	**Placebo (n=151; reassigned from placebo in Period 1)**	**Placebo (n=51)**	**Adalimumab Every Other Week (n=53)**	**Adalimumab Weekly (n=51)**

Any adverse event	90 (62.1%)	28 (57.1%)	22 (45.8%)	28 (58.3%)	68 (45.0%)	33 (64.7%)	30 (56.6%)	29 (56.9%)
Serious adverse events	3 (2.1%)	0 (0%)	1 (2.1%)	1 (2.1%)	7 (4.6%)	0 (0%)	2 (3.8%)	2 (3.9%)
Adverse events leading to study drug discontinuation	5 (3.4%)	1 (2.0%)	0 (0%)	0 (0%)	3 (2.0%)	0 (0%)	1 (1.9%)	1 (2.0%)
Infections	43 (29.7%)	16 (32.7%)	12 (25.0%)	14 (29.2%)	35 (23.2%)	13 (25.5%)	19 (35.8%)	18 (35.3%)
Serious infections	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)	1 (2.0%)

An open-label extension trial following PIONEER 1 and 2 also studied safety for at least 60 weeks after the 36 week RCT period.[13] In the population of patients which received adalimumab weekly throughout both the RCT and open-label extension trial periods (n=88), adverse events leading to treatment discontinuation occurred in 14.8% of patients (n=13) and serious adverse events occurred in 13.6% (n=12).[13] Infections occurred in 71.6% of the patients (n=63) and serious infections occurred in 3.4% (n=3).[13]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Improvement in symptoms
2) Improvement in quality of life (DLQI)
3) Reduction in complications and surgeries
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical response per HiSCR measure at week 12 (>50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count)

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Kimball et al.[2] (PIONEER I) MC Phase 3, RCT with 2 DB, PC periods	Period 1 1. Adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly starting at week 4 2. Placebo	Demographics: • Mean age: 37 y • Female: 64% • White: 76% • Median duration of HS: 9.1 y • Previous systemic therapy: 43%	ITT: *Period 1* Total: 307 1. 153 2. 154 *Period 2* Total: 290 1. 48 2. 48	Primary Endpoint: Clinical response per HiSCR measure at week 12 (≥50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count) 1. 41.8%	15.8%/7	*Period 1* Serious AEs 1. 2 (1.3%) 2. 2 (1.3%) AEs Leading to DC 1. 0 (0%) 2. 2 (1.3%) Infection	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized centrally and treatments assigned by IVRS. Balanced characteristics at baseline. Performance Bias: Low. Matching placebo was used. Protocol was approved at each site. Detection Bias: Low. Investigator and study site personnel blinded. Attrition Bias: High. Overall high attrition for Period 2 (41.3%). Low attrition for Period 1

36 weeks (period 1: 12 weeks; period 2: 24 weeks)	Period 2 *Pts previously assigned to adalimumab* 1. Adalimumab 40 mg weekly 2. Adalimumab 40 mg every other week 3. Placebo *Pts previously assigned to placebo* 4. Adalimumab 160 mg at week 12, 80 mg at week 14, followed by 40 mg weekly starting at week 16	• Prior surgery for HS: 11% • Total number of abscesses & inflammatory nodules: 14 • Modified Sartorius score: 149.1 Key Inclusion Criteria: • Age ≥18 y • HS ≥1 y • Moderate to severe HS (total abscess & inflammatory nodule count ≥3) at baseline • Inadequate response to oral antibiotics • Anti-TNF-a naïve Key Exclusion Criteria: • Prior anti-TNF therapy • Any active skin disease or condition that could interfere with assessment of HS • Antibiotic treatment within 28 days of baseline • Receipt of prescription topical therapies for HS ≤14 days prior to baseline	3. 49 4. 145 Attrition: *Period 1:* Total: 17 (5.5%) 1. 8 (5.2%) 2. 9 (5.8%) *Period 2:* Total: 120 (41.3%) 1. 20 (41.6%) 2. 21 (43.8%) 3. 27 (55.1%) 4. 52 (35.9%)	2. 26.0% P=0.003 RR & CI NR Secondary Endpoint: Total abscess and inflammatory-nodule count of 0, 1, or 2 in patients with Hurley stage II disease at week 12 1. 24/83 (28.9%) 2. 24/84 (28.6%) Difference: 0.3 (95% CI -13.4 to 14.1) P=0.96 ≥30% reduction and ≥1 unit reduction from baseline in pain score at week 12 1. 34/122 (27.9%) 2. 27/109 (24.8%) Difference: 2.8 (95% CI -8.6 to 14.2) P=0.63 Change in mean score from baseline in modified Sartorius score at week 12 1. -24.4 2. -15.7 Difference: -8.7 (95% CI -19.7 to 2.4) P=0.12	NA NA NA	1. 38 (24.8%) 2. 43 (28.3%) Serious Infection 1. 1 (0.7%) 2. 0 (0%) Cancer 1. 0 (0%) 2. 1 (0.7%) *Period 2* Serious AEs 1. 1 (2.1%) 2. 1 (2.1%) 3. 0 (0%) 4. 3 (2.1%) AEs Leading to DC 1. 0 (0%) 2. 0 (0%) 3. 1 (2.0%) 4. 5 (3.4%) Infection 1. 14 (29.2%) 2. 12 (25.0%) 3. 16 (32.7%) 4. 43 (29.7%) Serious Infection 1. 0 (0%) 2. 0 (0%) 3. 0 (0%) 4. 1 (0.7%) p-values, RR, 95% CI were NR		(5.5%) which was utilized for primary and ranked secondary outcomes. ITT used for efficacy analysis. LOCF utilized for analysis of missing continuous variables. Non-responder imputation utilized for analysis of missing categorical values. Reporting Bias: Unclear. Protocol available. Pre-specified primary and ranked secondary outcomes reported. Confidence intervals not reported for primary endpoint. Other Bias: High. Funded by AbbVie who participated in data collection, data analysis, data interpretation, and manuscript writing, review, and approval. **Applicability**: Patient: Moderate to severe HS at baseline appropriate for utilizing second-line therapies such as TNF-a inhibitors. Intervention: Adalimumab dosing appropriate and approved by FDA. Comparator: Placebo appropriate to establish efficacy. No other TNF-a inhibitor agents approved for this condition. Outcomes: Clinically meaningful symptom endpoints used appropriate for HS. However, minimum clinically important difference for this outcome is unclear. Majority of attrition in period 2 due to loss of response, worsening of symptoms, or absence of improvement. Setting: 50.5% of patients from the U.S. Other countries of origin included Australia, Canada, Czech Republic, Germany, and Hungary.

		• Receipt of systemic non-biologic therapies with potential impact on HS <28 days prior to baseline • Receipt of oral concomitant analgesics for HS pain ≤14 days prior to baseline						
2. Kimball et al.[2] (PIONEER II) MC Phase 3, RCT with 2 DB, PC periods 36 weeks (period 1: 12 weeks; period 2: 24 weeks)	Period 1 1. Adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly starting at week 4 2. Placebo Period 2 *Pts previously assigned to adalimumab* 1. Adalimumab 40 mg weekly 2. Adalimumab 40 mg every other week 3. Placebo *Pts previously assigned to placebo* 4. Placebo	Demographics: • Mean age: 35 y • Female: 68% • White: 84% • Median duration of HS: 9.5 y • Previous systemic therapy: 48% • Prior surgery for HS: 14% • Total number of abscesses & inflammatory nodules: 11 • Modified Sartorius score: 115.1 Key Inclusion Criteria: • See PIONEER 1 Key Exclusion Criteria: • Prior anti-TNF therapy • Any active skin disease or condition that could interfere	ITT: *Period 1* Total: 326 1. 163 2. 163 *Period 2* Total: 306 1. 51 2. 53 3. 51 4. 151 Attrition: *Period 1:* Total: 20 (6.1%) 1. 8 (4.9%) 2. 12 (7.4%) *Period 2:* Total: 190 (52.8%) 1. 23 (45.1%) 2. 28 (52.8%)	Primary Endpoint: Clinical response per HiSCR measure at week 12 (≥50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count) 1. 58.9% 2. 27.6% P<0.001 RR & CI NR Secondary Endpoint: Total abscess and inflammatory-nodule count of 0, 1, or 2 in patients with Hurley stage II disease at week 12 1. 44/85 (51.8%) 2. 28/87 (32.2%) Difference: 19.5 (95% CI 4.7 to 34.2) P=0.01 ≥30% reduction and ≥1 unit reduction from baseline in pain score at week 12 1. 48/105 (45.7%) 2. 23/111 (20.7%)	31.3%/4 19.6%/6 25%/4	Outcome: *Period 1* Serious AEs 1. 3 (1.8%) 2. 6 (3.7%) AEs Leading to DC 1. 4 (2.5%) 2. 6 (3.7%) Infection 1. 41 (25.2%) 2. 53 (32.5%) Serious Infection 1. 1 (0.6%) 2. 2 (1.2% Cancer 1. 0 (0%) 2. 0 (0%) *Period 2* Serious AEs 1. 2 (3.9%) 2. 2 (3.8%) 3. 0 (0%) 4. 7 (2.0%) AEs Leading to DC	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. See PIONEER 1. Performance Bias: Low. See PIONEER 1. Detection Bias: Low. See PIONEER 1. Attrition Bias: High. Overall high attrition for Period 2 (52.8%). Low attrition for Period 1 (6.1%) which was utilized for primary and ranked secondary outcomes. ITT used for efficacy analysis. LOCF utilized for analysis of missing continuous variables. Non-responder imputation utilized for analysis of missing categorical values. Reporting Bias: Unclear. See PIONEER 1. Other Bias: High. See PIONEER 1. **Applicability**: Patient: See PIONEER 1. Intervention: See PIONEER 1. Comparator: See PIONEER 1. Outcomes: See PIONEER 1. Setting: 27.3% of patients from the U.S. Other countries of origin included Australia, Canada, Denmark, France, Greece, the Netherlands, Puerto Rico, Sweden, Switzerland, and Turkey.

		with assessment of HS • Receipt of prescription topical therapies for HS ≤14 days prior to baseline • Receipt of systemic non-biologic therapies with potential impact on HS <28 days prior to baseline • Receipt of oral concomitant analgesics for HS pain ≤14 days prior to baseline	3. 28 (54.9%) 4. 111 (73.5%)	Difference: 25.1 (95% CI 12.7 to 37.6) P<0.001 Change in mean score from baseline in modified Sartorius score at week 12 1. -28.9 2. -9.5 Difference: -19.4 (95% CI -28.6 to -10.1) P<0.001	NA	1. 1 (2.0%) 2. 1 (1.9%) 3. 0 (0%) 4. 3 (2.0%) <u>Infection</u> 1. 18 (35.3%) 2. 19 (35.8%) 3. 13 (25.5%) 4. 35 (23.2%) <u>Serious Infection</u> 1. 1 (2.0%) 2. 0 (0%) 3. 0 (0%) 4. 2 (1.3%) p-values, RR, 95% CI were NR		

<u>Abbreviations</u> [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; DC = discontinuation; FDA = Food and Drug Administration; HiSCR = Hidradenitis Suppurativa Clinical Response; HS = hidradenitis suppurativa; ITT = intention to treat; IVRS = interactive voice-response system; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; Pts = patients; RCT = randomized controlled trial; RR = relative risk; TNF-a = tumor necrosis factor-alpha; U.S. = United States; y = years.

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Appendix 1: Search Strategy

Medline search on 8/2/2018 for hidradenitis suppurativa indication review
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Hidradenitis Suppurativa/ 1234
2 exp Adalimumab/ 4338
3 1 and 2 69
4 limit 3 to (English language and humans 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 reviews)) 26

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics 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 high value products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All biologics for autoimmune diseases (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 Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥18 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Baricitinib (OLUMIANT)						≥18 yo		
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
								HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo		
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 yo	≥18 yo	≥18 yo (Simponi)	
Guselkumab (Tremfya)				≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo	≥18 yo			
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo	≥18 yo	
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory 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?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5
5. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever • Giant Cell Arteritis • Cytokine Release Syndrome AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to #8	**No:** Go to #9
8. If the request is for a non-preferred agent, has the patient failed to respond to a Humira® product or an Enbrel® 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.

Approval Criteria		
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 (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Has the patient failed to respond 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 diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #16

Approval Criteria		
13. Has the patient failed to respond 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® product or an Enbrel® product for at least 3 months?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the request for tofacitinib?	**Yes:** Go to #15	**No:** Approve for up to 6 months.
15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 6 months.
16. 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 #17	**No:** Go to #18

Approval Criteria		
17. 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 • For Crohn's Disease patients only: 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.
18. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment.	**No:** Go to #19
19. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 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 6 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *1/18 (DM; JP); 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/21/13*

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
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Pharmacy Utilization Summary Report: April 2017 - March 2018

Eligibility	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
Total Members (FFS & Encounter)	991,147	991,908	994,823	982,276	963,901	959,096	961,528	962,260	963,814	961,458	959,824	963,504	971,295
FFS Members	144,374	130,857	135,409	143,784	127,100	130,304	128,336	118,961	126,786	121,061	121,425	120,975	129,114
OHP Basic with Medicare	33,156	33,179	33,308	33,513	33,453	33,651	33,710	33,679	33,770	33,777	34,033	34,222	33,621
OHP Basic without Medicare	12,803	12,559	12,546	12,903	12,546	12,333	12,541	11,983	12,096	12,068	12,220	12,198	12,400
ACA	98,415	85,119	89,555	97,368	81,101	84,320	82,085	73,299	80,920	75,216	75,172	74,555	83,094
Encounter Members	846,773	861,051	859,414	838,492	836,801	828,792	833,192	843,299	837,028	840,397	838,399	842,529	842,181
OHP Basic with Medicare	40,614	40,798	40,843	40,894	40,986	41,036	41,080	41,162	41,174	41,156	41,089	41,117	40,996
OHP Basic without Medicare	67,031	67,125	66,631	63,104	62,676	62,828	63,025	63,731	63,827	63,767	63,431	63,435	64,218
ACA	739,128	753,128	751,940	734,494	733,139	724,928	729,087	738,406	732,027	735,474	733,879	737,977	736,967

Gross Cost Figures for Drugs	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	YTD Sum
Total Amount Paid (FFS & Encounter)	$69,428,005	$77,001,371	$75,914,903	$71,990,171	$75,265,475	$69,805,528	$73,515,069	$73,049,175	$69,838,235	$80,436,514	$70,590,635	$78,375,828	$885,210,912
Mental Health Carve-Out Drugs	$7,737,458	$8,400,436	$8,178,231	$8,001,001	$8,125,739	$7,108,275	$7,579,045	$7,273,339	$7,027,263	$7,935,045	$7,126,865	$7,710,607	$92,203,303
OHP Basic with Medicare	$954	$912	$37	$52	$117	$28	$282	$61	$36	$2,895	$73	$2,609	$8,054
OHP Basic without Medicare	$3,171,809	$3,441,979	$3,335,909	$3,269,113	$3,297,165	$2,949,839	$3,121,094	$3,033,863	$3,000,431	$3,290,460	$3,034,846	$3,248,507	$38,195,014
ACA	$4,493,080	$4,876,528	$4,767,961	$4,654,019	$4,746,990	$4,102,564	$4,399,844	$4,177,247	$3,968,570	$4,586,681	$4,038,119	$4,408,989	$53,220,593
FFS Physical Health Drugs	$3,270,851	$3,496,171	$3,156,127	$2,859,529	$2,974,774	$2,968,882	$2,846,822	$2,636,053	$2,703,836	$3,502,822	$2,954,901	$3,003,690	$36,374,458
OHP Basic with Medicare	$238,677	$243,315	$230,766	$221,915	$230,877	$228,850	$240,229	$234,982	$205,637	$260,421	$236,474	$250,398	$2,822,540
OHP Basic without Medicare	$1,054,099	$1,121,385	$954,059	$859,906	$1,008,347	$1,051,314	$956,368	$858,096	$888,025	$1,255,433	$949,946	$933,230	$11,890,206
ACA	$1,822,695	$2,004,569	$1,813,784	$1,656,348	$1,605,005	$1,565,639	$1,534,564	$1,405,808	$1,494,814	$1,851,620	$1,630,650	$1,680,834	$20,066,330
FFS Physician Administered Drugs	$1,873,992	$2,914,735	$2,914,950	$2,081,543	$2,583,227	$1,762,687	$1,350,326	$1,814,032	$1,357,572	$2,177,809	$1,953,557	$1,624,208	$24,408,637
OHP Basic with Medicare	$438,077	$428,657	$348,496	$543,695	$473,237	$338,999	$382,224	$540,919	$463,531	$503,722	$401,496	$459,047	$5,322,100
OHP Basic without Medicare	$251,044	$1,254,358	$1,252,909	$477,012	$352,217	$250,921	$328,100	$504,716	$268,790	$492,459	$665,462	$297,752	$6,395,739
ACA	$774,666	$922,717	$927,370	$806,895	$858,623	$937,948	$432,236	$518,367	$437,718	$852,887	$588,226	$586,248	$8,643,903
Encounter Physical Health Drugs	$46,059,830	$50,324,016	$49,517,218	$47,759,831	$49,806,653	$46,916,028	$50,059,802	$49,485,357	$48,060,219	$54,016,338	$47,942,526	$54,338,942	$594,286,759
OHP Basic with Medicare	$115,187	$116,818	$110,316	$111,406	$116,332	$106,743	$124,317	$118,290	$101,540	$126,993	$130,445	$126,557	$1,404,943
OHP Basic without Medicare	$12,405,667	$13,568,247	$13,259,371	$13,237,535	$13,891,771	$12,752,385	$13,401,752	$13,332,188	$12,463,596	$13,931,163	$12,374,798	$14,277,057	$158,895,531
ACA	$32,949,200	$35,936,516	$35,469,133	$33,737,906	$35,054,854	$33,280,304	$35,820,676	$35,329,815	$34,794,996	$39,191,225	$34,752,113	$39,196,003	$425,512,741
Encounter Physician Administered Drugs	$10,485,874	$11,866,012	$12,148,378	$11,288,267	$11,775,082	$11,049,658	$11,679,075	$11,840,395	$10,689,346	$12,804,500	$10,612,787	$11,698,381	$137,937,755
OHP Basic with Medicare	$208,567	$269,732	$214,096	$226,683	$221,555	$185,801	$203,456	$193,999	$194,388	$304,155	$229,327	$288,250	$2,740,009
OHP Basic without Medicare	$2,410,309	$2,617,156	$2,388,158	$2,687,489	$2,659,060	$2,239,256	$2,229,793	$2,600,974	$2,247,234	$3,086,537	$2,402,352	$2,445,186	$30,013,503
ACA	$7,697,590	$8,710,007	$9,369,659	$8,242,442	$8,689,991	$8,445,629	$8,933,824	$8,778,012	$8,077,445	$9,233,032	$7,861,490	$8,802,613	$102,841,733

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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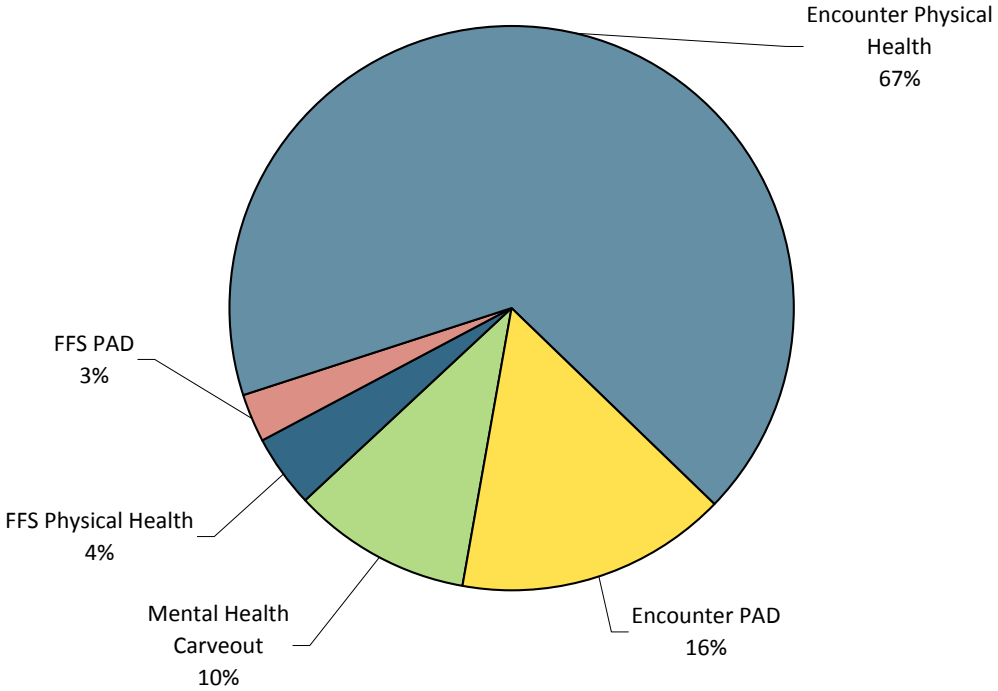
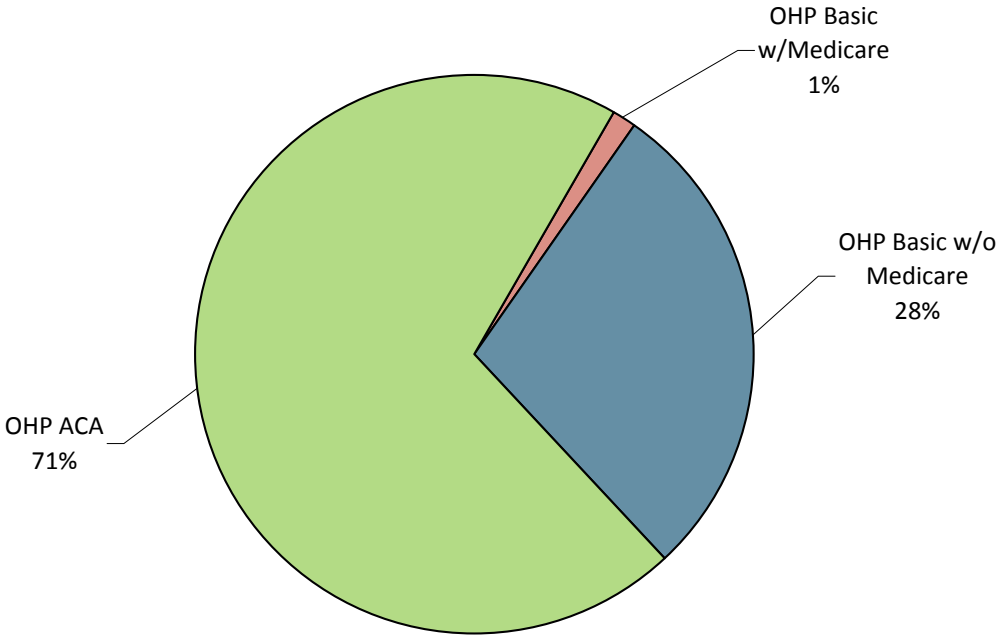
YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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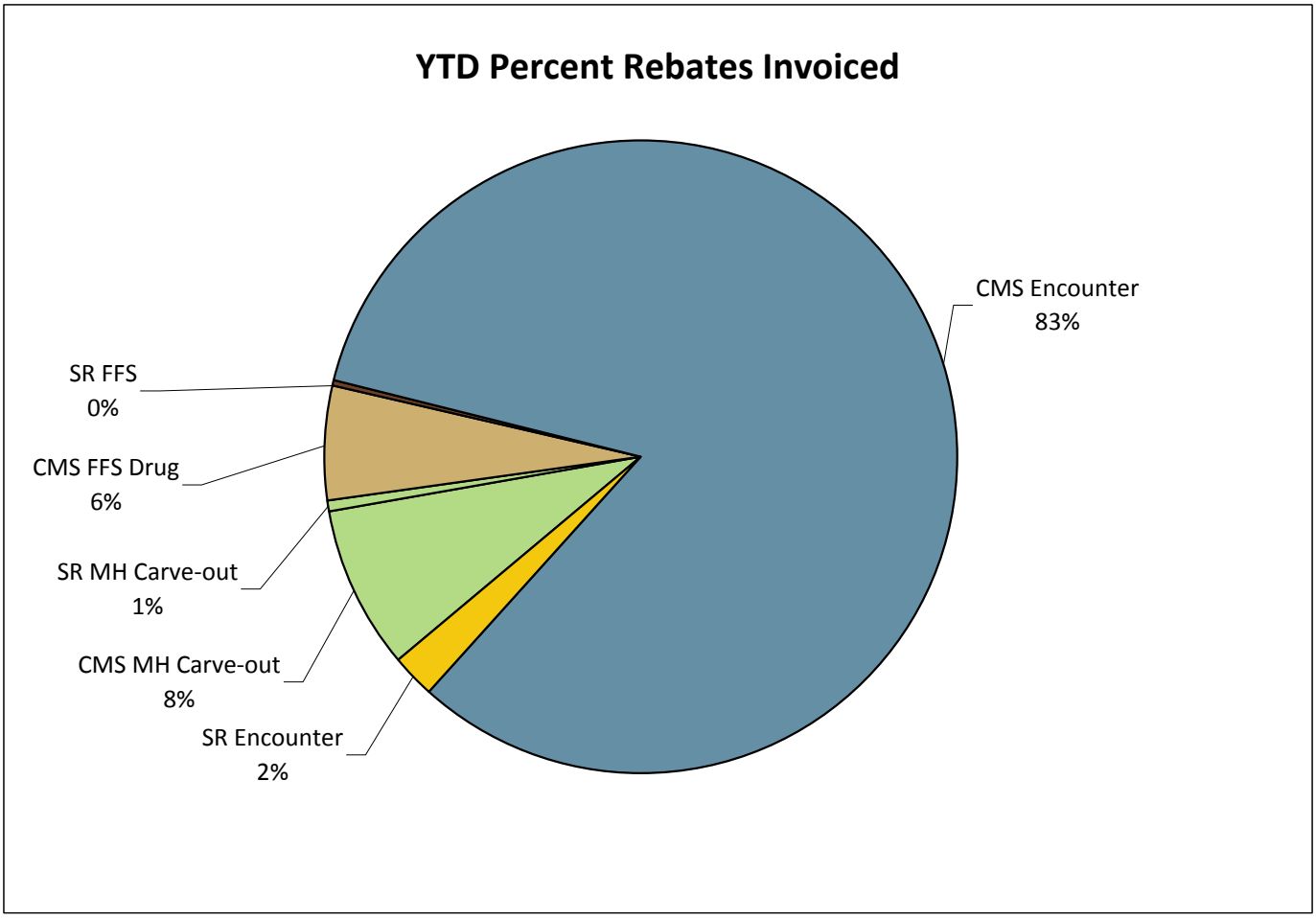
Pharmacy Utilization Summary Report: April 2017 - March 2018

Quarterly Rebates Invoiced	2017-Q2	2017-Q3	2017-Q4	2018-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$146,096,384	$100,237,403	$100,842,280	$107,788,973	$454,965,040
CMS MH Carve-out	$10,292,819	$9,381,248	$8,964,630	$9,710,394	$38,349,092
SR MH Carve-out	$594,561	$608,802	$655,183	$537,789	$2,396,336
CMS FFS Drug	$7,571,617	$6,503,087	$5,802,547	$6,975,449	$26,852,700
SR FFS	$218,469	$178,107	$200,156	$212,347	$809,079
CMS Encounter	$124,030,302	$81,307,062	$82,602,112	$88,432,811	$376,372,286
SR Encounter	$3,388,616	$2,259,097	$2,617,651	$1,920,183	$10,185,547

Quaterly Net Drug Costs	2017-Q2	2017-Q3	2017-Q4	2018-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$76,247,895	$116,823,772	$115,560,200	$121,614,004	$430,245,871
Mental Health Carve-Out Drugs	$13,428,744	$13,244,965	$12,259,833	$12,524,333	$51,457,875
FFS Phys Health + PAD	$9,836,740	$8,549,447	$6,705,938	$8,029,191	$33,121,316
Encounter Phys Health + PAD	$52,982,410	$95,029,361	$96,594,429	$101,060,480	$345,666,681



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

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: April 2017 - March 2018

Gross PMPM Drug Costs (Rebates not Subtracted)	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$70.05	$77.63	$76.31	$73.29	$78.08	$72.78	$76.46	$75.91	$72.46	$83.66	$73.55	$81.34	$75.96
Mental Health Carve-Out Drugs	$7.81	$8.47	$8.22	$8.15	$8.43	$7.41	$7.88	$7.56	$7.29	$8.25	$7.43	$8.00	$7.91
FFS Physical Health Drugs	$22.66	$26.72	$23.31	$19.89	$23.40	$22.78	$22.18	$22.16	$21.33	$28.93	$24.34	$24.83	$23.54
FFS Physician Administered Drugs	$12.98	$22.27	$21.53	$14.48	$20.32	$13.53	$10.52	$15.25	$10.71	$17.99	$16.09	$13.43	$15.76
Encounter Physical Health Drugs	$54.39	$58.44	$57.62	$56.96	$59.52	$56.61	$60.08	$58.68	$57.42	$64.27	$57.18	$64.50	$58.81
Encounter Physician Administered Drugs	$12.38	$13.78	$14.14	$13.46	$14.07	$13.33	$14.02	$14.04	$12.77	$15.24	$12.66	$13.88	$13.65

Claim Counts	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
Total Claim Count (FFS & Encounter)	1,016,332	1,087,626	1,037,658	988,295	1,030,215	985,177	1,048,749	1,017,815	1,003,158	1,107,860	962,701	1,066,197	1,029,315
Mental Health Carve-Out Drugs	146,749	158,987	152,279	147,184	153,351	144,433	153,728	149,636	145,556	159,855	141,783	155,489	150,753
FFS Physical Health Drugs	63,938	67,321	64,266	61,564	63,014	59,058	60,729	56,881	56,354	66,738	59,018	61,557	61,703
FFS Physician Administered Drugs	18,058	18,496	17,969	18,681	19,488	18,335	17,838	16,721	16,151	21,674	17,419	17,804	18,220
Encounter Physical Health Drugs	680,817	733,569	698,820	655,231	683,179	654,031	701,390	682,130	675,295	737,920	642,986	720,302	688,806
Encounter Physician Administered Drugs	106,770	109,253	104,324	105,635	111,183	109,320	115,064	112,447	109,802	121,673	101,495	111,045	109,834

Gross Amount Paid per Claim (Rebates not Subtracted)	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$68.31	$70.80	$73.16	$72.84	$73.06	$70.86	$70.10	$71.77	$69.62	$72.61	$73.33	$73.51	$71.66
Mental Health Carve-Out Drugs	$52.73	$52.84	$53.71	$54.36	$52.99	$49.22	$49.30	$48.61	$48.28	$49.64	$50.27	$49.59	$50.96
FFS Physical Health Drugs	$51.16	$51.93	$49.11	$46.45	$47.21	$50.27	$46.88	$46.34	$47.98	$52.49	$50.07	$48.80	$49.06
FFS Physician Administered Drugs	$103.78	$157.59	$162.22	$111.43	$132.55	$96.14	$75.70	$108.49	$84.05	$100.48	$112.15	$91.23	$111.32
Encounter Physical Health Drugs	$67.65	$68.60	$70.86	$72.89	$72.90	$71.73	$71.37	$72.55	$71.17	$73.20	$74.56	$75.44	$71.91
Encounter Physician Administered Drugs	$98.21	$108.61	$116.45	$106.86	$105.91	$101.08	$101.50	$105.30	$97.35	$105.24	$104.56	$105.35	$104.70

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$26.81	$26.94	$27.33	$27.32	$27.54	$27.10	$26.33	$26.35	$26.40	$26.50	$25.97	$25.80	$26.70
Mental Health Carve-Out Drugs	$30.99	$30.25	$30.10	$30.38	$29.10	$24.89	$24.67	$23.78	$23.45	$23.76	$23.88	$23.06	$26.53
FFS Physical Health Drugs	$22.06	$22.36	$22.30	$22.06	$22.34	$23.38	$22.35	$21.90	$22.66	$23.41	$23.90	$22.90	$22.64
Encounter Physical Health Drugs	$26.32	$26.61	$27.17	$27.10	$27.65	$27.95	$27.05	$27.32	$27.38	$27.39	$26.63	$26.67	$27.10

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$652.93	$666.34	$679.50	$710.04	$684.03	$615.97	$608.15	$667.93	$677.33	$702.45	$740.59	$765.90	$680.93
Mental Health Carve-Out Drugs	$852.69	$869.83	$882.82	$892.52	$899.61	$900.70	$928.32	$933.59	$964.21	$981.46	$1,013.51	$1,004.75	$927.00
FFS Physical Health Drugs	$445.98	$458.04	$420.52	$394.99	$390.14	$383.51	$343.25	$365.52	$375.00	$428.96	$400.53	$411.56	$401.50
Encounter Physical Health Drugs	$655.90	$668.03	$685.18	$722.12	$691.44	$613.57	$606.06	$670.82	$680.02	$704.52	$749.09	$775.49	$685.19

Multi-Source Drug Use Percentage	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
Multi-Source Drug Use Percentage	94.1%	94.1%	94.0%	94.1%	93.9%	93.3%	93.2%	93.7%	93.9%	93.9%	94.0%	94.1%	93.8%
Mental Health Carve-Out Drugs	97.4%	97.3%	97.2%	97.2%	97.3%	97.2%	97.3%	97.3%	97.4%	97.3%	97.3%	97.3%	97.3%
FFS Physical Health Drugs	93.1%	93.2%	93.3%	93.5%	93.2%	92.5%	92.4%	92.9%	92.8%	92.8%	93.1%	93.3%	93.0%
Encounter Physical Health Drugs	93.4%	93.5%	93.4%	93.4%	93.2%	92.5%	92.3%	93.0%	93.3%	93.2%	93.4%	93.5%	93.2%

Preferred Drug Use Percentage	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Avg Monthly
Preferred Drug Use Percentage	86.56%	86.42%	86.29%	86.41%	86.17%	87.06%	86.87%	86.69%	86.65%	87.05%	86.93%	86.82%	86.7%
Mental Health Carve-Out Drugs	75.65%	75.30%	75.09%	74.84%	74.81%	74.73%	74.65%	74.47%	74.52%	74.51%	74.35%	74.44%	74.8%
FFS Physical Health Drugs	95.15%	95.26%	95.23%	95.41%	95.39%	95.54%	95.47%	95.60%	95.56%	95.83%	95.69%	95.66%	95.5%
Encounter Physical Health Drugs	88.12%	87.99%	87.88%	88.13%	87.85%	89.01%	88.82%	88.63%	88.52%	88.99%	88.91%	88.73%	88.5%

Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,283,097	14.9%	4,451	$1,187	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,161,005	6.1%	1,205	$1,793	V
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,053,066	3.0%	547	$1,925	Y
4	REXULTI	Antipsychotics, 2nd Gen	$981,254	2.8%	939	$1,045	V
5	VRAYLAR	Antipsychotics, 2nd Gen	$714,627	2.0%	670	$1,067	V
6	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$648,216	1.8%	1,710	$379	V
7	INVEGA TRINZA	Antipsychotics, Parenteral	$581,513	1.6%	106	$5,486	V
8	SAPHRIS	Antipsychotics, 2nd Gen	$576,239	1.6%	838	$688	Y
9	FLUOXETINE HCL	Antidepressants	$571,579	1.6%	30,923	$18	Y
10	DULOXETINE HCL	Antidepressants	$529,188	1.5%	28,779	$18	V
11	SERTRALINE HCL	Antidepressants	$486,621	1.4%	41,341	$12	Y
12	ATOMOXETINE HCL*	ADHD Drugs	$446,961	1.3%	4,918	$91	Y
13	TRAZODONE HCL	Antidepressants	$417,761	1.2%	37,125	$11	
14	BUPROPION XL	Antidepressants	$389,455	1.1%	21,842	$18	V
15	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$373,279	1.1%	98	$3,809	Y
16	VIIBRYD	Antidepressants	$373,053	1.1%	1,421	$263	V
17	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$369,257	1.0%	407	$907	Y
18	TRINTELLIX	Antidepressants	$355,260	1.0%	968	$367	V
19	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$347,251	1.0%	2,079	$167	
20	VENLAFAXINE HCL ER	Antidepressants	$319,697	0.9%	1,741	$184	V
21	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$306,170	0.9%	1,754	$175	V
22	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$298,758	0.8%	13,828	$22	V
23	HUMIRA PEN*	Biologics for Autoimmune Conditions	$297,030	0.8%	118	$2,517	Y
24	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$267,914	0.8%	12	$22,326	Y
25	ESCITALOPRAM OXALATE	Antidepressants	$266,188	0.8%	23,275	$11	Y
26	LAMOTRIGINE	Antiepileptics (oral & rectal)	$265,245	0.7%	22,409	$12	Y
27	MAKENA*	Progestational Agents	$264,122	0.7%	92	$2,871	Y
28	ARISTADA	Antipsychotics, Parenteral	$259,600	0.7%	141	$1,841	Y
29	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$242,984	0.7%	17,244	$14	
30	AMITRIPTYLINE HCL	Antidepressants	$238,234	0.7%	14,747	$16	Y
31	CITALOPRAM HBR	Antidepressants	$226,276	0.6%	22,610	$10	Y
32	VENLAFAXINE HCL ER	Antidepressants	$196,131	0.6%	14,711	$13	Y
33	ENBREL*	Biologics for Autoimmune Conditions	$190,943	0.5%	36	$5,304	Y
34	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$190,370	0.5%	14,874	$13	Y
35	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$183,816	0.5%	637	$289	V
36	Factor Viii Recombinant Nos	Physican Administered Drug	$180,601	0.5%	8	$22,575	
37	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$175,005	0.5%	14	$12,500	Y
38	HUMIRA*	Biologics for Autoimmune Conditions	$150,649	0.4%	44	$3,424	Y
39	BUPROPION HCL SR	Antidepressants	$149,688	0.4%	10,487	$14	Y
40	Injection, Ramucirumab	Physican Administered Drug	$146,807	0.4%	6	$24,468	
		Top 40 Aggregate:	**$21,474,908**		**339,155**	**$2,946**	
		All FFS Drugs Totals:	**$35,400,758**		**653,373**	**$488**	

*** Drug requires Prior Authorization**

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

Last updated: October 24, 2018

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$373,279	3.0%	98	$3,809	Y
2	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$347,251	2.8%	2,079	$167	
3	HUMIRA PEN*	Biologics for Autoimmune Conditions	$297,030	2.4%	118	$2,517	Y
4	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$267,914	2.2%	12	$22,326	Y
5	MAKENA*	Progestational Agents	$264,122	2.1%	92	$2,871	Y
6	ENBREL*	Biologics for Autoimmune Conditions	$190,943	1.5%	36	$5,304	Y
7	Factor Viii Recombinant Nos	Physican Administered Drug	$180,601	1.5%	8	$22,575	
8	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$175,005	1.4%	14	$12,500	Y
9	HUMIRA*	Biologics for Autoimmune Conditions	$150,649	1.2%	44	$3,424	Y
10	Injection, Ramucirumab	Physican Administered Drug	$146,807	1.2%	6	$24,468	
11	LANTUS SOLOSTAR*	Diabetes, Insulins	$138,088	1.1%	407	$339	Y
12	ADVATE	Antihemophilia Factors	$132,395	1.1%	7	$18,914	
13	Factor Viii Recomb Novoeight	Physican Administered Drug	$129,426	1.0%	7	$18,489	
14	Infliximab Not Biosimil 10mg	Physican Administered Drug	$124,308	1.0%	106	$1,173	
15	STELARA*	Biologics for Autoimmune Conditions	$124,282	1.0%	12	$10,357	N
16	Inj Pembrolizumab	Physican Administered Drug	$122,447	1.0%	49	$2,499	
17	Factor Viii Pegylated Recomb	Physican Administered Drug	$116,674	0.9%	6	$19,446	
18	GENVOYA	HIV	$115,852	0.9%	47	$2,465	Y
19	NOVOLOG FLEXPEN	Diabetes, Insulins	$112,895	0.9%	226	$500	Y
20	Injection, Nivolumab	Physican Administered Drug	$112,396	0.9%	59	$1,905	
21	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$108,168	0.9%	1,740	$62	Y
22	ADVAIR DISKUS	Corticosteroids/LABA Combination, Inhaled	$106,726	0.9%	371	$288	Y
23	LANTUS	Diabetes, Insulins	$106,641	0.9%	303	$352	Y
24	ORKAMBI*	Cystic Fibrosis	$104,895	0.8%	11	$9,536	N
25	Etonogestrel Implant System	Physican Administered Drug	$102,358	0.8%	169	$606	
26	VENTOLIN HFA	Beta-Agonists, Inhaled Short-Acting	$101,862	0.8%	1,872	$54	Y
27	CONCERTA*	ADHD Drugs	$94,068	0.8%	507	$186	N
28	Drugs Unclassified Injection	Physican Administered Drug	$93,805	0.8%	6,302	$15	
29	Aflibercept Injection	Physican Administered Drug	$92,072	0.7%	173	$532	
30	Rituximab Injection	Physican Administered Drug	$91,116	0.7%	53	$1,719	
31	NUVARING	STC 63 - Oral Contraceptives	$89,118	0.7%	402	$222	
32	PULMOZYME	Cystic Fibrosis	$87,723	0.7%	49	$1,790	Y
33	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$87,198	0.7%	45	$1,938	
34	VYVANSE*	ADHD Drugs	$87,030	0.7%	588	$148	Y
35	TRUVADA	HIV	$86,501	0.7%	71	$1,218	Y
36	FLOVENT HFA	Corticosteroids, Inhaled	$83,887	0.7%	500	$168	Y
37	TRIUMEQ	HIV	$83,128	0.7%	36	$2,309	Y
38	Mirena, 52 Mg	Physican Administered Drug	$82,416	0.7%	146	$564	
39	Arsenic Trioxide Injection	Physican Administered Drug	$78,508	0.6%	65	$1,208	
40	LEVEMIR FLEXTOUCH*	Diabetes, Insulins	$74,344	0.6%	140	$531	Y
		Top 40 Aggregate:	**$5,463,924**		**16,976**	**$4,987**	
		All FFS Drugs Totals:	**$12,449,267**		**196,056**	**$497**	

*** Drug requires Prior Authorization**

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

Last updated: October 24, 2018

ProDUR Report for July through September 2018
High Level Summary by DUR Alert

DUR Alert	Description (major only)	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Sets if there is an association between an ingredient being billed and an allergy recorded in the recipient profile.	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	9	3	0	5	0.02%	33.33%
DC (Drug/Inferred Disease Interaction)	Sets if there is a drug on the recipients profile that is indicated for a disease state that interacts with the drug being filled.	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,547	325	4	1,211	1.43%	21.01%
DD (Drug/Drug Interaction)	Sets if there is an interaction between the drug being filled and another drug on the recipients profile.	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	122	23	0	97	0.10%	18.85%
ER (Early Refill)	Sets if the drug being billed is too early based on previous billing and days supply. Allow filling when 80% of previous fill has been used.	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	74,980	13,992	260	60,680	68.20%	18.66%
ID (Ingredient Duplication)	Sets if the drug being filled has a matching ingredient to another recently filled drug on the recipients profile.	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	23,662	6,096	61	17,431	21.57%	25.76%
LD (Low Dose)	Sets if the drug being billed, based on billed days supply, is below the minimum recommended daily quantity limit.	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	713	129	0	579	0.60%	18.09%
LR (Late Refill/Underutilization)	Sets if the drug being filled is late in being refilled for the recipient based on 125% of previous day supply billed	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	5	3	0	2	0.01%	60.00%
MC (Drug/Disease Interaction)	Sets if there is a disease Diagnosis (ICD-10) on the recipients claim profile that interacts with the drug being filled.	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	955	289	0	666	0.83%	30.26%
MX (Maximum Duration of Therapy)	Sets if the days supply on the claim is greater than the maximum days value.		Set alert/Pay claim	647	176	3	466	0.57%	27.20%
PG (Pregnancy/Drug Interaction)	Sets if the drug being filled is contraindicated for use in pregnancy and the patient profile indicates that the patient may be pregnant.	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	39	25	0	14	0.02%	64.10%
TD (Therapeutic Duplication)	Sets if the specific therapeutic class of drug being billed matches the drug class of another recently filled medication on the recipients profile.	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,081	2,025	7	5,009	6.47%	28.60%
			Totals	**109,760**	**23,086**	**335**	**86,160**	**99.82%**	**21.03%**

ProDUR Report for July through September 2018

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	857	137	720	7,423	11.5%	16.0%
ER	Hydrocodone/APAP	26	4	22	2,123	1.2%	15.4%
ER	Oxycodone	44	18	26	1,467	3.0%	40.9%
ER	Oxycodone/APAP	10	2	8	691	1.4%	20.0%
ER	Tramadol	31	9	22	598	5.2%	29.0%
ER	Buspirone (Buspar)	1,535	250	1,285	15,480	9.9%	16.3%
ER	Lorazepam	404	97	307	10,264	3.9%	24.0%
ER	Alprazolam	276	53	223	6,722	4.1%	19.2%
ER	Diazepam	162	41	121	3,746	4.3%	25.3%
ER	Lamictal (Lamotrigine)	2,934	561	2,372	23,830	12.3%	19.1%
ER	Abilify (Aripiprazole)	1,725	274	1,449	14,030	12.3%	15.9%
ER	Seroquel (Quetiapine)	2,254	422	1,830	16,669	13.5%	18.7%
ER	Risperdal (Risperidone)	1,335	285	1,045	9,273	14.4%	21.3%
ER	Wellbutrin (Bupropion)	2,899	471	2,428	32,244	9.0%	16.2%
ER	Zoloft (Sertraline)	3,710	659	3,050	35,453	10.5%	17.8%
ER	Prozac (Fluoxetine)	2,396	377	2,017	27,786	8.6%	15.7%
ER	Celexa (Citalopram)	1,587	216	1,371	18,768	8.5%	13.6%

ProDUR Report for July through September 2018
Early Refill Reason Codes

DUR Alert	3Q2018	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Totals =	8,145	334	599	2,121	7	5,084	0

Drug Use Research & Management Program
Oregon State University
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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Duloxetine 40mg caps to 2x20mg	Unique Prescribers Identified			125	
		Unique Patients Identified			148	
		Prescriptions Changed to Recommended Within 6 Months of Intervention			40	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention			$8,328	
	Fluoxetine Tabs to Caps	Unique Prescribers Identified			740	
		Unique Patients Identified			1100	
		Prescriptions Changed to Recommended Within 6 Months of Intervention			447	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention			$42,412	
	Lamotrigine ER to IR	Unique Prescribers Identified	324			
		Unique Patients Identified	645			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	142			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$147,523			
	QVAR to fluticasone	Unique Prescribers Identified	400			
		Unique Patients Identified	463			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	64			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	($7,927)			

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
	Venlafaxine Tabs to Caps	Unique Prescribers Identified		585		533
		Unique Patients Identified		807		717
		Prescriptions Changed to Recommended Within 6 Months of Intervention		340		178
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$384,491		$44,746

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	189	120	89	76
		Total Faxes Successfully Sent	75	46	52	44
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	34	47	20	6
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	27	16	7	5
		Prescriptions Unchanged after 3 Months of Fax Sent	96	37	45	22
		Safety Monitoring Profiles Identified	14	18	16	12
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$140,152	$246,829	$83,281	$8,941

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	49	25	33	24
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	8	1	5	5
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	49	27	21	28
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5	4	2	6
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed	6	15		12
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed				9
		RetroDUR_Letters Sent To Providers				1
		Provider Responses				1
		Provider Agreed / Found Info Useful				0
	Lock-In	RetroDUR_Profiles Reviewed	26	37	26	7
		RetroDUR_Letters Sent To Providers	1	5	2	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
		Locked In	1	5	2	0
	Polypharmacy	RetroDUR_Profiles Reviewed	33	53	157	84
		RetroDUR_Letters Sent To Providers	5	7	26	25
		Provider Responses	0	0	4	1
		Provider Agreed / Found Info Useful	0	0	2	0

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	ICS/LABA	Disqualified	25	23	26	24
		Disqualified - Erroneous denial	25	23	26	24
		Faxes Sent	5	3	6	10
		Fax Sent - SABA	1	1	2	5
		Fax Sent - Controller	2	2	1	
		Fax Sent - Combination Inhaler	2		2	1
		No Subsequent Pulmonary Claims			1	4

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Update on Treatment Options for Moderate to Severe Atopic Dermatitis

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Atopic dermatitis (AD) is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation.[1] Other clinical features may include xerosis, erythema, erosions, oozing, and lichenification of the skin. The cause is unknown, but may be due immunologic dysfunction.[2] Atopic dermatitis affects 15-20% of children in developed countries and approximately 11% of children in the United States (U.S.).[3,4] The estimated prevalence of AD in U.S. adults is 3%.[3] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life for people with AD.[5] The purpose of this newsletter is to review recently approved treatments for mild to moderate AD (crisaborole) and moderate to severe AD (dupilumab) and to evaluate their place in therapy for AD.

Policy

In the Oregon Health Plan, the Health Evidence Review Commission (HERC) recently modified conditions funded on line 424 (moderate/severe inflammatory skin disease) to include psoriasis, AD, lichen planus, Darier disease, pityriasis rubra pilaris and discoid lupus.[6] Prior to this update, AD treatment was not funded. Guideline Note 21 defines severe inflammatory skin disease as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: 1) at least 10% of body surface area involved; and/or 2) hand, foot or mucous membrane involvement.[6] Due to these recent changes to the HERC prioritized list, moderate to severe AD became a funded condition effective January 1, 2018. Mild AD is classified on line 530 and will therefore remain unfunded.[6]

Initial Treatment

The mainstays of therapy for AD are skin care with frequent application of an emollient to maintain the skin's epidermal barrier and avoidance of triggers. For patients with mild AD, initial treatment with a mild potency topical corticosteroid (TCS) applied 1-2 times a day for 2 to 4 weeks is recommended.[7] For moderate AD, short-term use of a medium to high potency TCS is recommended. Topical calcineurin inhibitor (TCIs) are nonsteroidal immunomodulating agents that are considered a second-line option in both adults and children with AD who have not responded to TCS or when those treatments are not advisable.[8,9] Tacrolimus 0.03% ointment and pimecrolimus cream are indicated for use in individuals age 2 years and older, whereas tacrolimus 0.1% ointment is only approved in those older than 15 years.[8,9]

The use of TCS and TCI therapies in AD is supported by the American College of Dermatology's 2014 guideline[7] and 2004 guidance from the National Institute for Health and Care Excellence (NICE).[10] Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of TCS can result in telangiectasia, increased hair, skin tears, and atrophic skin changes, which can be permanent.[11] The main rationale for use of TCIs is that they do not cause skin atrophy and are therefore of particular value in delicate skin areas such as the face, neck, and skin folds.[7]

A systematic review and meta-analysis was compiled by the Drug Effectiveness Review Project (DERP) to evaluate the effectiveness of TCIs.[12] Four fair quality head-to-head trials of tacrolimus ointment (0.03% or 0.1%) versus pimecrolimus 1% cream in patients with moderate to severe AD have been published.[13-16] All 4 trials reported response to treatment, with 3 trials using an Investigator Global Assessment (IGA) score of 0 or 1 to indicate disease clearing, while the 4th open label trial did not describe the method of determining treatment success. Improvements in the percent of body surface area affected by AD varied widely across the studies, from a 64.6% reduction with tacrolimus in one study down to a 7% improvement with tacrolimus in another study.[12] Common adverse reactions for TCIs are burning or stinging, itching, and erythema or irritation, with a similar incidence for pimecrolimus and tacrolimus.

The U.S. Food and Drug Administration (FDA) labeling for tacrolimus and pimecrolimus include boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with long-term TCI administration.[8,9] Therefore, continuous long-term use of TCIs in any age group should be avoided and application limited to areas of AD involvement.[8,9]

Pimecrolimus and tacrolimus are recommend after trial of first line therapies for moderate to severe AD and are preferred agents on the Oregon Health Plan preferred drug list (PDL)

New Treatments for Atopic Dermatitis

Two additional agents with novel mechanisms of action have recently been added to AD treatment algorithms. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor approved for mild-to-moderate AD in adults and children. PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity is increased in AD.[17] Crisaborole is available as an ointment that is applied twice daily.

To date, there are only 3 short-term trials of crisaborole, all compared to placebo in patients with mild to moderate AD.[18,19] A good quality systematic review compiled by the Institute for Clinical and Economic Review (ICER) evaluated the 3 studies.[17] Two 4-week studies similar in design enrolled children (n = 1522) with mild to moderate AD (39% mild), with 18% body surface area affected.[18] The other trial enrolled adults (n = 25) for 6 weeks and compared crisaborole with placebo.[19] Modest improvement was observed by investigators in more pediatric patients using crisaborole than placebo in erythema, exudation, excoriation, induration/papulation and lichenification.[18] In these trials there were no serious adverse events reported, and very few patients withdrew due to adverse events. Application site pain was the most common adverse event reported (crisaborole 4.6% vs. placebo 1.7%).[12] The other adverse events reported in the trials were not different between groups. No studies have evaluated crisaborole

with TCI or TCS formulations to assess comparative efficacy or harms.

The second new therapy approved by the FDA for systemic management of AD is dupilumab. Dupilumab is an injectable interleukin (IL)-4 receptor antagonist approved for use in adults with moderate to severe AD not controlled with topical therapy.[20] Binding the interleukin-4 receptor by dupilumab results in inhibition of IL-4 and IL-13 signaling which alters cell mediated immune responses and improves epidermal barrier abnormalities in AD.[21] Dupilumab therapy is initiated with a 600 mg subcutaneous (SC) injection loading dose followed by 300 mg SC every other week.[20]

In clinical trials, a 5-point Investigator Global Assessment (IGA) scale ranging from 0 (clear) to 4 (severe) was used to assess changes in the severity of skin lesions. In 2 placebo-controlled trials, the number of patients with clear or almost clear with at least a 2 point reduction in the Investigator Global Assessment (IGA) scale was higher with dupilumab every other week and weekly compared with placebo with an absolute risk reduction (ARR) of 27-28% and a number needed to treat (NNT) of 4.[22] A trial comparing dupilumab plus a TCA to placebo in adult patients with moderate to severe AD found the combination to be more effective than placebo (ARR 27%/NNT 4).[23] The most common adverse reactions were injection site reactions and conjunctivitis.[20] Limitations of the dupilumab trials include: 1) insufficient duration of the trials to assess long-term safety and 2) the trials only enrolled adults, although AD is more prevalent in children.

Safety and efficacy of dupilumab in pediatric patients has not been established, although trials are currently being conducted in this population. Clinical trials are currently underway with other biologics including ustekinumab, secukinumab, and apremilast to assess their efficacy in treating patients with moderate to severe AD.[1] **Table 1** summarizes the mechanism, dosage form and FDA approved populations for the 4 second-line drugs FDA-approved to treat AD after first line therapy with TCS has failed or is contraindicated.

Table 1. Drug Information for Second-Line Atopic Dermatitis Therapeutic Agents

Generic Name	Trade Name	Mechanism	Dosage Form	FDA-Approved Population
Crisaborole	Eucrisa™	PDE4 inhibitor	Ointment	Mild to moderate AD
Pimecrolimus	Elidel®	Calcineurin inhibitor	1% Cream	Mild to moderate AD
Tacrolimus	Protopic®	Calcineurin inhibitor	0.03% and 0.1% Ointment	Moderate to severe AD
Dupilumab	Dupixent®	Monoclonal antibody	Subcutaneous Injection	Moderate to severe AD

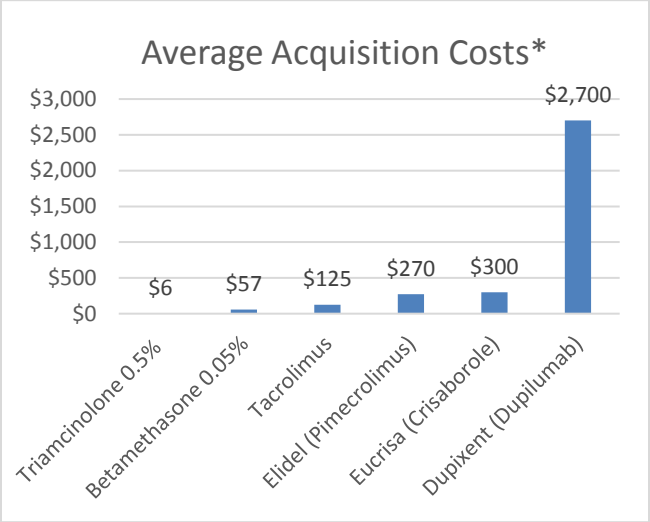
Abbreviations: AD = Atopic Dermatitis; FDA = Food and Drug Administration; PDE4 = Phosphodiesterase 4

Conclusion

In conclusion, first line pharmacologic therapy for AD is topical steroids. If TCS therapy is not effective or contraindicated, TCI therapy should be initiated. Crisaborole is a possible alternative to TCS or TCI treatments for patients with mild to moderate AD. For patients with moderate to severe AD unresponsive to topical therapy or systemic therapy with immunomodulators (i.e. cyclosporine, methotrexate, or azathioprine), dupilumab has proven efficacy in managing AD symptoms, although long-term safety has not been adequately evaluated.

The Fee-For-Service (FFS) PA criteria for TCIs and crisaborole requires: 1) documentation of functional impairment due to moderate or severe AD and 2) documented contraindication, intolerance or failed trial of at least 2 first line agents indicated for treatment of moderate to severe AD (topical steroids). The FFS PA criteria for dupilumab requires: 1) documentation of moderate to severe AD, 2) patient age ≥ 18 years, and 3) trial of at least 2 first line therapies for moderate to severe AD including moderate to high potency TCS, phototherapy, TCIs, or oral immunomodulators.

Table 2: Comparative Monthly Costs of Atopic Dermatitis Treatments



*Based on commonly prescribed maintenance doses as of July 2018

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Management Strategies for Patients with Prediabetes

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Introduction

The term prediabetes refers to a gray zone that includes patients with mild abnormalities of glucose tolerance who do not meet criteria for diabetes. There is no consensus on how to define this population, or what to call them. Terms include prediabetes, impaired fasting glucose, intermediate hyperglycemia, impaired glucose regulation, or high risk of diabetes. [1] Prediabetes is considered to be an impaired fasting glucose (IFG) of 100-125 mg/dL or a hemoglobin A1c (HbA1c) 5.7 to 6.4%.[2] A 2017 report from the Centers for Disease Control (CDC) cited the incidence of prediabetes in the United States to be more than 84 million people, based on 2015 data.[3] Pharmacotherapies have been promoted for the delay or prevention of type 2 diabetes mellitus (T2DM) in individuals with prediabetes without strong evidence. The purpose of this newsletter is to discuss evidence regarding management strategies of patients with prediabetes.

Delaying or preventing the onset of T2DM is desirable. However, there is no evidence that treatment of prediabetes with medication reduces or prevents mortality or any complications of diabetes.[4,5] The course of prediabetes is variable. The development of T2DM is dependent on a variety of risk factors. Positive family history, gestational diabetes, obesity, ethnicity, polycystic ovarian syndrome, impaired insulin secretion and insulin resistance, and elevated glucose levels have been shown to contribute to the increased risk.[2,4] Some patients with prediabetes will convert to normal glucose levels without lifestyle or pharmacotherapy interventions.[6] Guidelines recommend yearly screenings for T2DM in patients with prediabetes based on expert opinion.[2]

Lifestyle Modifications

Studies have shown that changes in lifestyle, such as diet modification, weight loss, and exercise, can slow the progression to diabetes in patients with impaired glucose tolerance (IGT).[4] Benefits of lifestyle changes have been shown to persist beyond the initial intervention for up to 20 years.[2,7] The Diabetes Prevention Program (DPP) studied overweight patients with IGT randomized to lifestyle interventions versus metformin, as well as both interventions versus placebo, over a mean follow up duration of 2.8 years.[7] The incidence of diabetes, based on cases per 100 person-years, was 11 for placebo, 7.8 for metformin and 4.8 for the lifestyle intervention group. The reduction in risk was statistically significantly more for the lifestyle intervention group compared to metformin. The Diabetes Prevention Program Outcomes Study (DPPOS) was an open label 15-year follow-up on the DPP study.[8] DPPOS found the incidence of diabetes to be reduced by 27% in the lifestyle intervention group compared to 18% in patients taking metformin.

A meta-analysis done by the CDC found that combined diet and physical activity interventions compared to usual care reduced the incidence of T2DM (risk ratio [RR] 0.59; 95% confidence interval [CI], 0.52 to 0.66), decreased body weight (-2.2%; 95% CI, -2.9% to -1.4%) and decreased fasting blood glucose levels (-2.2 mg/dL; 95% CI, -3.6 to -0.9 mg/dL).[9] A Cochrane systematic review and meta-analysis studied the effects of diet, physical activity, or both for prevention or delay of T2DM and its complications in people at increased risk.[10] Twelve trials of 5,238 patients were included. Combinations of diet and exercise interventions in individuals with IGT were found to prevent or delay T2DM based on moderate evidence (RR 0.57; 95% CI, 0.50 to 0.64). The evidence for diet alone or physical activity alone was not conclusive. A separate meta-analysis of 28 prospective cohort studies demonstrated a 26% reduced risk of developing diabetes with 150 min/week of moderate activity compared to those individuals who were inactive.[11]

Pharmacotherapy

Evidence suggests that metformin is more effective than placebo in reducing the transition from prediabetes to T2DM.[7] A systematic review and meta-analysis of patients taking metformin, who were at risk of developing diabetes, identified 31 trials of at least 8 weeks in duration. The risk of new-onset diabetes was reduced with metformin compared to placebo or no treatment (OR 0.60; 95% CI, 0.5 to 0.8; absolute risk reduction 6% over 1.8 years).[12] The absolute risk with or without treatment was not analyzed and would be helpful to determine if the benefit of drug therapy outweighed the potential risk of adverse events. As reviewed previously, the DDP trial found a benefit of metformin compared to placebo in delaying T2DM in patients with prediabetes; however it was inferior to lifestyle modifications.[7] Additionally, patients 60 years and older were found to only derive benefit from lifestyle changes and no benefit was associated with metformin.

Liraglutide was compared to placebo for T2DM risk reduction as an adjunct to diet and exercise.[13] Liraglutide 3 mg once daily was studied in a double-blind, placebo-controlled, randomized trial of adults with prediabetes, a body mass index of 30 kg/m^2, or a body mass index of 27 kg/m^2 with comorbidities. At 3 years, 2% of patients treated with liraglutide compared to 6% of placebo treated patients were diagnosed with T2DM (CI and p-values not provided).[13] Therefore, greater than 90% of patients did not develop diabetes, and had no benefit from treatment. Patients in the liraglutide group also lost a mean difference of -4.3 kg (95% CI, -4.9 to -3.7, $p<0.001$) compared to placebo. Liraglutide was also associated with more serious adverse events, 15% vs. 13%, respectively (p-value not reported), most commonly cholelithiasis, cholecystitis acute, and osteoarthritis.[13]

A 2016 Cochrane review evaluated the evidence for insulin secretagogues for the prevention and delay of developing T2DM; however, evidence was insufficient to draw any meaningful conclusions.[14] A second Cochrane review studied glycoprotein-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors for prevention of T2DM in patients at increased risk. There was no conclusive evidence that DPP-4 inhibitors or GLP-1 RAs prevent progression to diabetes when compared to placebo (based on low quality evidence).[15]

Guideline Recommendations

The National Institute for Health and Care Excellence (NICE) published guidance in 2012 for the prevention of T2DM in patients who are high risk.[16] NICE recommends that patients determined to be at high risk (i.e. prediabetic) should be referred to an intensive lifestyle change program. Metformin, in addition to lifestyle modifications, is recommended for patients at high risk with worsening HbA1c or fasting plasma glucose levels when lifestyle modifications alone have failed or they are unable to participate in an intensive lifestyle change program. Yearly follow-up on glucose levels should also be assessed.

Limitations

The majority of evidence on the prevention of T2DM in individuals who have prediabetes is of low quality and does not provide evidence of a mortality benefit or prevention of complications. Observational and cohort studies are the source of most of the evidence, with limited evidence from randomized controlled trials. The use of varying definitions of prediabetes also prevents pooling data and drawing strong conclusions on findings.

There are no Food and Drug Administration (FDA) approved medications for the management of prediabetes. No pharmacotherapy has proved to be more effective than lifestyle modifications in the prevention of progression from prediabetes to T2DM. With the use of any pharmacotherapy, the risk of adverse events must be balanced with the potential benefit. Despite improvement in surrogate outcomes, there is no evidence of morbidity or mortality benefits of lifestyle or pharmacotherapy interventions in patients with prediabetes.

Oregon Health Plan Fee-For-Service Policy

OHP FFS does not recommend drug treatment for patients with prediabetes

Patient Resources

The CDC created the National Diabetes Prevention Program (National DPP) to provide lifestyle management programs to individuals at high risk of T2DM.[3] A descriptive analysis of the program found 35% of participants achieved a goal of 5% weight loss and 41.8% met the goal of 150 minutes of physical activity a week.[17] More information on the National DPP can be found at: https://www.cdc.gov/diabetes/prevention/index.html.

Key Take Home Points

- There is a lack of high quality evidence on preventing or delaying T2DM in patients with prediabetes
- Lifestyle changes are the most appropriate option in individuals with prediabetes to prevent the transition to overt T2DM

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Drug Class Review: Severe Acne

Date of Review: November 2018 **End Date of Literature Search:** 08/28/2018

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

Purpose for Class Review:
To evaluate evidence for medications used in the treatment of severe cystic acne as requested by the Health Evidence Review Commission (HERC). In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, acne has historically been an unfunded condition with the exception of acne conglobata.[1] However, as of January 1, 2019, acne fulminans will be a covered condition, and as of January 1, 2020, severe cystic acne will also be a covered condition.[2]

Research Questions:
1. What is the comparative efficacy and effectiveness of treatments for severe acne (topical agents such as adapalene, adapalene/benzoyl peroxide, tretinoin, tazarotene, benzoyl peroxide, salicylic acid, dapsone, azelaic acid, clindamycin, erythromycin, sulfacetamide; oral systemic antibiotics such as doxycycline, minocycline, tetracycline, azithromycin, erythromycin, clindamycin, trimethoprim, and sulfamethoxazole/trimethoprim; hormonal agents such as oral contraceptives and spironolactone; and oral isotretinoin)?
2. What are the comparative harms of treatments for severe acne?
3. Are there subpopulations of patients in which a particular treatment for severe acne would be more effective or associated with less harm?

Conclusions:
- This drug class review is limited by the lack of high quality evidence from high quality systematic reviews and guidelines which evaluate the comparative efficacy and safety of treatments for severe acne. There are also limited randomized controlled trials in the severe acne population and the majority of the trials are older with methodological and conflict of interest concerns.
- There is insufficient evidence to determine comparative efficacy and safety of treatments for severe acne.
- There is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for severe acne.
- Though not of high methodological quality due to conflict of interest concerns, recent guidelines from the American Academy of Dermatology, European Academy of Dermatology and Venereology, and American Academy of Pediatrics recommend multiple treatment options for severe acne, all including isotretinoin.[3-5] Other recommended treatments include combination therapy with systemic antibiotics and topical therapies such as benzoyl peroxide, retinoids, or topical antibiotics.[3-5] Recommendations for treatment of mild to moderate acne generally includes the same therapies, either as monotherapy or in differing combinations, but isotretinoin is generally not recommended until acne is severe.[3-5]
- Isotretinoin has substantial safety concerns compared to other medications for acne.[6] There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin. Because of the teratogenicity risk, it is approved for marketing only under a REMS program called iPLEDGE™.[6]

Recommendations:

- Implement prior authorization (PA) criteria for the Acne preferred drug list (PDL) class, which contains federal legend topical medications that have an FDA-approved and OHA-funded indication for severe acne vulgaris as well as oral isotretoin, to limit use to funded conditions (**Appendix 5**).
- Designate at least one formulation of the following medications/classes as a preferred agent on the PDL due to guideline support for use in severe acne: oral isotretinoin, topical benzoyl peroxide, topical retinoid (adapalene or tretinoin), and topical antibiotics.
- Evaluate comparative costs in executive session.

Background:

Acne is a chronic inflammatory disease of the skin which affects approximately 50 million patients in the United States and around 85% of patients 12-24 years of age.[7,8] Acne may also persist into adulthood.[5,9] Pathogenic factors include androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles by *Propionibacterium acnes*.[10] Pathogenesis may also be influenced by family history, diet, and other factors.[5,7,10] Acne is characterized by seborrhea, non-inflammatory and inflammatory lesions, and scarring and is commonly located on the face (majority of cases), neck, chest, and back.[10] Acne, particularly severe acne, may result in permanent scarring and psychological morbidity such as poor self-esteem, depression, and anxiety.[5,11]

There is currently no universal acne classification system, but acne is commonly classified as mild, moderate, or severe.[5] Assessment tools may include factors such as type of acne, number of lesions, anatomic location, quality of life, and scarring.[5] A consensus statement from the Journal of the American Academy of Dermatology in 1990 defines severe acne as the presence of any of the following: persistent or recurrent inflammatory nodules, extensive papulopustular disease, ongoing scarring, persistent purulent and/or serosanguineous drainage from lesions, or presence of sinus tracks.[12] Moderate-to-severe acne is thought to affect around 20% of young patients.[7] Acne conglobata and acne fulminans are two forms of severe acne. Acne conglobata is a severe form of nodular acne which involves recurrent abscesses and communicating sinuses.[13] Acne fulminans is a severe variant of inflammatory acne characterized by an explosive onset of painful erosions and hemorrhagic crusts that lead to severe and often disfiguring scars.[14] Systemic systems such as fever and arthralgias may also be present with acne fulminans.[13,14]

Treatment for acne may include a variety of agents such as topical medications (i.e. retinoids, benzoyl peroxide, topical antibiotics, salicylic acid, azelaic acid, sulfacetamide), systemic antibiotics (i.e. doxycycline, minocycline, erythromycin, azithromycin, clindamycin, trimethoprim), hormonal agents (i.e. oral contraceptives, spironolactone, antiandrogens), and oral isotretinoin.[3-5] Choice of treatment depends on severity of disease, with isotretinoin specifically FDA-approved for severe recalcitrant nodular acne and recommended for severe acne.[3-6] Other treatments for severe acne usually include combination therapy with multiple classes of medications which can also be used for mild or moderate acne.[3-5] Recent guidelines for acne are discussed in detail later in this review. These classes of medications are well-established and all have been FDA-approved for many years. Isotretinoin was initially approved in 1982.[6] Selected medications with FDA-approved indications or common off-label use for acne are further described in **Table 1**.

Clinically meaningful outcomes for acne assessment include quality of life and symptom reduction as demonstrated by lesion counts or acne severity. Though there seems to be no universally determined minimal clinically important difference for these outcomes, a consensus view of the authors of the European Evidence-Based Guidelines for Treatment of Acne suggested a minimal clinically important difference of 10% greater reduction in number of lesions for a treatment to demonstrate superior efficacy.[4]

In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, acne has historically been an unfunded condition with the exception of acne conglobata.[1] However, as of January 1, 2019, acne fulminans will be a covered condition and as of January 1, 2020, severe cystic acne will also be a covered condition.[2,15] In the OHP FFS population, there are approximately 7,598 patients with a diagnosis of acne vulgaris (L70.0) and 56 patients with a diagnosis of acne conglobata (L70.1), the only severe form of acne with its own ICD-10 code.

Current OHP FFS policy management (beyond PDL status) of medications which can be used for acne (**Table 1**) includes the following:

- Oral tetracyclines: quantity limit of two 14 day supplies in a 3 month timeframe; PA required to ensure FDA-approved and OHP-funded diagnosis for requests over the quantity limit
- Topical tazarotene cream and gel: PA is required. The PA is focused on psoriasis and atopic dermatitis indications, but requests for acne would require that the diagnosis is funded by OHP.

A summary of relevant drug information for topical agents and isotretinoin (which make up the Acne PDL class) is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Acne Indications and Dosing[6,16]

Drug Name (Brand Name)	Acne Indication: FDA-Approved or Off-Label?	Acne Formulations	Acne Dosing
		TOPICAL AGENTS	
Adapalene (Differin)	FDA-approved for acne	• Cream • Gel • Lotion	Apply once daily
Adapalene/benzoyl peroxide (Epiduo; Epiduo Forte)	FDA-approved for acne	• Gel	Apply once daily
Azelaic acid (Azelex)	FDA-approved for acne	• Cream	Apply twice daily
Benzoyl peroxide (many brand names)	FDA-approved for acne	• Bar • Cream • Foam • Gel • Kits (miscellaneous formulations) • Liquid • Extended release liquid • Lotion • Foaming cloths	Topical formulations: apply once daily; gradually increase to 2-3 times/day if needed Topical cleansers: wash once or twice daily
Clindamycin (Cleocin T; ClindaMax; Clindagel, Evoclin)	FDA-approved for acne	• Foam • Gel • Lotion • Solution	-Gel (Cleocin; ClindaMax), lotion, solution: apply twice daily -Gel (Clindagel), foam (Evoclin): apply once daily
Dapsone (Aczone)	FDA-approved for acne	• Gel	-5%: apply twice daily -7.5%: apply once daily
Erythromycin (Ery; Erygel)	FDA-approved for acne	• Gel	-Gel: apply once or twice daily

		• Pad • Solution	-Ointment, pads: apply twice daily
Sulfacetamide (Klaron)	FDA-approved for acne	• Lotion	Apply twice daily
Tazarotene (Fabior; Tazorac)	FDA-approved for acne	• Cream • Foam • Gel	Apply once daily
Tretinoin (Atralin; Avita; Refissa; Renova; Renova Pump; Retin-A; Retin-A Micr; Retin-A Micro Pump)	FDA-approved for acne	• Cream • Gel	Apply once daily
ORAL SYSTEMIC ANTIBIOTICS			
Azithromycin (Zithromax; Zithromax Tri-Pak; Zithromax Z-Pak; Zmax)	Used off-label for acne	• Packet • Suspension reconstituted • Tablet	As adjunct to topical acne therapy: regimens in clinical trials have varied greatly but all used pulse-dosing regimens. Use shortest duration possible to minimize development of bacterial resistance.
Doxycycline (Acticlate; avidoxy; Doryx; Doryx MPC; Monodoxyne NL; Morgidox; Okebo; Oracea; Soloxide; TargaDOX; Vibramycin)	Used off-label for acne	• Capsule as hyclate • Capsule as monohydrate • Capsule delayed release as monohydrate • Kit as hyclate • Suspension reconstituted as monohydrate • Syrup as calcium • Tablet as hyclate • Tablet as monohydrate • Tablet delayed release as hyclate	-Immediate release: 50-100 mg twice daily or 100 mg once daily -Extended release: 100 mg twice daily on day 1, then 100 mg once daily
Erythromycin (E.E.S 400, E.E.S. Granules; Ery-Tab; EryPed 200; EryPed 400; Erythrocin Stearate)	Used off-label for acne	• Capsule delayed release particles as base • Suspension reconstituted as ethylsuccinate • Tablet as base • Tablet as ethylsuccinate • Tablet as stearate • Tablet delayed release as base	250-500 mg (base) twice daily initially, followed by 250-500 mg (base) once daily
Minocycline (Minocin; Ximino)	FDA-approved for acne and inflammatory, non-nodular, moderate to severe acne	• Capsule • Capsule extended release • Tablet	Acne: 50-100mg twice daily Acne (inflammatory, non-nodular, moderate to severe): -Extended-release capsule: 1 mg/kg once daily -Extended-release tablet: weight-based (various strengths)
Tetracycline	FDA-approved for acne	• Capsule	Initial dose 1 g daily in divided doses; reduce gradually to 125-500 mg/day once improvement noted
Trimethoprim (Primsol; Trimpex)	Used off-label for acne	• Solution • Tablet	100 mg 3 times daily or 300 mg twice daily
HORMONAL AGENTS			
Oral contraceptives	FDA-approved for acne	• Various	Usual dosing: once daily

	(varies by formulation)		
Spironolactone (Aldactone, CaroSpir)	Used off-label for acne	• Suspension • Tablet	Females: 50-200 mg once daily
ORAL ISOTRETINOIN			
Isotretinoin (Absorica; Amnesteem; Claravis; Myorisan; Zenatane)	FDA-approved for severe recalcitrant nodular acne	• Capsule	0.5 to 1 mg/kg/day in 2 divided doses for 15-20 weeks; may discontinue earlier if total cyst count decreases by >70%; may require adjustment up to 2 mg/kg/day for adults with very severe disease/scarring or primarily involves the trunk

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls 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:
Cochrane Collaboration – Minocycline
In 2012, the Cochrane Collaboration published an update to a 2000 systematic review assessing the efficacy and safety of minocycline in acne vulgaris.[17] This review identified 39 RCTs.[17] In general, it was found that minocycline is an effective treatment for moderate to moderately-severe acne vulgaris, but there is a lack of evidence to show superiority over other treatments.[17] Of the 39 trials, 24 included patients with severe acne but only three trials included severe acne exclusively.[17] Two of the three trials in severe acne compared minocycline to oral isotretinoin.[17] Both of these trials were open-label and of poor quality.[17] The third trial in severe acne was a fair quality double-blind 12 week RCT which compared minocycline 100 mg daily to doxycycline 100 mg daily.[17] Both groups in the trial also received 5% salicylic acid/5% resorcinol topically twice a day.[17] No difference was found between the two groups in change in overall symptom score from baseline, but the data is limited by the low number of participants (n=18).[17]

After review, 16 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), population studied (non-severe acne), or outcome studied (e.g., non-clinical).[18-33]

Guidelines:
High Quality Guidelines:
None identified.

Additional Guidelines for Clinical Context:

American Academy of Dermatology: Acne Vulgaris

In 2016, the American Academy of Dermatology published an updated guideline for the management of acne vulgaris.[5] Based on conflict of interest methodology, this guideline is not of high quality as one of the two co-chairs has served on an advisory board for four pharmaceutical companies, receiving honoraria and also served as a consultant for a fifth pharmaceutical company, receiving honoraria.[5] Less than half of the work group (10/22 members) had no relevant relationships to disclose.[5]

Recommendations for treatment of severe acne are outlined in **Table 2**.[5]

Table 2. American Academy of Dermatology Severe Acne Treatment Recommendations[5]

1st line treatment	Oral Antibiotic (tetracyclines generally recommended first-line) + Topical combination therapy (fixed combination or separate products for one of the following): • Benzoyl peroxide + antibiotic • Retinoid + benzoyl peroxide • Retinoid + benzoyl peroxide + antibiotic OR Oral isotretinoin
Alternative treatment	Consider change in oral antibiotic OR Add combined oral contraceptive or oral spironolactone (females) OR Consider oral isotretinoin

For mild and moderate acne, treatment options generally include all of the same agents recommended for severe acne alone or in different combinations.[5] Oral isotretinoin is the only unique agent recommended as first-line therapy for severe acne but not recommended first-line for mild or moderate acne, though it may be considered as an alternative treatment for moderate acne.[5] Recommendations for isotretinoin specifically include:

- Isotretinoin is a recommended treatment option for severe nodular acne.[5]
- Isotretinoin is appropriate for treatment of treatment-resistant moderate acne or management of acne producing physical scarring or psychosocial distress.[5]
- Low-dose isotretinoin can be effective in acne treatment and reduce frequency and severity of side effects.[5] Intermittent dosing is not recommended.[5]
- Routine monitoring is recommended for liver function tests, serum cholesterol, and triglycerides at baseline and until response to treatment is established.[5] Routine complete blood count monitoring is not recommended.[5]
- All patients must adhere to iPLEDGE™ risk management program.[5]
- Females of child-bearing potential should be counseled on contraceptive methods.[5]
- Patients should be educated on potential risks of therapy and monitored for indications of inflammatory bowel disease and depressive symptoms.[5]

Journal of the European Academy of Dermatology and Venerology: Acne

In 2012, the Journal of the European Academy of Dermatology and Venerology published the European Evidence-based Guidelines for the Treatment of Acne.[4] Based on conflict of interest methodology, this guideline is not of high quality as no conflict of interest mitigation strategies are documented for the creation of the guideline.[4] Additionally, the guideline was funded by the European Dermatology Forum (EDF), which has several pharmaceutical manufacturers listed as corporate partners, and the role of the funding source was not documented.[4,34] The lead author on the guideline also disclosed several conflicts of interest including institution grants from EDF, the sponsor of the guideline, for efforts on the guideline.[4]

Recommendations for treatment of severe types of acne are outlined in **Table 3.**[4]

Table 3. Journal of the European Academy of Dermatology and Venerology Severe Acne Treatment Recommendations[4]

Strength of Recommendation	Severe Papulopustular/Moderate Nodular Acne	Severe Nodular/Conglobate Acne
High	Isotretinoin	Isotretinoin
Medium	Systemic antibiotics + adapalene, or Systemic antibiotics + azelaic acid, or Systemic antibiotics + adapalene + benzoyl peroxide	Systemic antibiotics + azelaic acid
Low	Systemic antibiotics + benzoyl peroxide	Systemic antibiotics + benzoyl peroxide, or Systemic antibiotics + adapalene, or Systemic antibiotics + adapalene + benzoyl peroxide
Alternatives for Female Patients	Hormonal antiandrogens + topical treatment, or Hormonal antiandrogens + systemic antibiotics	Hormonal antiandrogens + systemic antibiotics

The guideline also provides recommendations for non-severe forms of acne.[4] Treatment recommended for comedonal acne includes topical retinoids (medium strength of recommendation), azelaic acid, or benzoyl peroxide (low strength of recommendation).[4] Treatments for mild-to-moderate papulopustular acne with high strength of recommendation include adapalene in combination with benzoyl peroxide or benzoyl peroxide in combination with clindamycin.[4] Multiple other treatments are also recommended based on medium and low strength of evidence.[4]

American Academy of Pediatrics: Pediatric Acne

In 2013, the American Acne and Rosacea Society (AARS) created a guideline on pediatric acne which was published and endorsed by the American Academy of Pediatrics (AAP).[3] Based on conflict of interest methodology, this guideline is not of high quality as conflicts of interest for authors are not available.[3] Therefore, it is not possible to evaluate the potential risk of bias.[3] It is noted that no corporate benefactor of the AARS or AAP had any input into content preparation, data review, or any involvement in the outcome of the meeting or publication.[3]

Recommendations for treatment of severe types of acne are outlined in **Table 4.**[3]

Table 4. AARS/AAP Pediatric Severe Acne Treatment Recommendations[3]

Initial Treatment	Combination therapy: Oral antibiotic + topical retinoid + benzoyl peroxide +/- topical antibiotic
Inadequate Response	Consider changing oral antibiotic, and Consider oral isotretinoin Females: consider hormonal therapy

The guideline also provides recommendations for non-severe forms of acne. Recommendations for pediatric initial treatment of mild and moderate acne include the following:

- Mild acne[3]:
  - Benzoyl peroxide or topical retinoid, OR
  - Topical combination therapy:
    - Benzoyl peroxide + antibiotic, OR
    - Retinoid + benzoyl peroxide, OR
    - Retinoid + antibiotic + benzoyl peroxide
- Moderate acne[3]:
  - Topical combination therapy:
    - Retinoid + benzoyl peroxide, OR
    - Retinoid + benzoyl peroxide + antibiotic, OR
    - Retinoid + antibiotic + benzoyl peroxide, OR
  - Oral antibiotic + (topical retinoid + BP) or (topical retinoid + antibiotic + benzoyl peroxide)

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Appendix 1: Current Status of PDL Class

RouteDesc	FormDesc	Brand	Generic	PDL
TOPICAL	GEL (GRAM)	ADAPALENE	adapalene	
TOPICAL	GEL (GRAM)	DIFFERIN	adapalene	
TOPICAL	CREAM (G)	ADAPALENE	adapalene	
TOPICAL	CREAM (G)	DIFFERIN	adapalene	
TOPICAL	SOLUTION	ADAPALENE	adapalene	
TOPICAL	MED. SWAB	PLIXDA	adapalene	
TOPICAL	LOTION	DIFFERIN	adapalene	
TOPICAL	GEL W/PUMP	ADAPALENE	adapalene	
TOPICAL	GEL W/PUMP	DIFFERIN	adapalene	
TOPICAL	GEL W/PUMP	ADAPALENE-BENZOYL PEROXIDE	adapalene/benzoyl peroxide	
TOPICAL	GEL W/PUMP	EPIDUO	adapalene/benzoyl peroxide	
TOPICAL	GEL W/PUMP	EPIDUO FORTE	adapalene/benzoyl peroxide	
TOPICAL	FOAM	FINACEA	azelaic acid	
TOPICAL	CREAM (G)	AZELEX	azelaic acid	
TOPICAL	CREAM (G)	FINEVIN	azelaic acid	
TOPICAL	BAR	PANOXYL	benzoyl peroxide	
TOPICAL	GEL (GRAM)	ACNE MEDICATION	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZAC W 10	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZAC W 2.5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	PANOXYL AQ 2.5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZAC W 5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	DEL-AQUA-5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	PANOXYL AQ 5	benzoyl peroxide	
TOPICAL	CREAM (G)	CLEARASIL DAILY CLEAR	benzoyl peroxide	
TOPICAL	CREAM (G)	DEL-AQUA-10	benzoyl peroxide	
TOPICAL	LOTION	ACNE MEDICATION	benzoyl peroxide	
TOPICAL	LOTION	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	CLEANSER	PANOXYL-4	benzoyl peroxide	
TOPICAL	CLEANSER	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	CLEANSER	PANOXYL	benzoyl peroxide	
TOPICAL	CLEANSER	PACNEX	benzoyl peroxide	
TOPICAL	FOAM	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZACLIN	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	CLINDAMYCIN-BENZOYL PEROXIDE	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOS-BENZOYL PEROX	clindamycin phos/benzoyl perox	

TOPICAL	GEL (GRAM)	DUAC	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	NEUAC	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	BENZACLIN	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	CLINDAMYCIN-BENZOYL PEROXIDE	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	ACANYA	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	CLINDAMYCIN PHOS-BENZOYL PEROX	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	ONEXTON	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	ONEXTON	clindamycin phos/benzoyl perox	
TOPICAL	KIT	CLINDACIN ETZ	clindamycin phos/skin clnsr 19	N
TOPICAL	KIT	CLINDACIN PAC	clindamycin phos/skin clnsr 19	N
TOPICAL	GEL (GRAM)	CLEOCIN T	clindamycin phosphate	N
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	SOLUTION	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	LOTION	CLEOCIN T	clindamycin phosphate	N
TOPICAL	LOTION	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLEOCIN T	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLINDACIN ETZ	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLINDACIN P	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	FOAM	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	FOAM	EVOCLIN	clindamycin phosphate	N
TOPICAL	CMB CR GEL	NEUAC	clindamycin/benzoyl/emol cmb94	
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOS-TRETINOIN	clindamycin/tretinoin	
TOPICAL	GEL (GRAM)	ZIANA	clindamycin/tretinoin	
TOPICAL	GEL (GRAM)	ACZONE	dapsone	
TOPICAL	GEL (GRAM)	DAPSONE	dapsone	
TOPICAL	GEL W/PUMP	ACZONE	dapsone	
TOPICAL	SOLUTION	DEL-MYCIN	erythromycin base	N
TOPICAL	MED. SWAB	ERY	erythromycin base in ethanol	N
TOPICAL	MED. SWAB	ERYTHROMYCIN	erythromycin base in ethanol	N
TOPICAL	GEL (GRAM)	ERYGEL	erythromycin base in ethanol	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN	erythromycin base in ethanol	N
TOPICAL	SOLUTION	ERYTHROMYCIN	erythromycin base in ethanol	N
TOPICAL	GEL (GRAM)	BENZAMYCIN	erythromycin/benzoyl peroxide	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN-BENZOYL PEROXIDE	erythromycin/benzoyl peroxide	N
TOPICAL	GEL (EA)	BENZAMYCINPAK	erythromycin/benzoyl peroxide	N
ORAL	CAPSULE	ABSORICA	isotretinoin	
ORAL	CAPSULE	AMNESTEEM	isotretinoin	

ORAL	CAPSULE	CLARAVIS	isotretinoin
ORAL	CAPSULE	ISOTRETINOIN	isotretinoin
ORAL	CAPSULE	MYORISAN	isotretinoin
ORAL	CAPSULE	ZENATANE	isotretinoin
TOPICAL	SUSPENSION	KLARON	sulfacetamide sodium
TOPICAL	SUSPENSION	SULFACETAMIDE SODIUM	sulfacetamide sodium
TOPICAL	FOAM	FABIOR	tazarotene
TOPICAL	GEL (GRAM)	RETIN-A	tretinoin
TOPICAL	GEL (GRAM)	TRETINOIN	tretinoin
TOPICAL	GEL (GRAM)	AVITA	tretinoin
TOPICAL	CREAM (G)	AVITA	tretinoin
TOPICAL	CREAM (G)	RETIN-A	tretinoin
TOPICAL	CREAM (G)	TRETINOIN	tretinoin
TOPICAL	GEL (GRAM)	ATRALIN	tretinoin
TOPICAL	GEL (GRAM)	RETIN-A MICRO	tretinoin microspheres
TOPICAL	GEL (GRAM)	TRETINOIN MICROSPHERE	tretinoin microspheres
TOPICAL	GEL W/PUMP	RETIN-A MICRO PUMP	tretinoin microspheres
TOPICAL	GEL W/PUMP	TRETINOIN MICROSPHERE	tretinoin microspheres

Appendix 2: Specific Drug Information for Medications in the Acne Class

Table 5. Clinical Pharmacology and Pharmacokinetics (for medications in the Acne class; non-acne formulations excluded)[6,16]

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
TOPICAL THERAPIES				
Adapalene	Retinoid-like compound	Minimal	Excretion: bile	• Half-life: 7-51 hours
Adapalene/benzoyl peroxide	Retinoid-like compound/ free-radical oxygen releaser	Via skin	*Metabolism* -Benzoyl peroxide: converted to benzoic acid in skin *Excretion* -Adapalene: primarily through bile -Benzoyl peroxide: urine	NA
Azelaic acid	Unknown; may decrease microcomedo formation	Cream: ~3-5% penetrates stratum corneum; up to 10% found in epidermis and dermis; 4% systemic	Metabolism: negligible after topical application; some beta-oxidation to shorter chain dicarboxylic acids Excretion: urine (primarily as unchanged drug)	• Half-life: 12 hours
Benzoyl peroxide	Releases free-radical oxygen	~5% via skin; gel more penetrating than cream	Metabolism: converted to benzoic acid in skin	NA
Clindamycin	Lincosamide antibiotic	Minimal for topical solution or foam	Metabolism: hepatic; forms metabolites (variable activity); clindamycin phosphate is converted to clindamycin HCl Excretion: urine (<0.2% with topical foam and solution)	NA
Dapsone	Unknown; may act as enzyme inhibitor or oxidizing agent; has numerous immunologic effects	~1% of the absorption of 100 mg tablet	NA	NA
Erythromycin	Macrolide antibiotic	NA	NA	NA
Salicylic acid	Produces desquamation of hyperkeratotic epithelium	Gel: >60% (under occlusion)	Excretion: urine	NA
Sulfacetamide	Sulfonamide derivative antibiotic	Significant absorption through skin; percutaneous absorption ~4%	Metabolism: sulfanilamide (major metabolite) Excretion: urine 0.08%-0.33%	• Half-life: 7-13 hours
Tazarotene	Synthetic, acetylenic retinoid	Minimal following cutaneous applications (≤6% of dose)	Metabolism: prodrug, rapidly metabolized via esterase hydrolysis to an active metabolite (tazarotenic acid) following topical application and systemic absorption; tazarotenic acid undergoes further hepatic metabolism Excretion: urine and feces (as metabolites)	• Half-life: ~18 hours (cream, gel) or 8.1 hours (foam)
Tretinoin	Vitamin A derivative	Minimal	Metabolism: hepatic; forms metabolites Excretion: urine and feces	NA
ISOTRETINOIN				
Isotretinoin	Reduces sebaceous gland size and reduces sebum production in acne treatment	Enhanced with high-fat meal; Absorica absorption is ~83% greater than Accutane when	Metabolism: hepatic via CYP2B6, 2C8, 2C9, 3A4; forms metabolites; major metabolite: 4-oxo-isotretinoin (active)	• Half-life: 21 hours (parent drug); 21-24 hours (metabolite)

		administered under fasting conditions; they are bioequivalent when taken with a high-fat meal	Excretion: urine and feces (equal amounts)	

Abbreviations: NA = not applicable

Table 6. Use in Specific Populations (for medications in the Acne class)[6,16]:

Drug Name	Warnings for Use in Pediatrics	Warnings for Use in Renal Impairment	Warnings for Use in Hepatic Impairment	Warnings for Use in Pregnancy
TOPICAL AGENTS				
Adapalene	NA	NA	NA	Adverse effects were observed in animal reproduction studies. Retinoids may cause harm when administered during pregnancy.
Adapalene/benzoyl peroxide	NA	NA	NA	Animal reproduction studies have not been conducted with this combination. Refer to individual drugs.
Azelaic acid	NA	NA	NA	Adverse events have been observed in animal reproduction studies following oral administration. The amount of azelaic acid available systemically following topical administration is minimal (<4%).
Benzoyl peroxide	NA	NA	NA	Topical products are recommended as initial therapy for the treatment of acne in pregnant females; benzoyl peroxide is one of the preferred agents.
Clindamycin	NA	NA	NA	If treatment for acne is needed during pregnancy, topical clindamycin may be considered if an antibiotic is needed. To decrease systemic exposure, pregnant women should avoid application to inflamed skin for long periods of time, or to large body surface areas.
Dapsone	NA	NA	NA	Topical products are recommended as initial therapy for the treatment of acne vulgaris in pregnant females; however, information specific to dapsone is lacking. Agents other than topical dapsone are preferred.
Erythromycin	NA	NA	NA	The amount of erythromycin available systemically following topical application is considered to be very low. Systemic absorption would be required in order for erythromycin to cross the placenta and reach the fetus. Topical erythromycin may be used for the treatment of acne in pregnancy.
Salicylic acid	Avoid prolonged use over large areas; may result in salicylism. Limit application area in children <12 years of age. Use may be associated with Reye syndrome; use caution in children or adolescents with varicella or influenza. Some products are contraindicated in children <2 years	Avoid prolonged use over large areas in patients with significant renal impairment; may result in salicylism	Avoid prolonged use over large areas in patients with significant hepatic impairment; may result in salicylism	For the topical treatment of acne or warts, salicylic acid can be used in pregnant women if the area of exposure and duration of therapy is limited, although other agents may be preferred

Sulfacetamide	NA	NA	NA	Amount systemically available after topical administration is unknown. Use of systemic sulfonamides during pregnancy may cause kernicterus in the newborn.
Tazarotene	NA	NA	NA	Use in pregnancy is contraindicated.
Tretinoin	NA	NA	NA	Adverse events were observed in animal reproduction studies following topical application of tretinoin. Teratogenic effects were also observed in pregnant women following topical use; however, a causal association has not been established. When treatment for acne is needed during pregnancy, other agents are preferred
ISOTRETINOIN				
Isotretinoin	NA	NA	Clinical hepatitis and mild to moderate elevated liver enzymes have been reported with use; liver enzymes may normalize with dosage reduction or with continued treatment. Discontinue therapy if hepatic enzymes do not normalize or if hepatitis is suspected	Use is contraindicated in females who are or may become pregnant; REMS program (iPLEDGE™) required.

Abbreviations: NA = not applicable

Drug Safety for Medications in the Acne Class:

Boxed Warnings[6,16]:

- *Isotretinoin:* Must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin. Because of the teratogenicity, it is approved for marketing only under a special restricted distribution called iPLEDGE™.
- *Tretinoin:* Patients with acute promyelocytic leukemia (APL) can have severe adverse reactions to tretinoin including retinoic acid-APL (RA-APL) syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure.

Risk Evaluation Mitigation Strategy Programs[6,16]:

- *Isotretinoin:* Goal of the program is to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions.

Contraindications[6,16]:

- *Adapalene:* hypersensitivity to adapalene or any of the components of the product
- *Benzoyl peroxide:* hypersensitivity to benzoyl peroxide or to any component of the product

- *Clindamycin:* history of antibiotic-associated colitis, including pseudomembranous colitis; history of regional enteritis; history of ulcerative colitis; hypersensitivity to clindamycin or other lincosamides, such as lincomycin
- *Erythromycin:* hypersensitivity to erythromycin or any component of the product
- *Isotretinoin:* hypersensitivity to isotretinoin or any of its components; hypersensitivity to vitamin A; pregnancy, known or suspected (risk of teratogenic effects; required to use 2 effective contraception methods or continuous abstinence for 1 month prior, during, and 1 month after isotretinoin therapy)
- *Sulfacetamide:* hypersensitivity to sulfonamides or any component of the formulation; kidney disease (Ovace Plus Wash, Ovace Plus Lotion, Ovace Plus foam)
- *Tazarotene:* hypersensitivity to tazarotene or any component of the product; pregnancy
- *Tretinoin:* hypersensitivity to tretinoin or any component of the product; sensitivity to parabens (preservative in oral gelatin capsules)

Table 7. Summary of Warnings and Precautions for Medications in the Acne Class[6,16]

	TOPICAL AGENTS										
Warning/ Precaution	**Adapalene**	**Adapalene/ benzoyl peroxide**	**Tretinoin**	**Tazarotene**	**Benzoyl peroxide**	**Salicylic acid**	**Dapsone**	**Azelaic acid**	**Clindamycin**	**Erythromycin**	**Sulfacetamide**
Hypersensitivity reactions	X		X		X	X		X			X
Photosensitivity	X	X	X	X							
Skin irritation	X	X	X	X	X			X			
Avoid use with sulfone products		X			X						
Bleaching effects		X			X						
Drug-drug interactions		X	X				X				X
Fish allergies			X (Atralin)								
Caution in eczema			X								
Avoid use with salicylates						X					
Localized discoloration							X				
Hemolysis							X				
Methemoglobinemia							X				
Hypopigmentation								X			
Asthma exacerbation								X			
Colitis									X		
Caution in atopic patients									X		
Superinfection										X	
Cumulative irritation with concurrent topical acne therapy										X	
Autoimmune effects, blood dyscrasias, dermatologic reactions, hepatic effects: fatalities associated with severe reactions											X

Sulfonamide ("sulfa") allergy											X
Systemic effects with application to large, infected, abraded, denuded, or burned skin											X
Infection with nonsusceptible organisms											X
Metabisulfites-allergy											X
Not compatible with silver-containing products											X

Summary of Warnings and Precautions for Isotretinoin[6,16]

- Concerns related to adverse effects
  - Auditory impairment
  - Bone mineral density loss
  - Dermatologic effects
  - Growth effects
  - Hematologic effects
  - Hepatic effects
  - Hypersensitivity reactions
  - Inflammatory bowel disease
  - Musculoskeletal effects
  - Ocular effects
  - Pancreatitis
  - Photosensitivity
  - Pseudotumor cerebri
  - Psychiatric effects
- Disease-related concerns
  - Use with caution in patients with diabetes
  - Use with caution in patients with hypertriglyceridemia or those who may be at high risk
- Concurrent drug therapy issues
  - Potential significant drug-drug interactions may exist
- Other warnings/precautions
  - Patients should not donate blood during therapy and for 1 month following discontinuation of therapy due to risk of donated blood being given to a pregnant female
  - Should only be prescribed by health care providers competent in treating severe recalcitrant nodular acne and experienced with the use of systemic retinoids
  - Safety of long-term use is not established and not recommended; effect on bone loss is unknown
  - Avoid skin resurfacing procedures
  - REMS program (iPLEDGE™) required for all patients, prescribers, wholesalers, and dispensing pharmacists

Appendix 3: Medline Search Strategy on 08/28/2018

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to August 03, 2018

1 exp TRETINOIN	*21313*
2 exp ADAPALENE, BENZOYL PEROXIDE DRUG COMBINATION/ or exp ADAPALENE/	*337*
3 tazarotene.mp.	*475*
4 exp ISOTRETINOIN/	*3350*
5 exp Benzoyl Peroxide/	*1054*
6 exp CLINDAMYCIN/	*5436*
7 exp ERYTHROMYCIN/	*23830*
8 exp DAPSONE/	*4665*
9 azelaic acid.mp.	*578*
10 exp Salicylic Acid/	*7869*
11 exp TETRACYCLINE/	*19335*
12 exp DOXYCYCLINE/	*8941*
13 exp MINOCYCLINE/	*5533*
14 exp TRIMETHOPRIM/	*11473*
15 exp AZITHROMYCIN/	*4584*
16 exp Contraceptives, Oral/	*44530*
17 exp SPIRONOLACTONE/	*6450*
18 exp SULFACETAMIDE/	*348*
19 exp SULFUR/	*23859*
20 acne.mp. or exp Acne Vulgaris/	*15114*
21 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	*180130*
22 20 and 21	*4603*
23 limit 22 to (English language and humans)	*3705*
24 limit 23 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 meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	*1153*
25 limit 24 to yr="2003-Current"	*602*

Appendix 4: Key Inclusion Criteria

Population	Patients with severe cystic acne, acne conglobata, or acne fulminans
Intervention	• Topical agents: adapalene, adapalene/benzoyl peroxide, tretinoin, tazarotene, benzoyl peroxide, salicylic acid, dapsone, azelaic acid, clindamycin, erythromycin, sulfacetamide • Oral systemic antibiotics: doxycycline, minocycline, tetracycline, azithromycin, erythromycin, clindamycin, trimethoprim, and sulfamethoxazole/trimethoprim • Hormonal agents: oral contraceptives and spironolactone • Oral isotretinoin
Comparator	Any drug in the "Intervention" inclusion criteria
Outcomes	Symptom improvement; quality of life; severe adverse events
Timing	Any study length; lit search from 1/1/2003-08/06/2018
Setting	Outpatient

Acne Medications

Goal(s):

- Ensure that medications for acne are used appropriately for OHP-funded conditions.

Length of Authorization:

Up to 12 months

Requires PA:

- All drugs in the Acne medications class

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for 12 months.

P&T/DUR Review: 11/18 (JP)
Implementation: TBD

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

Hepatitis C Policy Discussion

Purpose of the Discussion:
The purpose of this policy discussion is to evaluate necessary changes to the current prior authorization [PA] criteria and preferred drug list (PDL) if the Oregon Health Authority determines it has the fiscal capacity to expand access to all patients with chronic hepatitis C without fibrosis restrictions.

Recommendation:

- Approve updated prior authorization (PA) criteria (**Appendix 1**).
- Evaluate comparative costs in executive session.

Background:
Chronic hepatitis C (CHC) infection is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). It is also the leading indication for liver transplantation in the Western world.[1] About 10-20% of people with CHC develop cirrhosis (8-16% of all people infected with HCV), and the time to progress to cirrhosis varies at an average of 40 years.[1] Progression of fibrosis is commonly categorized using METAVIR staging (F0 to F4) with higher scores indicating more severe fibrosis.

The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment.[1] Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment.[1] As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease. Current drug policies in place approve treatment for patients with fibrosis Metavir stage 2 or greater, or patients with extrahepatic manifestations or HIV at any stage of fibrosis, and patients in the setting of solid organ transplant (see **Appendix 1**).

References:

1. Drug Use Research & Management Program. Class Update with New Drug Evaluations: Hepatitis C Direct-Acting Antivirals. September 2017; http://www.orpdl.org/durm/meetings/meetingdocs/2017_09_28/archives/2017_09_28_HepatitisC_ClassUpdate.pdf. Accessed August 24, 2018.

Hepatitis C Direct-Acting Antivirals

Goals:

Approve use of cost-effective treatments supported by the medical evidence.
Provide consistent patient evaluations across all hepatitis C treatments.
Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-16 weeks

Requires PA:

All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection (defined by positive HCV RNA detection in a patient with no suspicion of transmission in the previous 6 months OR persistent HCV detection for ≥6 months OR diagnosis of chronic viral hepatitis C (B18.2) for ≥ 6 months, OR positive HCV RNA with evidence of clinically significant fibrosis [≥F1])?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
4. Has all of the following pre-treatment testing been documented: a. Genotype testing in past 3 years for patients with cirrhosis, patients with any prior treatment experience, and for regimens which are not pan-genotypic; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient d. Current HBV status of patient e. Pregnancy test in past 30 days for a woman of child-bearing age; and f. History of previous HCV treatment and outcome ~~f.~~g. Presence or absence of cirrhosis as determined by clinical evidence of complications from cirrhosis, a serum test (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF], Fibrosure), biopsy, OR imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE])? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAB status.	**Yes:** Record results of each test and go to #5 Note: If the patient has HIV or HBV co-infection, it is highly recommended that a specialist be consulted prior to treatment. Currently treatment is not recommended during pregnancy due to lack of safety and efficacy data	**No**: Pass to RPh. Request updated testing.
5. Which regimen is requested?	Document and go to #6	
~~6. Does the patient have HIV coinfection and is under treatment by a specialist with experience in HIV?~~ ~~Note: persons with HIV/HCV coinfection are at risk for rapidly progressing fibrosis~~	~~**Yes:** Go to #10~~	~~**No:** Go to #7~~

Approval Criteria		
~~7.~~6. Does the patient have: ~~a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate portal fibrosis with septa (METAVIR F2) advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4);~~ ~~**OR**~~ Clinical, radiologic or laboratory evidence of complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma, esophageal varices)?	**Yes:** Go to #7~~10~~ ~~Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy. However, if imaging testing is not regionally available, a serum test (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF], Fibrosure) can be used to confirm METAVIR F2 or greater but cannot be used for denial~~. ~~For results falling in a range (e.g. F1 to F2), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Evidence-based-Reports-Blog.aspx?View=%7b2905450B-49B8-4A9B-AF17-5E1E03AB8B6B%7d&SelectedID=237) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.~~	**No:** Go to #8

Approval Criteria		
~~1. Does the patient have one of the following extrahepatic manifestations of Hepatitis C?~~ ~~b) Lymphoproliferative disease, including type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or~~ ~~c) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or~~ ~~d) Porphyria cutanea tarda or lichen planus~~ ~~e) Lymphomas (B-cell non-Hodgkin lymphoma)~~ ~~f)~~a)~~Type 2 Diabetes~~	~~**Yes:** Go to #10~~	~~**No:** Go to #9~~
~~1. Is the patient in one of the following transplant settings:~~ ~~b) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or~~ a) ~~Post solid organ transplant?~~	~~**Yes:** Go to #10~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~8. If METAVIR F4: Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR**~~ ~~9.~~7. ~~If METAVIR F3:~~ Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist? ~~**OR**~~ ~~If METAVIR ≤F2: The regimen does not need to be prescribed by or in consultation with a specialist.~~	**Yes:** Go to #8~~11~~	**No:** Pass to RPh. Deny; medical appropriateness. Recommend prescriber document referral to a specialist prior to initiating treatment. ~~Forward to DMAP for further manual review to determine appropriateness of prescriber.~~

Approval Criteria		
~~10.~~8. Is there attestation that the patient and provider will comply with all case management interventions to promote the best possible outcome for the patient and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load? Case management includes assessment of treatment barriers and offer of patient support to mitigate potential barriers to regimen adherence as well as facilitation of SVR12 evaluation to assess treatment success.	**Yes**: Go to #9~~12~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~11.~~9. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #10~~3~~	**No:** Go to #11~~4~~
~~12.~~10. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #16? Note: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #11~~4~~ Document test and result.
~~13.~~11. Is the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #12~~5~~	**No:** Go to #13~~6~~
~~14.~~12. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #13~~6~~

Approval Criteria		
~~15.~~13. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or lost to follow-up?	**Yes:** Pass to RPh; Deny and refer to medical director for review	**No:** Go to #14~~7~~
~~16.~~14. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1**)?	**Yes:** Approve for 8-16 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *11/18; 9/18 (MH); 1/18; 9/17; 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 1/1/2019; 3/1/2018; 1/1/2018; 2/12/16; 4/15; 1/15*

Public Health Response to HCV in Oregon: Need for Screening and Treatment

Ann Thomas, MD, MPH
Acute and Communicable Disease Prevention

Oregon Health Authority

November 29, 2018

Outline

I. Epidemiology of HCV in OR
- acute HCV, chronic HCV in persons <30
- chronic HCV, liver cancer and mortality

II. Public Health Response
- Harm reduction approaches
- Treatment as prevention
- Lessons learned from HIV prevention

Estimates of number of Oregonians with HCV

- **75,090**
  - Number reported to Oregon's HCV registry by September 2018
- **100,000 +**
  - Actual number assuming that at least 50% of persons with HCV are unaware of their diagnosis

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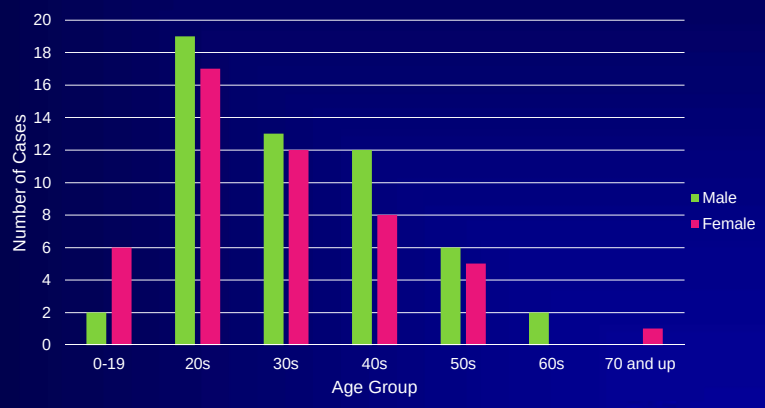
Acute HCV cases by sex and age, Oregon, 2012-2016 (n=103)



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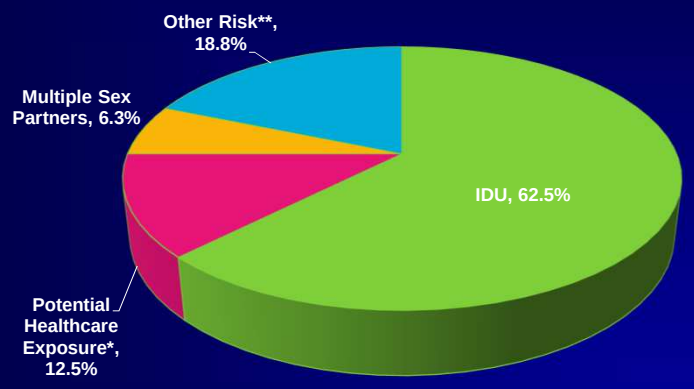
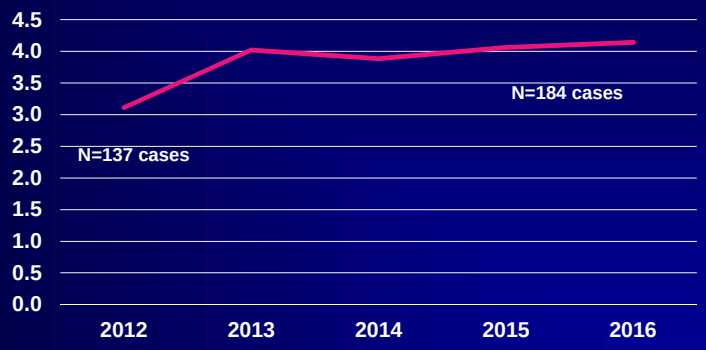
Reported Risk Factors for Acute Hepatitis C, Oregon, 2016



*Transfusion, infusions, dialysis and surgery
**street drugs, needle stick, tattoo, piercing, contact of a case, and other blood exposure

Rate of women who are HCV+, as reported on birth certificate (per 1,000 live births), Oregon 2012-2016



- 34% increase between 2012 and 2016

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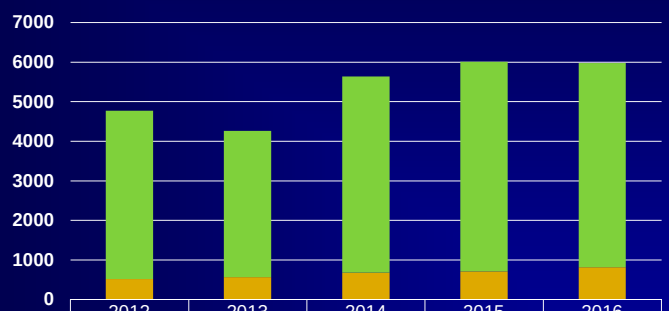
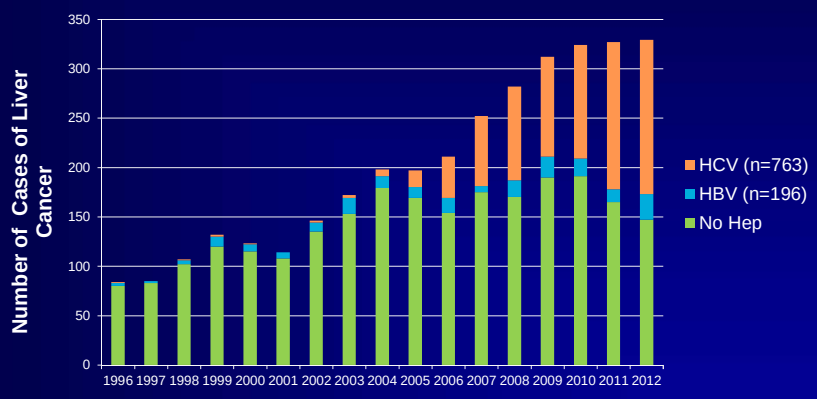
Number of Chronic HCV cases, Oregon, 2012-2016



	2012	2013	2014	2015	2016
30+	4249	3696	4960	5290	5156
< 30	515	561	676	712	816

- **58% increase in cases < 30 years**

Cases of liver cancer with HBV and HCV Oregon, 1996-2012



- **In 2012, 47% of persons with liver cancer had chronic HCV**

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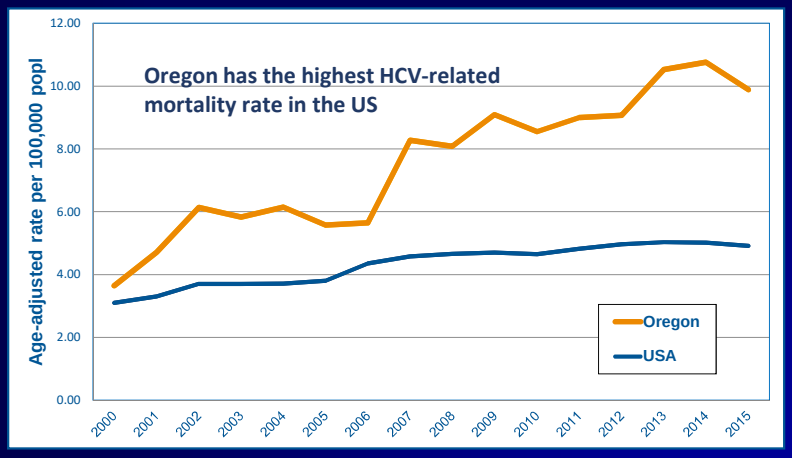
Hepatitis C-related deaths in Oregon and US, 2000–2015



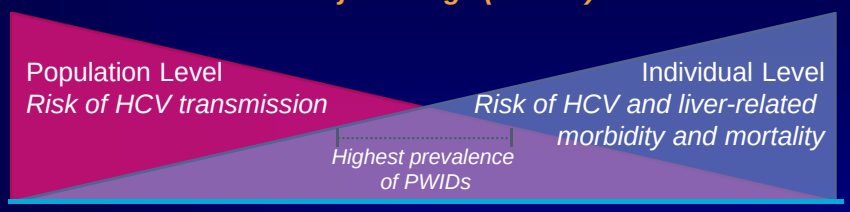
Source: Oregon Center for Health Statistics

Epidemiology Summary

- High prevalence (3rd highest in country according to CDC) and mortality of HCV in Oregon
- Most common in baby boomers, who bear biggest burden of sequelae of HCV-related liver cancer, death
- Increasing cases in younger Oregonians, more likely to be associated with injection drug use

Public Health Perspective:

Risk of HCV Transmission and HCV Progression of Persons Who Inject Drugs (PWIDS)



- Highest risk of HCV transmission due to tendency of people new to injection drug use to share injection equipment

- Highest prevalence of PWIDs
- Moderate risk of advanced liver disease
- Moderate risk of HCV transmission

- Highest prevalence and risk of advanced liver disease
- Lower risk of HCV transmission

Classic Public Health Approach

- **Primary Prevention (prevent new infections)**
  - Harm reduction, Medication Assisted Treatment, and Syringe Exchange Programs
  - Treat with DAAs to reduce transmission
- **Secondary Prevention (screen and treat before disease progresses)**
  - Screening of persons at risk and all persons born 1945-1965
  - Monitor for liver cancer
  - Treat with DAAs to reduce morbidity and mortality

HCV treatment as prevention

- Recent studies modeling the impact of DAAs on HCV transmission:
  1. Can eliminate HCV in 10 years by treating 12% of PWID population
  2. Treat 25% ***OR*** treat 15% plus MAT and SEP for 90% reduction in 15 years

High impact on disease transmission with modest numbers needed to treat

1. Zelenev Lancet Infect Dis 2018;18:215; 2. Fraser Addiction 2018;113:173

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Advantages of dropping fibrosis score requirements

- Lack of available treatment has been barrier to screening
- If fibrosis score not required, work-up is simplified
  - Can determine if cirrhosis present from serum fibrosis markers
  - No Fibroscan or ultrasound elastography needed
  - Easier for primary care clinicians to treat HCV

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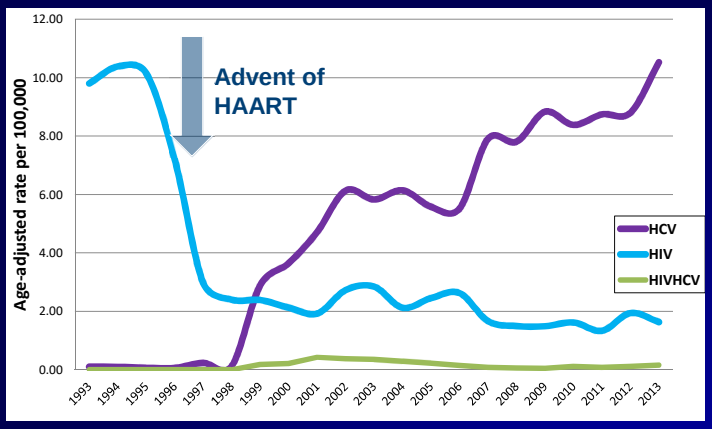
Age-adjusted Death Rates for HCV and HIV, Oregon, 1993–2013



How antiretroviral treatment changed the curve for HIV

Public Health Lessons for HCV from HIV

- Case management should be acuity-based
- Training and supporting primary care clinicians (ECHO, MAT training)

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Questions

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Extra Slides

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Resources

Clinic Program Development and Management

- Clinic Consultation
- Quality Improvement
- Practice Transformation
- Guidelines and Toolkits (e.g. HRSA-AETC)

Provider Education and Mentoring (HCV and HIV)

- Clinician Consultation Center (UCSF CCC "Warm line")
- Tele-education and mentoring
- 1 to 1 Clinician detailing
- Online self-paced study

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Oregon Resources

- Oregon AIDS Education Training Center (OR -AETC)
  - Clinic consultation, quality improvement, public health detailing and practice transformation support (HIV/HCV)
  - Oregon HIV ECHO
  - Contact Dayna@oraetc.org
- Oregon ECHO Network (OEN)
  - Builds capacity of primary care clinicians and teams
  - Technology, Disease Management Model and Case Based Learning
  - Contact oen@ohsu.edu
- Oregon Hepatitis C Screening Initiative (OR-HCV)
  - Clinic consultation and quality improvement support
  - Small stiped: implement HCV EHR report and determine site's baseline HCV screening rate, share screening rates quarterly and implement at least one provider focused intervention.
  - Contact Judith.m.leahy@state.or.us

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

New Drug Evaluation: Elagolix tablet, oral

Date of Review: November 2018
Generic Name: elagolix sodium

End Date of Literature Search: September 2018
Brand Name (Manufacturer): Orilissa™ (AbbVie, Inc)
Dossier Received: yes

Research Questions:

1. What is the efficacy of elagolix compared to placebo or currently available therapy for the treatment of moderate to severe pain associated in women with endometriosis?
2. Is elagolix safe for the treatment of moderate to severe pain associated in women with endometriosis?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with elagolix?

Conclusions:

- There is moderate quality evidence from two phase 3 studies that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant difference in dysmenorrhea symptoms as measured by the Endometriosis Daily Pain Impact Diary (EDPID) score at 3 months when treated with elagolix 150 mg daily and 200 mg twice daily versus placebo (absolute risk reduction [ARR]=27%/number needed to treat [NNT]=4 and ARR=56%/NNT=2, respectively for Elaris EM-1; ARR=21%/NNT=5 and ARR=50%/NNT=2, respectively for Elaris EM-2).[1,2,3] The clinical significance of this difference is unclear.
- There is moderate quality evidence from two phase 3 studies that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant difference in non-menstrual pelvic pain symptoms as measured by the EDPID score at 3 months when treated with elagolix 150 mg daily and 200 mg twice daily versus placebo (ARR=14%/NNT=8 and ARR=18%/NNT=6, respectively for Elaris EM-1; ARR=13%/NNT=8 and ARR=21%/NNT=5, respectively for Elaris EM-2). [1,2,3] The clinical significance of this difference is unclear.
- There is moderate quality evidence from two phase 3 studies that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant reduction in dyspareunia symptoms as measured by a decreased dyspareunia pain score (5-point scale, from 0 to 4) at 3 months when treated with elagolix 200 mg twice daily versus placebo (-0.49 vs -0.20, respectively; p<0.001 for Elaris EM-1; -0.60 vs -0.30, respectively; p<0.001 for Elaris EM-2). [1,2,3] The clinical significance of this difference is unclear.
- There is insufficient evidence to evaluate the long-term safety of elagolix. The safety population included 1686 patients. Serious adverse events were similar compared to placebo. Adverse events more common with either elagolix 150mg daily or 200mg twice daily versus placebo included hot flush (elagolix 150 mg daily, 10%; elagolix 200 mg BID, 16%; placebo, 13%) and headache (elagolix 150 mg daily, 17%; elagolix 200 mg BID, 20%; placebo, 12%).[1,2,3]

- There is insufficient evidence to compare the safety and efficacy of elagolix to any other analgesics, oral contraceptives, gonadotropin-releasing hormone (GnRH) analogs, danazol, or progestins for treatment of endometriosis-related pain in specific subpopulations.

Recommendations:
- Create a new preferred drug list (PDL) class for gonadotropin-releasing hormone (GnRH) receptor antagonists.
- Implement prior authorization criteria for elagolix (**Appendix 2**).

Background:
Endometriosis is a gynecological inflammatory condition commonly associated with chronic pain and infertility caused by the growth of estrogen-dependent endometrial-like tissue implanted outside of the uterine cavity.[4] In 2017, the prevalence of endometriosis in the United States was estimated to be roughly 5 million people.[5] It is estimated that 1 in 10 women between the ages of 15-49 may experience endometriosis with the highest incidence among those between 25 and 29 years of age.[5] Quality of life and work productivity are negatively impacted by endometriosis pain.[6] In the United States alone, it is estimated that endometriosis results in over $10,000 in additional health care costs as well as $15,000 in lost productivity per patient year.[7] Epidemiologic studies have concluded that women with early menarche (<10 years old) with more frequent menstrual cycles (<28 days) and longer menstrual flows (>5-6 days) are at higher risk for endometriosis.[5] There are more than 1500 women currently in Oregon Medicaid Fee-for-Service (FFS) with claims indicative of an endometriosis-related diagnosis between July 2016 and June 2017.

As the most common cause of unexplained pelvic pain, endometriosis may be suspected through ultrasound and confirmed by histologic confirmation of lesions through laparoscopy.[8] Ectopic lesions occur most commonly around the ovaries but may also be found elsewhere in the body including the uterosacral ligaments, uterovesical peritonium, and other pelvic and even non-pelvic area locations.[9,10] During menstruation, the endometriotic tissue responds to hormonal stimulation similarly to the endometrium itself with associated bleeding and inflammation.[11] Over time, the inflammation leads to fibrosis and adhesions which may result in pelvic anatomical changes that range from symptoms of slight discomfort to severe disabling pelvic pain and dyspareunia.[11] The type, duration, and magnitude of pain may vary greatly among individuals and often manifests independently of the menstrual cycle.[7] Up to 50% of women with endometriosis become infertile.[5] It is not uncommon for endometriosis patients to experience depression and other mental health issues because of their condition.[7]

Endometriosis treatment varies based on duration and severity of symptoms. Surgery is an option in women with endometriosis who do not respond to medical therapy, especially for those with plans to become pregnant.[9,12] Due to the response of ectopic endometrial tissue to ovarian hormones, efforts to produce a hypoestrogenic state form the basis of therapeutic approaches to endometriosis symptom management.[9,12] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[9,12] Therefore, most women are given a steady administration of combined hormonal contraceptives, or progestin alone, for first-line treatment of endometriosis pain.[6,9] Hormonal therapies such as gonadotropin-releasing hormone (GnRH) agonists have also been used for management of endometriosis.[6,9] Continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[9,12] Goserelin, leuprolide, and nafarelin are all FDA-approved for endometriosis therapy.[2] Danazol, a gonadotropin inhibitor, was the first FDA-approved agent for endometriosis, but its utility has been undermined by a significant adverse effect profile.[2,9] Another group of estrogen biosynthesis blockers under investigation are the aromatase inhibitors which are currently used off-label for endometriosis treatment.[9] FDA-approved agents for the management of endometriosis are listed in **Table 1**.

Table 1. Summary of FDA-approved Therapies for Endometriosis (modified)[2]

Drug	Dosing/Administration	Select Safety Precautions
Danazol	200 to 400 mg orally given in 2 divided doses; adjust depending on clinical response; OR 800 mg orally in 2 divided doses; titrate downward depending on clinical response	-Thrombotic events including strokes -Peliosis hepatis and benign hepatic adenoma -Intracranial hypertension -Lipoprotein changes -Androgen effects -Use in pregnancy is contraindicated
Goserelin acetate	3.6 mg implant subcutaneously placed every 28 days for 6 months maximum	-Hyperglycemia and increased risk of developing diabetes -Loss of bone mineral density (BMD) -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Leuprolide acetate (monthly depot and 3-month depot)	3.75 mg IM depot injection monthly for 6 months OR Initial, 11.25 mg IM depot injection once every 3 months for 1 or 2 doses (maximum 6 months)	-Loss of BMD -Worsening depression and memory disorders -Convulsions -Breakthrough bleeding/risk of pregnancy
Nafarelin acetate	400 mcg/day INTRANASALLY by 1 spray (200 mcg) into 1 nostril in the morning and 1 spray (200 mcg) into the other nostril in the evening; MAX 800 mcg/day; initiate treatment between days 2 and 4 of the menstrual cycle; recommended duration 6 months	-Loss of BMD -Worsening depression -Hypoestrogenism -Serum lipid changes
Medroxyprogesterone acetate	1 injection (104 mg per 0.65 mL) subcutaneously into the anterior thigh or abdomen once every 3 months (12 to 14 weeks); do not use for longer than 2 years	-Loss of BMD -Thromboembolic disorders -Breast cancer risk -Ocular disorders -Ectopic pregnancy -Bleeding irregularities
Leuprolide acetate + norethindrone acetate	See leuprolide acetate dosing above plus 5 mg norethindrone acetate orally daily	-Loss of BMD -Recurrence of depression -Convulsions

The National Institute for Health and Care Excellence (NICE) has recently updated guidance documents for management of endometriosis with various treatments including diagnostic recommendations, pharmacotherapy options for pain, and surgery.[13] It is recommended that endometriosis be diagnosed through abdominal and pelvic examination, magnetic resonance imaging (MRI) or ultrasound, and diagnostic laparoscopy with biopsy when needed.[13] NICE recommends that pain from endometriosis be treated with a short trial of NSAIDs and/or acetaminophen, then an oral contraceptive or progestin.[13] Surgical

excision is recommended for women with suspected or confirmed endometriosis with bowel, bladder, or ureter involvement.[13] GnRH agonists may be considered as adjunct treatment prior to surgery for deep endometriosis.[13] NICE recommends a hysterectomy with or without oophorectomy for women with endometriotic complications unresponsive to other treatments.[13]

There are several non-specific assessment scales that have been used to measure patient response to medical treatment intervention. The Patient Global Impression of Change (PGIC) is a general tool used to evaluate the overall health status as perceived by the patient using a seven-point single-item scale ranging from 'very much worse' to 'very much improved'. [14] The PCIG has been applied as a valid tool in many clinical trials of analgesics but it lacks ability to reflect degrees of change within specific domains.[14] For pain assessment, the visual analogue or verbal rating scale is a numeric rating scale which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable).[15] The ease of administration and scoring allows this tool to be used in a variety of settings, however, it may not be appropriate for low literacy patients.[15] A similar pain assessment tool commonly used is the Brief Pain Inventory (BPI) which has the added benefit of assessing both pain severity and interference it has on various aspects of daily activities.[16] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[16] A specific tool known as the Biberoglu and Behrman (B&B) Scale is patient-reported symptom assessment tool for dysmenorrhea, chronic pelvic pain, dyspareunia, as well as pelvic tenderness and induration.[16] The B&B is graded on a scale from 0 to 3 (or 4 for dyspareunia) with higher scores representative of more symptoms.[16] However, several organizations including the National Institutes of Health have indicated that the B&B has never been validated nor administered consistently.[16] Quality of Life (QoL) assessment tools such as the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the European Quality of Life in 5 Dimensions (EQ-5D) have been developed for use in many medical conditions, but there has not been a strong correlation found between QoL and pain intensity with use of these scales in endometriosis patients.[16] The Endometriosis Health Profile (EHP) is a disease-specific instrument used to assess the quality of life in women with endometriosis.[16] The EHP-5 is a shorter version of the EHP-30.[16] Both explore the same five core dimensions including pain, control and powerlessness, emotional well-being, social support, and self-image.[16] The EHP-30 has been validated for use in women with endometriosis, while the EHP-5 has not. [16]

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

Clinical Efficacy:
Elagolix is an oral, nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis.[2,3] GnRH antagonists are thought to reduce gonadotropin secretion from the pituitary gland in a dose dependent manner to decrease estradiol and progesterone concentrations.[17] In women with endometriosis, a reduction in estrogen may limit the growth of endometriotic tissue which is the source of localized pain and inflammation characteristic of the condition.[17] The FDA approval of elagolix for the treatment of women with endometriosis pain was based on two pivotal trials which are described and evaluated below in **Table 4**.[2,3]

Elaris Endometriosis 1 and 2 (EM-1 and EM-2) were virtually identical phase 3, randomized, double blind studies designed to evaluate the effectiveness of two different doses of elagolix versus placebo in the treatment of women with moderate to severe endometriosis-associated pain.[1,2] EM-1 (N=872) took place in the United States and Canada, while EM-2 (N=817) enrolled patients from U.S., Europe, South America, Australia, New Zealand, and South Africa.[1,2] Baseline demographics, inclusion criteria, and exclusion criteria are reported in **Table 4**.[1,2] After a washout period, patients were screened for up to 100 days with assessment of baseline pain scores to verify moderate to severe endometriosis-associated pain.[1,2] Study subjects were switched from their usual analgesic to an

approved rescue analgesic of naproxen and/or a select opioid followed by a 6-month treatment period.[1,2] Eligible patients were randomized in a 2:2:3 ratio to receive oral elagolix 150 mg tablet once daily (low dose), 200 mg twice daily (high dose), or placebo.[1,2]

The co-primary endpoints for efficacy in Elaris EM-1 and Elaris EM-2 were the proportion of women with dysmenorrhea and proportion of women with non-menstrual pelvic pain who responded to treatment based on the mean results of a patient-reported Endometriosis Daily Pain Impact Diary (EDPID) at month 3.[1,2] The EDPID was a modified version of the B&B Scale assessment tool created to assess endometriosis symptom severity.[1,2] Four questions regarding dysmenorrhea, non-menstrual pelvic pain, and dyspareunia were graded on a 3-point pain score scale: 0/1=no/mild, 2=moderate, 3=severe (total score range of 0-12).[1,2] For each of the co-primary endpoints, a logistic regression model was used to analyze the data.[1,2] A subject was considered a responder if the reduction of pain at month 3 compared to baseline met or exceeded the calculated minimal clinically important difference (MCID) as determined by a receiver operating characteristics (ROC) analysis.[1,2] The ROC analysis used last observation carried forward for missing data on subjects who prematurely discontinued the study before month 3.[1,2] The authors reported that the clinically meaningful threshold for mean change from baseline was -0.81 for Elaris EM-1 and -0.85 for Elaris EM-2 compared to placebo for dysmenorrhea symptoms.[1,2] For non-menstrual pelvic pain, the authors reported that the patient responder threshold was a minimum improvement of -0.36 for Elaris EM-1 and -0.43 for Elaris EM-2 compared to placebo.[1,2] The PGIC scale was also co-administered monthly to assess secondary endpoints and to serve as an anchor for the ROC analysis.[1,2] Results for each co-primary endpoint at week 6 were also analyzed.[1,2] Dyspareunia, a key secondary endpoint, was assessed by patient response to a daily 5-question, 3-point pain rating scale, which was averaged monthly.[1,2] The ROC MCID threshold for dyspareunia was estimated to be -0.29 (-35.1%).[1,2]

In both trials, statistically significant reductions in dysmenorrhea pain were reported by roughly 44% of the low-dose elagolix group, 74% of the high-dose elagolix group, and 21% of the placebo group (P<0.001).[1,2] Non-menstrual pelvic pain was also reported to decrease in treatment groups, with roughly 50% of low dose, 56% of high dose, and 36% of placebo groups demonstrating a statistically significant benefit (P<0.001).[1,2] See **Table 4** for percentages from each individual trial. For dyspareunia, only the 200 mg twice daily high-dose elagolix reported a statistically significant drop in pain rating score versus placebo for Elaris EM-1 (-0.49 vs. -0.20, respectively; p<0.001) and Elaris EM-2 (-0.60 vs. -0.30, respectively; p<0.001).[1,2] The clinical significance of a -0.2 to -0.3 change on a dyspareunia pain assessment scale that ranges from 0 to 3 is unclear.

Limitations

Details of the ROC analysis and development of the statistical prediction models used to map the author's calculations to clinical outcome thresholds were not reported. Use of the PGIC scale has not been established as a well-defined and reliable measure of endometriosis-associated pain. Neither the EDPID nor the B&B symptom scale has been validated as an assessment tool for endometriosis pain measurements. However, the authors used their PGIC data from the trial as an anchor to establish the MCID on the EDPID. Use of an unvalidated tool with no clear MCID threshold in endometriosis assessment presents a major challenge for the determination of true patient response and the clinical usefulness of the reported findings.

Clinical Safety:

The safety of elagolix was evaluated in women who completed the six months of treatment and met eligibility criteria for continued treatment in two uncontrolled, blinded six-month extension trials, Elaris EM-3 and Elaris EM-4, for a total treatment duration of up to 12 months.[1,2,3] The most common serious adverse events reported for elagolix subjects in Elaris EM-1 (N=475) and Elaris EM-2 (N=477) included appendicitis (0.3%), abdominal pain (0.2%), and back pain (0.2%).[1,2,3] In these trials, 0.2% of subjects treated with elagolix 150 mg once daily and 0.2% of subjects treated with elagolix 200 mg twice daily discontinued therapy due to serious adverse reactions compared to 0.5% of those given placebo.[1,2,3] For the two trials, the study discontinuation rates due to adverse reactions for low dose elagolix, high-dose elagolix, and placebo were 5.5%, 9.6%, and 6.0% respectively. [1,2,3] The most common treatment-emergent adverse

events which lead to study discontinuation for low dose and high dose elagolix were hot flushes/night sweats (1.1% and 2.5% respectively), and nausea (0.8% and 1.5%, respectively). Adverse events appeared to be dose-related.[1,2,3] Most discontinuations due to hot flushes or night sweats (10 of 17, 59%) and nausea (7 of 11, 64%) occurred within the first 2 months of therapy.[1,2,3] In the long-term phase 3 analysis which included studies Elaris EM-3 and Elaris EM-4, there were several discontinuations in the high dose elagolix group due to decreased BMD (3.6%) compared to low-dose (0.3%).[1,2,3] Common adverse reactions reported in 5% or more women in the low and high-dose elagolix treatment groups versus placebo were hot flush or night sweats, headache, nausea, mood swings, amenorrhea, depressive symptoms, anxiety, and arthralgia which are summarized below in **Table 2**. [1,2,3]

Table 2. Percentage of Subjects in Studies EM-1 and EM-2 with Treatment-Emergent Adverse Reactions in ≥5% of Subjects and ≥2% than Placebo [2,3]

	Elagolix 150 mg Once Daily; % N=475	Elagolix 200 mg Twice Daily; % N=477	Placebo; % N=734
Hot flush or night sweats	24	46	9
Headache	17	20	12
Nausea	11	16	13
Insomnia	6	9	3
Altered mood swings	6	5	3
Amenorrhea	4	7	<1
Depressed mood	3	6	2
Anxiety	3	5	3
Arthralgia	3	5	3

Severe adverse events with elagolix treatment included bone loss in both the higher dose (7%) and lower dose (2%) compared to placebo (<1%).[2,3] Other serious adverse events with elagolix therapy included suicidal ideation and mood disorders, hepatic transaminase elevations, and potential for reduced efficacy with estrogen-containing contraceptives. These occurred at a higher than placebo but still roughly 1% or less overall.[2,3]

For women with moderate hepatic impairment (Child-Pugh B), elagolix 150 mg once daily should be the maximum dose not to be used for more than 6 months.[3] Elagolix is contraindicated in women with severe hepatic impairment (Child-Pugh C), in women who are pregnant, have known osteoporosis, or are taking any strong organic anion transporting polypeptide (OATP) 1B1 Inhibitors.[3]

The FDA labeling limited the use of elagolix to a 6-month treatment period due to concerns of dose-dependent bone loss.[2,3] Both studies combined revealed a decline in BMD of greater than 8% at any anatomic site in 2 (0.4%) placebo subjects, 5 (1%) in the elagolix 150 mg once daily arm and 24 (6%) in the elagolix 200 mg BID arm. [2,3] The extension studies demonstrated 12 (5%) additional patients on elagolix 150 mg once daily and 51 (21%) additional patients in the elagolix 200 mg BID group had bone loss of greater than 8% at any site compared to pre-treatment baseline. [2,3] Elagolix treatment was also associated with greater incidence of depressive symptoms in both elagolix 200 mg and 150mg groups versus placebo (6% and 3% vs. 2%, respectively).[2,3]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Pain relief
2) Health-related quality of life
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Proportion of women with clinical response to dysmenorrhea as measured by the EDPID score at 3 months
2) Proportion of women with clinical response to non-menstrual pelvic pain as measured by the EDPID score at 3 months

Table 3. Pharmacology and Pharmacokinetic Properties. [2,3]

Parameter	
Mechanism of Action	GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland which results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone.
Oral Bioavailability	~50%
Distribution and Protein Binding	80%; to human plasma proteins
Elimination	Hepatic metabolism
Half-Life	4-6 hours
Metabolism	CYP3A (major); Minor pathways include: CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs)

Abbreviations: GnRH = gonadotropin releasing hormone; CYP = cytochrome P

Table 4. Comparative Evidence Table.[1,2]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
Taylor, et al (Study M12-665; Elaris EM-1) Phase 3 RCT, DB, PC study of patients with endometriosis	1. Placebo orally twice daily 2. Elagolix 150 mg orally once daily and oral placebo once daily	Demographics: -Mean age: 32 years -Race: -White: 87% -Black: 9% -Other: 4% -Mean BMI (kg/m^2): 28 -Analgesic Use (NSAID, Opioid, or both): >90% Key Inclusion Criteria:	ITT: 1. 374 2. 249 3. 248 PP: 1. 274 2. 195 3. 183 Attrition: 1. 27% 2. 22%	Primary Endpoints: Proportion of women with a clinical response to dysmenorrhea as measured by the EDPID score at 3-months: 1. 73/373 (19.6%) 2. 115/248 (46.4%) 3. 185/244 (75.8%) p<0.001 6-months: 1. 23.1%	27%/4 56%/2	D/C due to AE 1. 6% 2. 6% 3. 9% Bone density loss: 1. 1% 2. 2% 3. 7% Hot flush 1. 7% 2. 24%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. IVR system; overall similar baseline characteristics and prognostic variables Performance Bias: Unclear. All subjects required to self-administer study drug twice a day; Elagolix identical in appearance to placebo; all patients took 2 doses per day of respective treatment; patients were blind to study drug allocation for the 6-month placebo-controlled portion of trial. High incidence of hot flush adverse effects in

	3. Elagolix 200 mg orally twice daily 6-month trial	-Premenopausal woman between 18 to 49 years of age -Diagnosis of endometriosis established by surgical documentation within prior 10 years -Moderate or severe pain for DYS and NMPP <u>Key Exclusion Criteria</u>: -Any clinically relevant gynecological surgical history -Any medical condition that makes the woman an unsuitable candidate per investigator discretion -Any chronic pain condition not caused by endometriosis -History of osteoporosis, bone fracture, or evidence of metabolic bone disease revealed by DXA scan Z-score < 1.5 for lumbar spine, femoral neck, or total hip at screening	3. 26%	2. 42.1% 3. 75.3% p <0.001 Proportion of women with a clinical response to non-menstrual pelvic pain as measured by the EDPID score at 3-months: 1. 136/373 (36.5%) 2. 125/248 (50.4%) 3. 133/244 (54.5%) p <0.001 6-months: 1. 34.9% 2. 45.7% 3. 62.1% p <0.001 <u>Key Secondary Endpoints</u>: Change from baseline on a 0- to 3-point dyspareunia pain scale: 1. -0.29 2. -0.39 (p=0.144; NS) 3. -0.49 (p<0.01) Dysmenorrhea EDPID score change at 6 months from baseline: 1. -0.44 2. -0.89 (p<0.001) 3. -1.75 (p<0.001) Non-menstrual Pelvic Pain EDPID score change at 6 months from baseline: 1. -0.31 2. -0.48 (p<0.001) 3. -0.72 (p<0.001) (All primary outcomes used 97.5% CI)	19%/6 52%/2 14%/8 18%/6 14%/8 18%/6 NA NA NA NA NA NA	3. 42% Headache 1. 10% 2. 15% 3. 17% Insomnia 1. 2% 2. 6% 3. 7% Night Sweats 1. 1% 2. 2% 3. 6% 95% CI and p-values NR for all outcomes		treatment groups versus placebo may have unblinded participants. <u>Detection Bias</u>: Low. All study site personnel and pathologists at central laboratories used for evaluation were blinded. <u>Attrition Bias</u>: Unclear. Overall 25%; modified intention-to-treat analysis performed with LOCF. 28% of subjects had protocol deviations which included entry, withdrawal, receipt of incorrect or wrong dose, and receipt of excluded concomitant treatments <u>Reporting Bias</u>: Unclear. Regression model used to determine responder status was not adequately described and/or reported; calculation of point threshold for definitions of DYS and NMPP responders not adequately described a priori; Imputation details for subjects in primary analysis not given; LOCF before 3-month assessment unknown effects on 6 month analysis; Sponsor designed the trial, analyzed the data, and wrote first draft of study manuscript. <u>Other Bias</u>: Numerous authors reports grant support and personal fees from multiple manufacturers including the sponsor during the conduct of the study and serve in leadership roles of relevant medical journals outside the submitted work. **Applicability**: <u>Patient</u>: Extensive exclusion criteria may limit generalizability due to lack of patients with depressive and/or psychiatric disorders; significant comorbidity exclusions left up to the discretion of the provider; women with history of osteoporosis or bone disorders excluded <u>Intervention</u>: Low-dose elagolix given once daily and high dose given twice daily; patients able to continue naproxen and/or select opioids (hydrocodone, codeine, tramadol +/- acetaminophen) concurrently throughout study <u>Comparator</u>: Placebo comparator <u>Outcomes</u>: Subjective pain diaries used to formulate response on modified unvalidated

								symptom assessment tool; MCID values not available for any pain instruments utilized in study; Setting: United States, Puerto Rico and Canada; Three quarters (74.8%) of the subjects were enrolled at study sites in the U.S. and Canada
Taylor, et al (Study M12-671; Elaris EM-2) Phase 3 RCT, DB, PC study of patients with endometriosis	1. Placebo 2. Elagolix 150 mg orally once daily 3. Elagolix 200 mg orally twice daily 6-month trial	Demographics: -Similar to EM-1 Key Inclusion Criteria: -Same as EM-1 study Key Exclusion Criteria: -Same as EM-1 study	ITT: 1. 360 2. 226 3. 229 PP: 1. 270 2. 178 3. 184 Attrition: 1. 25% 2. 21% 3. 20%	Primary Endpoints: Proportion of women with a clinical response to dysmenorrhea as measured by the EDPID score at 3-months: 1. 80/353 (22.7%) 2. 96/221 (43.4%) 3. 163/225 (72.4%) p <0.001 6 months: 1. 25.4% 2. 46.2% 3. 76.9% p<0.001 Proportion of women with a clinical response to non-menstrual pelvic pain as measured by the EDPID score at 3-months: 1. 129/353 (36.5%) 2. 110/221 (49.8%) 3. 130/225 (57.8%) p <0.001 6-months: 1. 40.6% 2. 51.6% 3. 62.2% Secondary Endpoints: Change from baseline on a 0- to 3-point dyspareunia pain scale: 1. -0.30 2. -0.39 (p=0.172; NS) 3. -0.60 (p<0.001)	21%/5 50%/2 21%/5 52%/2 13%/8 21%/5 11%/10 22%/5 NA NA	D/C due to AE 1. 6% 2. 4% 3. 10% Bone density loss: 1. 1% 2. 2% 3. 7% Hot flush 1. 10% 2. 23% 3. 48% Headache 1. 14% 2. 19% 3. 23% Insomnia 1. 3% 2. 6% 3. 11% Total cholesterol % changes from baseline 1. -0.6 2. 4.6 3. 10.4	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. See EM-1 study Performance Bias: Unclear. See EM-1 study Detection Bias: Low. See EM-1 study Attrition Bias: Unclear. See EM-1 study; Overall 23%; 25% of subjects with protocol violations which included similar issues identified in EM-1 Reporting Bias: Unclear. See EM-1 study **Applicability**: Patient: See EM-1 study Intervention: See EM-1 study Comparator: See EM-1 study Outcomes: See EM-1 study; Setting: Argentina, Austria, Australia, Brazil, Czech Republic, Hungary, Italy, New Zealand, Poland, South Africa, Spain, the United States, and the United Kingdom; Three quarters (74.8%) of the subjects were enrolled at study sites in the U.S. and Canada

				Dysmenorrhea EDPID score change from baseline: 1. -0.52 2. -1.06 (p<0.001) 3. -1.65 (p<0.001) Non-menstrual Pelvic Pain EDPID score change from baseline: 1. -0.48 2. -0.63 (p<0.001) 3. -0.80 (p<0.001) (All primary outcomes used 97.5% CI)	 NA NA NA NA			

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; D/C = discontinuation; DXA = dual energy X-ray absorptiometry scan; DYS = dysmenorrhea; EDPID = Endometriosis Daily Pain Impact Diary; ITT = intention to treat; MCID = minimal clinically important difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NMPP = Non-menstrual pelvic pain; NR = not reported; NS = not significant; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial.

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Appendix 1: Prescribing Information Highlights

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

ORILISSA™ (elagolix) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ORILISSA is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis. (1)

----------DOSAGE AND ADMINISTRATION----------
Normal liver function or mild hepatic impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months. (2.1)

Moderate hepatic impairment: 150 mg once daily for up to 6 months. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Oral tablets: 150 mg and 200 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4)
- Known osteoporosis (4)
- Severe hepatic impairment (4)
- Strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (4)

----------WARNINGS AND PRECAUTIONS----------
- Bone Loss: Dose- and duration-dependent decreases in bone mineral density (BMD) that may not be completely reversible. Assess BMD in women with additional risk factors for bone loss (5.1)
- Reduced Ability to Recognize Pregnancy: ORILISSA may alter menstrual bleeding, which may reduce the ability to recognize pregnancy. Perform testing if pregnancy is suspected. Discontinue if pregnancy is confirmed (5.2)
- Suicidal Ideation and Mood Disorders: Advise patients to seek medical attention for suicidal ideation, suicidal behavior, new onset or worsening depression, anxiety, or other mood changes (5.3)
- Hepatic Transaminase Elevations: Dose-dependent elevations in serum alanine aminotransferase (ALT). Counsel patients on signs and symptoms of liver injury (5.4)
- Potential for Reduced Efficacy with Estrogen-Containing Contraceptives: Use non-hormonal contraception during treatment and for one week after discontinuing ORILISSA (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions and mood changes (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
See full prescribing information for a list of clinically important drug interactions (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2018

Elagolix

Goal(s):

- Promote safe use of elagolix in women with endometriosis-associated pain.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Initial: Up to 6 months
- Renewal: Up to 6 months for 150 mg daily dose with total cumulative treatment period not to exceed 24 months.

Requires PA:

- Elagolix

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 diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Has the patient tried and failed an adequate trial of preferred first line therapy options including continuous administration of combined hormonal contraceptives or progestins alone +/- acetaminophen +/- non-steroidal anti-inflammatory drugs (NSAIDs) -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness • First-line therapy options such as hormonal contraceptives or progestins do not require PA
7. Does the patient have a diagnosis of osteoporosis or related bone-loss condition?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors? (e.g. cyclosporine, gemfibrozil, etc.)	**Yes:** Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #11	**No:** Approve for 6 months
11. Is the dose for elagolix 150 mg once daily?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been receiving therapy with elagolix 150 mg once daily?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
2. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B?	**Yes:** Pass to RPh; Deny; medical appropriateness. (Elagolix 150 mg once daily is limited to 6-month maximum treatment duration in patients with moderate hepatic impairment per FDA labeling)	**No:** Go to #3
3. Has the patient's condition improved as assessed and documented by the prescriber?	**Yes:** Approve for up to 6 months. Total cumulative treatment period not to exceed 24 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

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Prior Authorization Update: Nusinersen

Purpose of Review:
The Oregon Health Authority (OHA) is seeking P&T support to participate in the Spinal Muscular Atrophy Research: The Effectiveness of Nusinersen (SMARTEN) project with the Center for Evidence-based Policy. The SMARTEN project is a collaboration of multiple state Medicaid agencies whose goal is to collect and analyze long-term, clinical outcomes data for nusinersen in type 1 and 2 spinal muscular atrophy. The purpose of this prior authorization update is to present changes to the Oregon Medicaid Fee-for-Service (FFS) prior authorization criteria which would be required for FFS participation in the project. These recommendations are not based on evidence. However, participating in the SMARTEN program would provide an opportunity to collect relevant clinical outcomes for an orphan drug for which there may not be additional clinical outcome data in the future from clinical trials.

If the OHA participates in SMARTEN, updates to FFS prior authorization criteria would be required to ensure that all outcomes of interest are collected at times specified in the SMARTEN protocol (at baseline, 6 months, then yearly until the 30 month follow-up period is complete). Motor skills are measured in SMARTEN by the Hammersmith Infant Neurological Examination Section 2 (HINE-2) for patients 2 years and younger, by the Hammersmith Functional Motor Scale-Expanded (HFMSE) for ambulatory patients 3 years and older, and by the revised Upper Limb module (RULM) for non-ambulatory patients 3 years and older. The SMARTEN project is approved through the Oregon Health and Science University Institutional Review Board and state Medicaid agencies are currently developing data use agreements for the SMARTEN project.

Recommendation:
- Consider updating the prior authorization criteria to document necessary outcomes data for OHA participation in the SMARTEN project.

Proposed Prior Authorization Criteria:

Nusinersen

Goal(s):
- Approve nusinersen for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

Length of Authorization:
- Up to 6~~8~~ months for initial approval and up to 12 months for renewal.

Requires PA:

- Nusinersen (billed as a pharmacy or physician administered claim)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code. Go to #2	
2. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Have all of the following information been documented by the provider: • Date of SMA diagnosis • Prior enrollment in clinical trials for nusinersen	**Yes:** Go to #4 Document the following: • Date of SMA diagnosis: _____ • Has the patient has previously been enrolled in nusinersen clinical trials? _____	**No:** Pass to RPh. Request additional information.
~~3.~~4. Does the patient have type 1, 2 or 3 Spinal Muscular Atrophy documented by genetic testing and at least 2 copies of the SMN2 gene?	**Yes:** Go to #5~~4~~ Document SMA type: _____	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~4.~~5. Is a baseline motor assessment available such as one of the following functional assessment tools: Type 3 SMA: • Hammersmith Infant Neurological Examination (HINE-2) • Hammersmith Functional Motor Scale (HFSME) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • Upper Limb Module (ULM) • 6-Minute Walk Test Type 1 and 2 SMA: • Patients <2 years old: Hammersmith Infant Neurological Examination (HINE-2) • Patients >3 years old: Hammersmith Functional Motor Scale (HFSME) (for ambulatory patients) or revised Upper Limb Module (RULM)(for non-ambulatory patients)	**Yes:** Go to #6~~5~~ Document the following: • Baseline motor assessment score: _____ • Tool used: _____ • Measurement date: _____ • Provider type who administered the tool: _____	**No:** Pass to RPh. Deny; medical appropriateness.
~~5.~~6. Is the patient ventilator dependent (using at least 16 hours per day on at least 21 of the last 30 days)? Note: This assessment does not apply to patients who require ventilator assistance	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7~~6~~.
~~6.~~7. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating spinal muscular atrophy?	**Yes:** For initial approval, approve 4~~5~~ doses over ~~8~~6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the following information been documented by the provider: a. Recent assessment of motor function with one of the following scales (preferably the same scale used at baseline): i. For ≤2 years old: Hammersmith Infant Neurological Examination (HINE-2) ~~i.~~ii. For patients >3 years old: Hammersmith Functional Motor Scale (HFSME) (for ambulatory patients) or revised Upper Limb Module (RULM)(for non-ambulatory patients) b. Need for permanent ventilation (i.e., 16 hours or greater in a day) and date of initiation if applicable	**Yes:** Go to #2 Document the following: • Motor assessment score: _____ • Tool used: _____ • Measurement date: _____ • Provider type who administered the tool: _____ Document date of permanent ventilator initiation if applicable: _____	**No:** Pass to RPh. Request additional information.
~~2. Has the patient's motor function improved as demonstrated by:~~ ~~o Improvement from baseline motor function score documented within one month of renewal request~~ ~~o~~ ~~o AND~~ ~~o More areas of motor function improved than worsened~~	~~**Yes:** Approve for 12 months~~	~~**No:** Pass to RPh; Deny; medical appropriateness.~~

Renewal Criteria		
2. Has the patient experienced any serious adverse events related to nusinersen treatment?	**Yes:** Pass to RPH; Deny; medical appropriateness Document the following: • Serious adverse event: _____ _____ • Date: _____	**No:** Approve for 12 months

P&T Review: *11/18 (JP); 7/17; 3/17*
Implementation: *TBD; 9/1/17; 5/17*

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Prior Authorization Criteria Update: Growth Hormones

Purpose of Update:

The purpose of this prior authorization (PA) update is to align current fee-for-service PA criteria with the Health Evidence Review Commission (HERC) guidance for use of growth hormones (GH). Growth hormones are indicated for a variety of childhood and adult conditions. FDA approved indications for GH vary by brand name product and are presented in **Table 1**. In August 2018, the HERC updated guidelines to remove restrictions on the types of childhood diseases that are covered for treatment with GH. Guidance continues to specify that treatment with GH for children should only continue until adult height, as determined by bone age, is achieved.[1] Treatment for adult human growth hormone deficiency is currently not listed as a funded condition on the prioritized list.[1]

Table 1. Pediatric and Adults FDA Approved Indications for Growth Hormone[2,3]

	Genotropin®	Humatrope®	Norditropin®	Nutropin AQ®	Omnitrope®	Saizen®	Serostim®	Zomacton®	Zorbtive®
Pediatric Indications									
GHD	X	X	X	X	X	X		X	
Prader-Willi Syndrome	X		X		X				
Noonan Syndrome			X						
Turner Syndrome	X	X	X	X	X			X	
Idiopathic Short Stature	X	X	X	X	X			X	
SHOX Deficiency		X						X	
CKD with Growth Failure				X					
Small for Gestational Age	X	X	X		X			X	
HIV Associated Cachexia							X		
Adult Indications									
GHD	X	X	X	X	X	X		X	
HIV Associated Cachexia							X		
Short Bowel Syndrome									X

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

Recommendation:

- Update the prior authorization criteria to align with HERC coverage guidance.

Author: Sarah Servid, PharmD November 2018

References:

1. Health Evidence Review Commission. HERC Draft Meeting Minutes. August 9, 2018. https://www.oregon.gov/oha/HPA/CSI-HERC/MeetingDocuments/HERC-Minutes-8-9-2018.pdf Accessed September 19, 2018.
2. Somatropin, E-Coli Derived. In: IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. https://www-micromedexsolutions-com.liboff.ohsu.edu/ Accessed September 18, 2018.
3. Somatropin. In: Lexicomp (electronic database). Wolters Kluwer. Hudson, OH. http://online.lexi.com.liboff.ohsu.edu/action/home. Accessed September 18, 2018.

Appendix 1. Proposed Prior Authorization Criteria

Growth Hormones

Goal(s):

- Restrict use of growth hormone (GH) for funded diagnoses where there is medical evidence of effectiveness and safety.

NOTE: ~~Treatment with growth hormone (GH) is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, short stature homeobox-containing gene (SHOX), chronic kidney disease (stage 3 or higher) and those with renal transplant.~~ Treatment with GH in children should continue only until adult height as determined by bone age is achieved. Treatment is not included for isolated deficiency of human growth hormone ~~or other conditions~~ in adults.

Length of Authorization:

- Up to 12 months

Requires PA:

- All GH products require prior authorization for OHP coverage. Treatment of human growth hormone deficiency ~~GH treatment~~ for adults is not funded by the OHP.

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/

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

Initial Approval Criteria		
2. Is the request for an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for initiation of growth hormone?	**Yes:** Go to #4	**No:** Go to **Renewal Criteria**
~~2.~~4. Is the patient an adult (>18 years of age)?	**Yes:** ~~Pass to RPh. Deny; not funded by the OHP~~Go to #9	**No:** Go to #5~~4~~
~~Is this a request for initiation of growth hormone?~~	~~**Yes:** Go to #5~~	~~**No:** Go to **Renewal Criteria**~~
~~3.~~5. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
~~4.~~6. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #7
~~Is the diagnosis one of the following?~~ ~~Turner's syndrome (ICD10 Q969)~~ ~~Noonan's syndrome (ICD10 E7871-7872, Q872-873, Q875, Q8781, Q8789, Q898)~~ ~~Prader-Willi syndrome (PWS) (ICD10 Q871)~~ ~~Pituitary dwarfism (ICD10 E230)~~ ~~Short stature homeobox-containing gene (SHOX) (ICD10 R6252)~~ ~~Chronic kidney disease (CKD, Stage ≥3) (ICD10 N183-N185)~~ ~~Renal transplant (ICD10 Z940)~~	~~**Yes:** Document and go to #7~~	~~**No:** Pass to RPh. Deny; not funded by the OHP.~~
~~5.~~7. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
8. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the request for isolated human growth hormone deficiency in an adult (E23.0)?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #10
~~6.~~10. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #11
~~7.~~11. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Is the request for continuation of therapy which was initiated as an adult (>18 years of age)?	**Yes:** Go to #5	**No:** Go to #3
~~2.~~3. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
~~3.~~4. Is male bone age <16 years or female bone age <14 years?	**Yes:** Go to #6~~4~~	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for isolated human growth hormone deficiency in an adult (E23.0)?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #6
~~4.~~6. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #7~~5~~

~~5.~~7. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 12 months

P&T Review: 11/18 (SS); 9/17; 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
Implementation: TBD; 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03

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Prior Authorization Criteria Update: Androgens, Topical and Parenteral

Purpose of Update:

The purpose of this prior authorization (PA) update is to align current fee-for-service PA criteria with the Health Evidence Review Commission (HERC) guidance for use of testosterone replacement for testicular hypofunction. Testosterone products are used in a variety of conditions such as transgender health, primary hypogonadism, metastatic breast cancer, and weight loss with HIV-associated wasting. Currently for adults, topical formations and non-preferred products require PA. In patients less than 18 years of age, a PA is required for all patients. In October 2018, HERC recommended the following guidance on use of testosterone in patients with testicular hypofunction for implementation in January 2019.[1] Previous HERC guidance on androgens has only addressed use specifically for transgender health. This new guideline note does not apply to testosterone replacement therapy for HIV-associated weight loss, delayed puberty, treatment of metastatic breast cancer, or transgender health.

Line 467 Gonadal Dysfunction, Menopausal Management: Testosterone replacement therapy is included on this line for testicular hypofunction or dysfunction only when all of the following inclusion criteria are met and none of the exclusion criteria apply.

Inclusion criteria:

1) The patient is a male 18 years of age or older; AND
2) The patient has had TWO morning (between 8 a.m. to 10 a.m.) tests (at least 1 week apart) at baseline demonstrating low testosterone levels as defined by the following criteria:
    a. Total serum testosterone level less than 300ng/dL (10.4nmol/L); OR
    b. Total serum testosterone level less than 350ng/dL (12.1nmol/L) AND free serum testosterone level less than 50pg/mL (or 0.174nmol/L); AND
3) Patient has received ONE of the following diagnoses:
    a. Primary Hypogonadism (congenital or acquired): defined as testicular failure due to such conditions as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, trauma, or toxic damage from alcohol or heavy metals; OR
    b. Hypogonadotropic Hypogonadism (congenital or acquired): as defined by idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma or radiation

Exclusion criteria:

1) Patient has ANY of the following contraindications:
    a. Breast cancer or known or suspected prostate cancer

b. Elevated hematocrit (>50%)
c. Untreated severe obstructive sleep apnea
d. Severe lower urinary tract symptoms
e. Uncontrolled or poorly-controlled heart failure

2) Patient has experienced a major cardiovascular event (such as a myocardial infraction, stroke, acute coronary syndrome) in the past six months
3) Patient has uncontrolled or poorly-controlled benign prostate hyperplasia or is at a higher risk of prostate cancer, such as elevation of PSA after initiating testosterone replacement therapy

Recommendation:

- Update the prior authorization criteria to align with HERC coverage guidance.

References:

1. Health Evidence Review Commission. HERC Draft Meeting Minutes. October 4, 2018. https://www.oregon.gov/oha/HPA/DSI-HERC/MeetingDocuments/HERC-Materials-10-4-18.pdf. Accessed October 22, 2018.

Appendix 1. Proposed Prior Authorization Criteria

Testosterone

Goal(s):

- Restrict use to medically appropriate conditions funded under the Oregon Health Plan (use for sexual dysfunction or body-building is not covered)

Length of Authorization:

- Up to 12 months

Requires PA:

- All ~~topical~~ testosterone products ~~and non-preferred injectable testosterone products in adults~~
- ~~All testosterone products in pediatric patients <18 years of age~~

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication requested for AIDS-related cachexia?	**Yes:** Go to #8	**No:** Go to #3
3. Is the medication requested for one of the following diagnoses? a. Primary Hypogonadism (congenital or acquired): defined as testicular failure due to such conditions as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, trauma, or toxic damage from alcohol or heavy metals; OR b. Hypogonadotropic Hypogonadism (congenital or acquired): as defined by idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma or radiation ~~Does the diagnosis for the medication requested include any of the following?~~ ~~• Testicular Hypofunction; or~~ ~~• Hypopituitarism and related disorders; or~~ • ~~AIDS-related cachexia?~~	**Yes:** Go to #~~5~~4	**No:** Go to #~~3~~6

Approval Criteria		
4. Is there documentation of 2 morning (between 8 a.m. to 10 a.m.) tests (at least 1 week apart) demonstrating low testosterone levels at baseline as defined by the following criteria: a. Total serum testosterone level less than 300ng/dL (10.4nmol/L); OR b. Total serum testosterone level less than 350ng/dL (12.1nmol/L) AND free serum testosterone level less than 50pg/mL (or 0.174nmol/L);	**Yes:** Go to #5	**No:** Deny; medical appropriateness
5. Is there documentation based on submitted chart notes of any of the following diagnoses: a. A recent major cardiovascular event (i.e., myocardial infarction, stroke or acute coronary syndrome) within the past 6 months b. Heart failure with uncontrolled symptoms (i.e., NYHA Class III-IV, presence of edema, or evidence of fluid retention) c. Benign prostate hyperplasia with uncontrolled symptoms or presence of severe lower urinary tract symptoms (i.e., frequent symptoms of incomplete emptying, increased frequency, intermittency, urgency, weak stream, straining, or nocturia) d. Breast cancer e. Prostate cancer (known or suspected) or elevated PSA with prior use of testosterone f. Untreated obstructive sleep apnea with symptoms ~~a.~~g. Elevated hematocrit (>50%)	**Yes:** Deny; medical appropriateness	**No:** Go to #8

Approval Criteria		
~~2.~~6. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #7	**No:** Go to #9~~6~~
~~3.~~7. Have **all** of the following criteria been met? • Patient has the capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.	**Yes:** Go to #8~~5~~	**No**: Pass to RPh. Deny; medical appropriateness
~~4.~~8. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a co-pay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
~~5.~~9. RPh only: all other indications need to be evaluated to see if funded under the OHP. Note: Testosterone should not be prescribed to patients who have any contraindicated diagnoses listed in question #5.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If not funded: Deny; not funded by the OHP

P&T Review: *11/18 (SS); 11/15; 2/12; 9/10; 2/06; 2/01; 9/00*
Implementation: *TBD; 5/1/16; 1/1/16; 7/31/14; 5/14/12, 1/24/12, 1/1/11, 9/1/06*

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Drug Class Update with New Drug Evaluation: Substance Use Disorders

Date of Review: November 2018
Generic Name: Lofexidine

End Date of Literature Search: 8/10/2018
Brand Name (Manufacturer): Lucemyra™ (US World Meds)
Dossier Received: Yes

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

Purpose for Class Update:
Review new published data for management of substance use disorders to help inform whether current Oregon Health Plan (OHP) policies remain appropriate for access to these medications. To review evidence for a new alpha2-adrenergic agonist, lofexidine, recently approved by the United States (U.S.) Food and Drug Administration (FDA) for short term mitigation of withdrawal symptoms after abrupt discontinuation of short-acting opioids.

Research Questions:
1. Is there new evidence for differences in efficacy or harms between drug therapies for substance use disorder (SUD)?
2. Are there subpopulations based on demographics (i.e., adolescents, elderly, pregnant women) in which a drug for SUD may be more effective or less harmful than other drugs?
3. What is evidence for the safety and efficacy for lofexidine to mitigate withdrawal symptoms from opioid discontinuation?

Conclusions:
CLASS REVIEW:
- Since the last review, the following new evidence has been identified for management of SUD: 3 systematic reviews and meta-analyses, [1-3] 1 randomized controlled trial (RCT), [4] and 1 clinical practice guideline.[5] In addition, 1 new formulation,[6] and 1 new indication has been approved.[7] Due to the opioid epidemic, most of recent evidence is focused on management of opiate use disorder (OUD) with a focus on withdrawal symptoms and completion of withdrawal treatment. There is insufficient data to assess long term outcomes such as relapse rates and sustained abstinence.
- A high quality systematic review evaluated evidence on safety and efficacy of alpha2-adrengeric agonists (lofexidine and clonidine) in managing the acute phase of opioid withdrawal. Moderate quality evidence from three studies comparing alpha2-adrenergic agonists and placebo showed completion of withdrawal treatment was significantly more likely with an adrenergic agonist (Risk Ratio (RR) 1.95; 95% confidence interval (CI) 1.34 to 2.84) and severe withdrawal was significantly less likely with an adrenergic agonist (RR 0.32; 95% CI 0.18 to 0.57).[2] For the comparison of alpha2-adrenergic agonists with tapering doses of methadone, moderate quality evidence suggests there is no significant difference in severity of the withdrawal episode (Standardized Mean Difference (SMD) 0.13; 95%CI -0.24 to 0.49).[2] Moderate quality evidence also shows no significant differences were observed in incidence of adverse

events (RR 2.02; 95% CI 0.62 to 6.64; 203 participants) or completion rates of withdrawal treatment (RR 0.91; 95% CI 0.75 to 1.11; 8 trials; 489 participants) for the adrenergic agonists versus methadone comparisons.[2]

- A moderate quality systematic review and meta-analysis assessed comparative evidence for the use of buprenorphine in management of opioid withdrawal.[1] The included trials compared buprenorphine to clonidine, lofexidine, and methadone or different buprenorphine dosing regimens.[1] A meta-analysis of 5 moderate quality trials supports a conclusion of no difference between buprenorphine and methadone for withdrawal completion rates (RR 1.04; 95% CI 0.91 to 1.20; N=457).[1] Relative to clonidine or lofexidine, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) during the treatment episode with an effect size that is considered to be small to moderate (SMD −0.43; 95% CI −0.58 to −0.28; N = 902; studies = 7; moderate quality).[1] Patients receiving buprenorphine stayed in treatment more days than adrenergic agonists (mean days in treatment with buprenorphine ranged from 25% to 97%; mean days in treatment with adrenergic agonists ranged from 21% to 70%; SMD 0.92, 95% CI 0.57 to 1.27; N=558; studies=5; moderate quality) and were more likely to complete withdrawal treatment (RR 1.59, 95% CI 1.23 to 2.06; N=1264; studies=12; moderate quality).[1] The authors did not report absolute risk reduction for these outcomes.
- In 2017 the Canadian Agency for Drugs and Technologies in Health (CADTH) published a rapid response report to evaluate the comparative effectiveness of monotherapy buprenorphine and buprenorphine-naloxone formulations (e.g., sublingual films, sublingual tablets, implants) for treatment of OUD.[3] Of the 5 RCTs which met inclusion criteria, all but two were industry-sponsored and there were limitations with respect to study design (e.g., non-inferiority, open-label), clinically relevant outcomes and treatment duration.[3] All the buprenorphine formulations examined in the selected studies showed a similar clinical response in patients with OUD, with significantly higher rates of abuse, misuse and diversion found in sublingual buprenorphine-naloxone tablet formulations compared to the film preparations.[3] The use of buprenorphine implants was associated with high rates of treatment retention.[3] The rates of adverse effects were low among buprenorphine formulations with no significant differences observed.[3] The findings indicate that the use of newer buprenorphine formulations may be safe to use in this population, but the included trials were relatively short in duration and may have been underpowered to detect rarer adverse effects.[3]
- The Canadian Research Initiative in Substance Misuse (CRISM) developed a national guideline for treatment of OUD.[5] Using the AGREE-II instrument, the guidelines were appraised has having high methodological quality.[8] Key recommendations for first and second-line OUD treatments in adults based on high quality evidence include:
    - While shown to be essentially as efficacious as methadone in clinical trials, buprenorphine–naloxone has several safety advantages over methadone, including a reduced risk of fatal overdose because of its lower potential for respiratory depression.[5] Given the superior safety profile of buprenorphine–naloxone and its potential for flexible take-home dosing in comparison to other opioid agonist medications, initiate opioid agonist treatment (with buprenorphine–naloxone whenever feasible), to reduce the risk of toxicity, morbidity and death, and to facilitate safer take-home dosing (strong recommendation).[5]
    - For individuals responding poorly to buprenorphine–naloxone, consider transition to methadone treatment (strong recommendation).[5]
    - Initiate opioid agonist treatment with methadone when treatment with buprenorphine–naloxone is not the preferred option such as those individuals with a high opioid tolerance, severe opioid withdrawal symptoms or those requiring supervised administration due to poor adherence (strong recommendation).[5]
- The FDA approved buprenorphine extended-release injection (Sublocade™) to treat patients with moderate-to-severe OUD who have first received treatment with a transmucosal buprenorphine-containing product for at least 7 days.[6] Buprenorphine extended-release injection is a 100 or 300 mg subcutaneous injection administered once a month by a health care professional (HCP).[6]
- In April 2017, Bunavail® (buprenorphine and naloxone) buccal film received expanded approval to use this formulation during the induction phase of treatment for patients dependent on heroin or short-acting opioid products.[7] The previous approved dosing for Bunavail® only addressed the maintenance phase of treatment.[7]

- No sub-group analyses were available for data specific to Medicaid patients or specific populations (e.g., pregnant women, incarcerated individuals, adolescents, or elderly patients).

LOFEXIDINE NEW DRUG EVALUATION

- There is poor quality evidence from one published trial that adults undergoing acute withdrawal from opioids or heroin experienced less symptoms with lofexidine compared to placebo as assessed by the mean Short Opioid Withdrawal Scale (SOWS)-Gossop on day 3 of treatment.[9] For this trial, the investigators assumed a minimal clinically significant difference of 5 points.[9] The mean SOWS-Gossop scores on day 3 were 8.67 and 6.32 for placebo and lofexidine, respectively, which demonstrated a significant statistical difference between the 2 arms (least squares mean difference (LSMD) = -2.24, 95% CI -3.88 to -0.6; p=0.009).[9] However, this difference did not meet the pre-specified clinical significance of a 5 point difference.
- Comparison of time-to-dropout between placebo and lofexidine was selected as a co-primary endpoint by the investigators.[9] Each study day was divided into four 6 hour time quadrants (i.e., 6am–12pm; 12pm–6pm; 6pm–12am; and, 12am–6am) and time-to-dropout was measured as the number of 6 hour time quadrants until withdrawal during the 5-day treatment phase.[9] Poor quality evidence showed that early termination was statistically higher in the placebo group compared to lofexidine as assessed by the mean number of time quadrants (6.4 vs. 6.9 respectively; p=0.0034).[9] However, the calculated difference was 0.5 time quadrants, or 3 hours, which is not a clinically significant difference in time to withdrawal.
- Moderate quality evidence showed early termination of opioid withdrawal treatment was significantly more common in the placebo group compared to lofexidine (61% versus 44% of subjects, respectively).[9]
- In clinical trials the most common adverse reactions that occurred with lofexidine in 10% or more of subjects compared to placebo, were orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth during 5 to 7 days of treatment.[10] Rates of serious and severe adverse effects requiring treatment discontinuation were relatively low.
- There is insufficient data to evaluate the efficacy of lofexidine to other treatment options such as clonidine.

Recommendations:

- Make lofexidine non-preferred on the Prioritized Drug List (PDL) and implement PA criteria to ensure appropriate utilization (**Appendix 5**).
- Add extended release subcutaneous buprenorphine injection (Sublocade™) to PA criteria for buprenorphine and buprenorphine/naloxone products (**Appendix 6**).
- Evaluate comparative drug costs in executive session.

Summary of Prior Reviews and Current Policy

Treatment for SUD was last reviewed by the Pharmacy and Therapeutics Committee in September 2016. High quality evidence was identified for use of acamprosate and oral naltrexone to decrease alcohol consumption in patients with alcohol use disorder when used concurrently with psychosocial interventions; however, there is insufficient evidence to support their use based on an improvement in clinically relevant health outcomes (i.e., morbidity or mortality) alone.[11] The 2014 clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) for the management of substance abuse disorders strongly recommends that treatment choice between acamprosate, disulfiram, naltrexone (oral or extended-release injection) or topiramate be individualized based on specific needs and patient preferences.[12] In all cases, strong psychosocial interventions are needed to successfully treat patients with alcohol use disorder.[12]

For patients with a diagnosis of OUD, the VA/DoD guideline strongly recommends buprenorphine/naloxone or methadone in an Opioid Treatment Program (OTP) depending on specific patient needs or preferences.[12] An OTP is an accredited program with Substance Abuse and Mental Health Services Administration (SAMHSA) certification and Drug Enforcement Administration (DEA) registration in which providers may administer and dispense medications FDA-approved to treat opioid addiction including methadone and buprenorphine.[13] Alternatively, buprenorphine without naloxone is strongly recommended to be used in patients who are pregnant, and extended-release injectable naloxone is recommended as an option for patients for whom buprenorphine/naloxone or methadone is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for a sufficient period of time.[14] In all cases, strong psychosocial interventions are needed to successfully treat patients with opioid use disorder. Otherwise, there is insufficient evidence to know with certainty whether buprenorphine products are more effective or safer when given in designated OTP or in private physician offices, or whether daily supplies should be administered or multi-day supplies may be administered.

In the Oregon Health Plan (OHP) Fee-For-Service (FFS) program, preferred agents on the Preferred Drug List (PDL) include: buprenorphine/naloxone film and sublingual tablets, acamprosate tablets, naltrexone extended-release injection, and naltrexone tablets. **Appendix 1** lists the current PDL status for medications used in treatment of SUD. Buprenorphine sublingual tablets are restricted for use in pregnant females and all buprenorphine monotherapy products require prior authorization (PA) as outlined in the clinical PA criteria listed in **Appendix 6.** In the first quarter of 2018 (January 2018 through April 2018), 75% of OHP FFS claims for SUD medications were for buprenorphine/naloxone, 22% of claims were for naltrexone, and 3% of claims were for acamprosate.

Background:

Substance use disorders can develop in individuals who use tobacco, alcohol, opioids, or other addicting drugs in harmful quantities.[12] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) specifically recognizes SUDs related to substances such as tobacco, alcohol, opioids, cannabis, sedatives, and anxiolytics.[15] According to the DSM-V, SUDs are associated with a pattern of inappropriate substance use that adversely affects one's personal or professional life or results in noticeable distress.[15] Opioid use disorder is the diagnostic term used for a chronic neurobiological disease characterized by a problematic pattern of opioid use leading to significant impairment or distress and includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, the opioid is used in doses far greater than the amount needed for treatment of that medical condition.[16]

In 2016, over 63,000 persons died of a drug overdose in the United States; 66% involved an opioid.[17] In July 2018, the Center for Disease Control (CDC) issued an update to alert health care providers about new developments in the opioid epidemic related to increasing trends of overdoses and deaths due to synthetic opioids related to fentanyl and fentanyl analogs.[18] The CDC guidance states multiple dosages of naloxone may need to be administered per overdose event because of fentanyl and fentanyl analog's increased potency relative to other opioids.[18] A recently published study characterizes trends for synthetic opioid involvement (primarily illicit fentanyl) in drug overdose deaths using 2010-2016 mortality data.[19] In 2016, synthetic opioids eclipsed prescription opioids as the most common drug involved in overdose deaths in the United States.[19] The researchers found that 46% of the 42,249 opioid-related overdose deaths in 2016 involved synthetic opioids, up from 14% of 21,089 opioid-related deaths in 2010 ($p < 0.01$).[19] Of 42,249 opioid-related overdose deaths in 2016, synthetic opioids were involved in 19,413 deaths, prescription opioids in 17,087 deaths, and heroin in 15,469 deaths.[19] In August 2018, the CDC issued an additional alert regarding increasing trends in OUD observed in pregnant women.[20] Nationally, the prevalence of opioid use disorder in pregnant women more than quadrupled during 1999–2014 (from 1.5 per 1,000 delivery hospitalizations to 6.5; $p<0.05$).[20] According to the CDC, continued national, state, and provider efforts to prevent, monitor, and treat opioid use disorder among reproductive-aged and pregnant women are needed.[20]

Medication-assisted treatment (MAT) is a comprehensive approach that combines approved medications with counseling and other behavioral therapies to treat SUDs associated with alcohol, tobacco and opioids. Methadone, buprenorphine, or naltrexone are the 3 FDA-approved medications used to manage OUD. For treatment of OUD, methadone can only be administered at a SAMHSA-certified OTP.[13] Buprenorphine can be prescribed and administered in a primary care setting by physicians, physician's assistants, and nurse practitioners with a Drug Addiction Treatment Act (DATA) waiver.[13] Naltrexone is not subject to these federal regulations.[13] The long acting injectable formulation of naltrexone can be given in both general healthcare and specialty substance use disorder treatment settings. According to the VA/DoD guidelines, there is insufficient evidence at this time to recommend oral naltrexone because it requires a highly motivated patient to be successful and it has not consistently demonstrated superiority to control groups at treatment retention or in opioid consumption.[12] Patients who initiate naltrexone treatment must be free of opioid dependence (i.e., greater than 7 days without acute withdrawal symptoms).[16]

Buprenorphine, a partial opioid agonist, was originally FDA approved as an immediate release injection administered every six to eight hours to manage acute pain.[21] The daily buccal film and weekly transdermal patch formulations of buprenorphine are FDA-approved to manage chronic pain, but not OUD.[21] In 2016, the U.S. Food and Drug Administration (FDA) approved Probuphine®, a monotherapy buprenorphine product administered via subdermal implant for management of OUD.[22] The implant embeds buprenorphine in four matchstick-size rods in a patient's upper arm that release medication over a 6 month period.[22] The buprenorphine implant is designed only for patients who have received buprenorphine/naloxone maintenance therapy for at least 3 months.[22] In November 2017, the FDA approved Sublocade™ a once-monthly buprenorphine extended-release subcutaneous injection for management of OUD.[6] Sublocade™ uses a proprietary delivery system that induces the drug to form a solid deposit inside the patient, gradually biodegrading to an active therapeutic agent.[6] The FDA approved this product using priority and fast track pathways due to the dramatic increase in people diagnosed with OUD requiring treatment.[6] The safety and efficacy of Sublocade™ were evaluated in two clinical studies in adults with a diagnosis of moderate-to-severe OUD who began treatment with buprenorphine/naloxone sublingual film for at least 7 days before transitioning to the extended-release subcutaneous injection.[6]

The combination of buprenorphine and naloxone was FDA approved as an indication for OUD in 2002.[23] Co-formulation of buprenorphine with naloxone reduces the risk of diversion and non-medical use compared to monotherapy preparations. The naloxone component exerts no antagonist effect when taken sublingually as directed, but can precipitate withdrawal symptoms in opioid-tolerant individuals if injected.[5] The once daily buprenorphine/naloxone combinations are available in a variety of doses and formulations including sublingual tablets, buccal film, and sublingual film. **Table 1** provides an overview of the 4 medications FDA-approved to manage opioid withdrawal and dependence in patients with OUD.

Table 1. Comparison of medication-assisted treatment options for moderate-to-severe opioid use disorder[24]

	Methadone	**Naltrexone**	**Buprenorphine/Naloxone**	**Buprenorphine**
Mechanism of Action at mu-Opioid Receptor	Agonist	Antagonist	Partial Agonist/Antagonist	Partial Agonist
DEA Schedule	Schedule II	Legend Drug	Schedule III	Schedule III
Phase of Treatment	-Medically supervised withdrawal -Maintenance of opioid dependence	-Prevention of relapse to opioid dependence, following medically supervised withdrawal	-Treatment of opioid dependence	-Treatment of opioid dependence in stable patients initiated on buprenorphine/naloxone therapy for at least 7 days (Sublocade™) or 3 months (Probuphine®).

Setting	Administered at SAMHSA-certified OTP	Tablets provided as take-home medication. Monthly injection requires administration by a health care provider.	Prescribing restricted to a health care provider with DATA waiver. Can be provided as take-home medication.	-Prescribing and administration restricted to a health care provider with DATA waiver. -Providers who insert/remove inserts must obtain special live training and be certified through Probuphine® REMS program. -Sublocade™ can only be dispensed and administered by pharmacies and health care providers that have enrolled in REMS program and are certified to dispense/purchase. Prescriber offices that only order Sublocade® from a certified pharmacy for a specific patient are exempt from certification.
Brand Name and Formulation	Dolophine®: Oral Tablets Intensol™, Methadose™: Oral Concentrate Diskets®: Dispersible Tablets	Generic: Oral Tablets Vivitrol®: Extended Release IM Injection	Generic: SL Tablets Zubsolv®: SL Tablets Bunavail®: Buccal Film Suboxone®: SL or Buccal Film	Generic: SL Tablets Probuphine®:Subdermal Implant Sublocade™: Extended Release SC Injection
Recommended Dosing for OUD	Withdrawal: Up to 40 mg per day Maintenance: 60 to 120 mg once daily	Tablet: 50 mg once daily IM injection: 380 mg once monthly	For maintenance dosing all forms are administered once daily. Maximum recommended daily dose: buprenorphine 24 mg/naloxone 6 mg	SL tablets: 8 to 16 mg once daily (recommended for pregnant women) Subdermal: 4 X 80 mg (320mg) implants inserted into one upper arm and removed after 6 months Extended release SC injection: 300 mg x 2 months followed by 100 mg once monthly

Abbreviations: DATA = Drug Addiction Treatment Act; DEA = Drug Enforcement Agency; IM = intramuscular; OTP = Opioid Treatment Program; REMS = Risk Evaluation and Mitigation Strategy; SAMHSA = Substance Abuse and Mental Health Services Administration; SC = subcutaneous, SL = sublingual

Clinically important outcomes for studies that assess efficacy of substance use disorders can include: treatment retention/completion; illicit substance use or any alcohol consumption; risk behaviors (injecting, sexual, polysubstance use, overdoses, hospital admissions); quality of life as assessed by validated scales (e.g. World Health Organization (WHO) Quality of Life scale), employment, physical health as assessed by validated scales (e.g., 36-item Short Form), adverse effects and aberrant opioid-related behaviors (e.g., multiple prescribers, lost medications, or unauthorized dose increases).[25] Validated clinical scales that measure opioid withdrawal symptoms, for example, the Objective Opioid Withdrawal Scale (OOWS), SOWS, and Clinical Opioid Withdrawal Scale (COWS), may be used to

assist in the evaluation of patients with opioid use disorder.[26] The SOWS-Gossop is a 10 item assessment in which patients use a 4 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) to rate their withdrawal symptoms in the previous 24 hours.[27] Studies indicate that a change score of 2–4 points on the SOWS-Gossop scale is clinically meaningful improvement.[28] Symptoms assessed on the SOWS-Gossop questionnaire include: feeling sick, stomach cramps, muscle spasms, feeling cold, heart pounding, muscle tension, aches and pains, yawning, runny eyes, and insomnia.[27] Certain relevant symptoms of withdrawal including vomiting, sweating, agitation, diarrhea, depression, and anxiety are not assessed by the SOWS scale, which is a drawback of this instrument.[29] The OOWS-Handelsman is a clinician-rated assessment of physical signs of withdrawal which ranges from 0 to 13 points.[29]

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, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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 Review: Alpha2-adrenergic Agonists for Management of Opioid Withdrawal

A high quality systematic review and meta-analysis evaluated the evidence for the effectiveness of alpha2-adrenergic agonists (clonidine, lofexidine, and guanfacine) in symptomatic management of the acute phase of opioid withdrawal.[2] The literature search was completed through November 2015 and found 26 randomized controlled trials involving opioid-dependent participants in which an alpha2-adrenergic agonist was compared to another adrenergic agonist, placebo, or a tapering methadone regimen.[2] In total, 607 participants were treated with clonidine, 215 were treated with lofexidine, and 174 received guanfacine.[2] Treatment was scheduled to last for one to two weeks in most studies; the shortest duration was 3 days, and the longest was 30 days.[2] Most of the trials were conducted on inpatients, 7 studies were in an outpatient setting.[2] The majority of subjects were withdrawing from heroin or a short acting opioid. Outcomes of interest included the withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects, and completion of treatment. The authors reported no conflicts of interest.

Moderate quality evidence compared alpha2-adrenergic agonists with placebo.[2] Based on three studies with 148 participants, completion of withdrawal treatment was significantly more likely with an adrenergic agonist compared with placebo (RR 1.95; 95% CI 1.34 to 2.84).[2] Severe withdrawal was significantly less likely with adrenergic agonist treatment compared with placebo (RR) 0.32; 95% CI 0.18 to 0.57).[2] Absolute risk reduction was not calculated by the authors. None of the studies reported the average time in treatment, but 2 studies reported that more participants receiving placebo dropped out within the first week of treatment.[2] One of the trials reported sedation and dry mouth to be approximately twice as common in participants treated with clonidine, compared with participants who received placebo.[2] In another trial blood pressure was significantly decreased in the lofexidine group on days four to seven of treatment.[2] Asthenia, dizziness, hypotension (18% versus 0%) and insomnia (42% versus 9%) all occurred more frequently in the lofexidine group compared to placebo.[2]

The Cochrane reviewers found insufficient data were available to evaluate the relative effectiveness of clonidine and lofexidine in terms of rates of completion of withdrawal treatment.[2] Furthermore, there are insufficient data available to support a conclusion on the efficacy of guanfacine in managing OUD.[2]

For the comparison of alpha2-adrenergic agonists with tapering doses of methadone, evidence from 9 studies including 659 participants was evaluated as low to moderate quality.[2] The key reasons for the low quality assessment were due to: 1) small numbers of studies reporting some outcomes; 2) low rates of occurrence of some events (for example drop-out due to adverse effects); and 3) variability between studies.[2] For these reasons, only moderate quality evidence will be described in this report. Three moderate quality studies including 119 participants indicated peak withdrawal scores and mean withdrawal severity were similar (SMD=0.22; 95% CI -0.02 to 0.46 and SMD=0.13; 95% CI -0.24 to 0.49, respectively).[2] The mean duration of treatment was significantly longer for the group treated with reducing doses of methadone compared to adrenergic agonists (SMD -1.07; 95% CI -1.31 to -0.83; moderate quality).[2] The incidence of adverse effects was not significantly different between methadone and adrenergic agonists (RR 2.02; 95% CI 0.62 to 6.64; 3 trials; 203 participants; moderate quality).[2] The risk of drop-out due to adverse effects was not statistically significant when adrenergic agonists were compared to methadone (RR 4.48; 95% CI 0.76 to 26.34; 3 trials; 105 participants; moderate quality).[2] Overall, the Cochrane meta-analysis of 8 moderate quality trials indicates no significant difference in rates of completion of withdrawal treatment for alpha2-adrenergic agonists compared with tapering doses of methadone (RR 0.91; 95% CI 0.75 to 1.11; 489 participants).[2]

Cochrane Review: Buprenorphine for Managing Opioid Withdrawal

A moderate quality systematic review and meta-analysis assessed the comparative evidence for buprenorphine in management of opioid withdrawal.[1] The summary includes 27 studies published through December 2016 involving 3048 participants. Fourteen trials compared buprenorphine to alpha2-adrenergeric agonists (clonidine or lofexidine), 6 studies compared buprenorphine versus methadone, and 7 studies compared different buprenorphine dosing regimens.[1] Outcomes of interest included intensity of withdrawal, duration of treatment, treatment completion rates, and adverse effects. In most of the studies, participants were withdrawing from heroin, only one study evaluated participants withdrawing from oxycodone.[1] Nine of the 27 studies included in the review reported using sublingual buprenorphine tablets, and an additional five studies used the combination buprenorphine-naloxone tablets.[1] Three trials administered buprenorphine as a sublingual solution and three studies administered intramuscular buprenorphine injections.[1] Six trials did not report details of which buprenorphine formulation was used in their investigation.[1] None of the studies evaluated the film preparation of buprenorphine. The authors reported no conflicts of interest.

A meta-analysis of 5 moderate quality trials supports a conclusion of no difference between buprenorphine and methadone for withdrawal completion rates (RR 1.04; 95% CI 0.91 to 1.20; N=457).[1] A meta-analysis was not possible to evaluate the intensity of the outcome or duration of withdrawal treatment.[1] Three studies stated there were no significant adverse effects in either the buprenorphine or methadone groups; the other studies did not comment on adverse effects.[1]

There is insufficient evidence to make conclusions on the safety and efficacy of different buprenorphine dosing regimens in managing symptoms associated with withdrawal in patients with OUD.[1] No meta-analysis was possible to assess different dosing regimens of buprenorphine for intensity of withdrawal, duration of withdrawal treatment, and nature of adverse effects.

Fourteen studies compared buprenorphine (n=750) to clonidine (n=512) or lofexidine (n=103).[1] Relative to clonidine or lofexidine, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) during the treatment episode with an effect size that is considered to be small to moderate (SMD −0.43; 95% CI −0.58 to −0.28; N=902; studies=7; moderate quality).[1] Patients receiving buprenorphine stayed in treatment for longer than

adrenergic agonists (mean days in treatment with buprenorphine ranged from 25% to 97%; mean days in treatment with adrenergic agonists ranged from 21% to 70%; SMD 0.92, 95% CI 0.57 to 1.27; N=558; studies=5; moderate quality) and were more likely to complete withdrawal treatment (RR 1.59, 95% CI 1.23 to 2.06; N=1264; studies=12; moderate quality).[1] The authors did not report absolute risk reduction for these outcomes. There was no significant difference between buprenorphine and alpha2-adrenergic agonists in terms of the number of participants experiencing adverse effects.[1]

Canadian Agency for Drugs and Technologies in Health: Buprenorphine Formulations: A Review of Comparative Clinical Effectiveness
In 2017 CADTH published a rapid response report to evaluate the comparative effectiveness of monotherapy buprenorphine and buprenorphine-naloxone formulations (e.g., sublingual films, sublingual tablets, implants,) for treatment of OUD.[3] The review focused on evaluating the comparative evidence for different buprenorphine formulations published from 2012 through June 2017, which is quite sparse.[3] Five RCTs and 3 observational, retrospective cohort analyses were identified for the CADTH publication. Of the 5 RCTs which met inclusion criteria, all but two were industry-sponsored and there were limitations with respect to study design (e.g., non-inferiority, open-label), clinically relevant outcomes and treatment duration.[3] No systematic reviews comparing the various buprenorphine formulations were identified.[3] There were no Canadian or American clinical practice guidelines identified to specifically compare and evaluate different formulations of buprenorphine for OUD.[3]

In two of the RCTs, patients were randomized to receive either the rapidly dissolving buprenorphine-naloxone sublingual tablet for the entire trial or buprenorphine sublingual tablets for 2 days followed by buprenorphine-naloxone film for the remainder of the trial.[3] The treatment duration in these RCTs ranged from 22 days to 29 days.[3] One additional RCT conducted over 31 days compared buprenorphine-naloxone film to the buprenorphine-naloxone sublingual tablet.[3] In 2 RCTs the intervention was four buprenorphine implants compared to placebo and evaluated over 24 to 26 weeks.[3] However, open-label sublingual buprenorphine-naloxone or buprenorphine was available as a rescue medication to all included patients.[30] The addition of open-label rescue medication (buprenorphine or buprenorphine-naloxone) may have confounded the assessment of the efficacy of the implants.[3]

All the buprenorphine formulations examined in the selected studies showed a similar clinical response in patients with opioid use disorder, with significantly higher rates of abuse, misuse and diversion found in sublingual buprenorphine-naloxone tablet formulations.[3] The use of buprenorphine implants was associated with high rates of treatment retention.[3] The rates of adverse effects were low among buprenorphine formulations with no significant differences observed.[3] The findings indicate that the use of newer available buprenorphine formulations may be safe to use in this population, but the included trials were relatively short in duration and may have been underpowered to detect rarer adverse effects.[3] Larger studies with longer treatment durations are required to better understand the efficacy and safety profiles of these newer formulations.[3] Conclusions on the best practices regarding the use of buprenorphine formulations for patients with opioid use disorder cannot be drawn as no relevant systematic reviews or evidence-based guidelines which consider all available evidence were identified by the CADTH authors.[3]

New Guidelines:
Canadian Research Initiative in Substance Misuse: Management of Opioid Use Disorders: A National Clinical Practice Guideline.
The Canadian Research Initiative in Substance Misuse (CRISM) was funded by the Canadian Institute of Health Research (CIHR) to develop a national clinical practice guideline on management of OUD.[5] Four interdisciplinary regional networks identified relevant experts and stakeholders to participate on the 43-member review committee. The guideline research and development was entirely funded through the CIHR-funded CRISM network without pharmaceutical industry support.[5] No current or ongoing direct competing interests were disclosed by the 43 members of the review committee or the four CRISM principal investigators on screening for participation in the review committee.[5] A structured literature review approach was used to develop recommendations using the

Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.[5] Using the AGREE-II instrument, the guidelines were appraised has having high methodological quality.[8] Key recommendations for first and second-line OUD treatments in adults based on high quality evidence include:

- While shown to be essentially as efficacious as methadone in clinical trials, buprenorphine–naloxone has several safety advantages over methadone including a reduced risk of fatal overdose because of its lower potential for respiratory depression.[5] Given the superior safety profile of buprenorphine–naloxone and its potential for flexible take-home dosing in comparison to other opioid agonist medications, initiate opioid agonist treatment (with buprenorphine–naloxone whenever feasible), to reduce the risk of toxicity, morbidity and death, and to facilitate safer take-home dosing (strong recommendation).[5]
- For individuals responding poorly to buprenorphine–naloxone, consider transition to methadone treatment (strong recommendation).[5]
- Initiate opioid agonist treatment with methadone when treatment with buprenorphine–naloxone is not the preferred option such as those individuals with a high opioid tolerance, severe opioid withdrawal symptoms or those requiring supervised administration due to poor adherence (strong recommendation).[5]

The recommendation for use of oral naltrexone as an adjunct medication in treating OUD is a weak recommendation based on low quality evidence.[5] Recommendations for the role of extended release naltrexone injection in treating OUD are not included in these guidelines because this medication is not widely available in Canada.[5] Best practices for treating specific populations, including adolescents and young adults, the elderly, individuals living with concurrent chronic pain, incarcerated individuals, and indigenous populations are not addressed in these guidelines. Additionally, the publication offers a brief overview of the available evidence specifically related to OUD treatment in pregnant women; however, it emphasizes the importance of specialist referral and further research and training in this area.[5]

New Formulations or Indications:

1.The FDA approved buprenorphine extended-release injection (Sublocade™) in November 2017 to treat patients with moderate-to-severe OUD who have first received treatment with transmucosal buprenorphine for at least 7 days.[6] The application for this formulation was given priority review and approved through the FDA's fast track process, which is designed to expedite the review of drugs that fill an unmet medical need. Buprenorphine extended-release injection is a 100 or 300 mg subcutaneous injection administered once a month by a HCP.[6] The safety and efficacy of extended-release buprenorphine were evaluated in two clinical studies (one randomized, placebo-controlled clinical trial and one open-label clinical trial) of 848 adults with a diagnosis of moderate-to-severe OUD who began treatment with buprenorphine/naloxone sublingual film.[6] Response to therapy was measured by urine drug screening and self-reporting of illicit opioid use during the six-month treatment period. Results indicated that buprenorphine-treated patients had more weeks without positive urine tests or self-reports of opioid use, and a higher proportion of patients had no evidence of illicit opioid use throughout the treatment period, compared to the placebo group.[6] The most common side effects from treatment with extended-release buprenorphine injection include constipation, nausea, vomiting, headache, drowsiness, injection site pain, pruritus at the injection site and abnormal liver function tests.[6] The safety and efficacy of extended-release buprenorphine have not been established in children or adolescents less than 17 years of age or adults over the age of 65 years.[6]

Sublocade™ has a boxed warning regarding the risks of intravenous self-administration.[6] If the product were to be administered intravenously rather than subcutaneously, the solid mass the drug is contained within could cause occlusion, tissue damage or embolus.[6] Sublocade™ must be prescribed and dispensed as part of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the product is not distributed directly to patients.[6] Sublocade will be provided to HCPs through a restricted program, administered only by HCPs in a health care setting, and will require health care settings and pharmacies that dispense Sublocade™ to complete an enrollment form attesting that they have procedures in place to ensure that Sublocade™ is dispensed only to HCPs and not directly to patients.[6] The FDA is requiring postmarketing studies to assess which patients would benefit from a higher Sublocade™ dosing regimen, to determine whether extended-

release buprenorphine can be safely initiated without a dose stabilization period of sublingual buprenorphine, to assess the feasibility of administering the extended-release injection at a longer inter-dose interval than once-monthly, and to determine a process for transitioning patients with long-term stability on a transmucosal buprenorphine to a monthly dose of extended-release buprenorphine without the use of a higher dose (300mg) for the first two months of treatment.

2. In April 2017, Bunavail® (buprenorphine and naloxone) buccal film received expanded approval to use this product during the induction phase of treatment for patients dependent on heroin or short-acting opioid products.[7] For patients dependent on methadone or long-acting opioid products, combination therapy with buprenorphine and naloxone has not been adequately studied.[7] For this reason, buprenorphine monotherapy is recommended in patients taking long-acting opioids starting treatment for OUD.[7] The previous indication for Bunavail® only addressed administration during the maintenance phase of OUD treatment.[7]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[31]

Generic Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Buprenorphine (all products)	2/2018	Warnings and Precautions	Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. As a routine part of orientation to buprenorphine treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, and alcohol.
Methadone (all products)	2/2018	Warnings and Precautions	Concomitant use of methadone and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. Reserve concomitant prescribing of benzodiazepines or other CNS depressants in patients in methadone treatment to those for whom alternatives to benzodiazepines or other CNS depressants are inadequate. Follow patients for signs and symptoms of respiratory depression and sedation. If the patient is visibly sedated, evaluate the cause of sedation and consider delaying or omitting daily methadone dosing.

Randomized Controlled Trials:

A total of 141 citations were manually reviewed from the initial literature search. After further review, 140 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 1 trial is summarized in **Table 3** below. The full abstract is included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Law et al[4]	1.Buprenorphine/naloxone 4mg/1mg Vs.	80 opiate-dependent subjects	Compare efficacy of 1 vs 2 on opiate withdrawal symptoms as assessed via the OWS during detoxification phase	Mean OWS 1. 16.7 2. 14.0 Mean Difference: 2.7

	2.Methadone 30 mg/lofexidine PRN			95% CI 3.0 to 8.3 p=0.01

Abbreviations: CI = Confidence Interval; OWS = Opiate Withdrawal Scale; PRN = as needed

NEW DRUG EVALUATION: Lofexidine (Lucemyra™)

Lofexidine, a centrally acting alpha2-adrenergic receptor agonist, is structurally and pharmacologically similar to clonidine.[10] A new drug application submitted to the FDA in 1983 for use of lofexidine in hypertension did not receive approval due to lack of efficacy.[29] However, in 1992 Britannia began marketing lofexidine in the United Kingdom under the trade name Britlofex™ for the treatment of symptoms in patients undergoing opioid detoxification.[29] In May 2018, lofexidine (Lucemyra™) received FDA approval for short-term (up to 14 days) mitigation of severe opioid withdrawal symptoms in adults to facilitate abrupt opioid discontinuation.[10] Lofexidine reduces the release of norepinephrine and decreases sympathetic tone, which lessens the symptoms of withdrawal.[10] Lofexidine may not completely prevent withdrawal symptoms and is not a treatment for OUD as a single agent, but can be used as part of a broader, long-term treatment plan for managing OUD.[10] 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:

The FDA approval of lofexidine was based primarily on efficacy and safety evidence from 2 inpatient phase 3 clinical trials. Study 3003 and Study 3002 were completed in a total of 866 patients with opioid addiction. Only the results of Trial 3002 have been published; information about Trial 3003 was accessed at clinicaltrials.gov (http://clinicaltrials.gov/ct2/show/NCT01863186) and the FDA website.[29]

Study 3002 was an inpatient, randomized, multicenter, double-blind, placebo-controlled study conducted at 15 U.S. sites in 264 patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, or oxycodone).[9] Subjects were randomized 1:1 to receive lofexidine 2.88 mg/day (n=134) or placebo tablets (n=130) for 5 days, followed by an additional 2 days of treatment with placebo prior to discharge on Day 8.[9] Most participants were white males (average age 37 years); 60% reported intravenous opioid use, the most common being heroin.[9] Patients also had access to a variety of support medications for withdrawal symptoms including guaifenesin, an antacid combination, dioctyl sodium sulfosuccinate, psyllium hydrocolloid, bismuth sulfate, zolpidem, acetaminophen, and nicotine replacement therapy. Placebo-treated subjects used more of each concomitant support medication than lofexidine-treated subjects.[9] Overall, 37% of participants allocated to lofexidine and 27% allocated to placebo completed the 8-day treatment course; the overall retention rate was 32.2%.[9] The primary reason for study withdrawal was subject request (35% vs. 40%; lofexidine vs. placebo) and lack of efficacy (13% vs. 28%; lofexidine vs. placebo).[9] The higher incidence of discontinuations in the placebo group due to lack of efficacy is consistent with lofexidine having a treatment effect on withdrawal symptoms.[29]

The co-primary efficacy endpoints in Study 3002 were mean SOWS-Gossop total score on day 3 of treatment and time to study dropout. Day 3 was chosen to be at or near the anticipated peak of withdrawal as per FDA recommendation.[9] The SOWS-Gossop assessment is a 10 item, patient-reported outcome instrument. Each item represents a symptom and is evaluated on a scale ranging from a total score of 0 (no symptoms) to 30 (severe symptoms).[27] A higher score indicates a greater withdrawal symptom severity. Studies indicate that a change score of 2–4 points on the SOWS-Gossop scale is clinically meaningful improvement.[28] For this trial, the investigators assumed a minimal clinically significant difference of 5 points.[9] The mean SOWS-Gossop scores on day 3 were 8.67 and 6.32 for placebo and lofexidine, respectively, which demonstrated a statistically significant difference between the 2 arms (LSMD = -2.24, 95% CI -3.88 to -0.6; p=0.009).[29] However, this assessment did not meet the pre-specified clinical significance of a 5 point difference. Time-to-dropout was chosen as a global assessment of

efficacy (i.e. treatment retention) by the investigators.[9] Each study day was divided into four 6 hour time quadrants (i.e., 6am–12pm; 12pm–6pm; 6pm–12am; and, 12am–6am) and time-to-dropout was measured as the number of 6 hour time quadrants until withdrawal or completion of the 5-day treatment phase.[9] Early termination was statistically higher in the placebo group compared to lofexidine as assessed by the mean number of time quadrants (6.4 vs. 6.9 respectively; p=0.0034).[9] However, the calculated difference was 0.5 time quadrants, or 3 hours, which is not a clinically significant difference in time to withdrawal.

Secondary endpoints included mean SOWS-GOSSOP scores for Days 1 through 5 and the proportion of patients that completed 5 days of treatment. The estimated treatment effect on average SOWS-Gossop scores from Day 1 through Day 5 also showed a significant difference between lofexidine and placebo. The overall mean SOWS-Gossop score from Day 1 through Day 5 for placebo was 10.64 compared to 8.31 for lofexidine (LSMD -2.33; 95% CI -3.42 to -1.25; p<0.001).[29] Although this difference was statistically significant, it did not meet the minimal clinical difference of a change in 5 points on the SOWS-Gossop scale. The proportion of 5-day treatment completers was significantly higher in the patients receiving lofexidine (49%) compared with patients receiving placebo (33%), p=0.009; number needed to treat (NNT) = 7.[9] Early termination of treatment was significantly more common in the placebo group compared to lofexidine (61% vs. 44% of subjects, respectively).[9] Missing data was estimated using a multiple imputation technique.

Unpublished Trial

Study 3003 was a dose-response study conducted in 602 patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, or oxycodone) at 18 U.S. sites.[29] Part 1 of the study was an inpatient, double-blind study in which subjects were randomized 3:3:2 to lofexidine 2.16 mg/day (n=229), lofexidine 2.88 mg/day (n=222) or placebo (n=151) for 7 days.[29] Most of the participants were white males (average age 35 years), primarily dependent on heroin. Patients also had access to a variety of support medications for withdrawal symptoms similar to Study 3002. Overall, placebo-treated subjects used more concomitant medications than lofexidine-treated subjects.[29] A total of 225 participants (37.3%) completed the double-blind phase of the study. The reason most patients in the placebo arm withdrew from the study was due to lack of efficacy. Patients who withdrew from the lofexidine arms reported lack of efficacy or an adverse effect related to the study medication. Part 2 of this study enrolled patients who completed the first 7 days of treatment into an open-label, variable lofexidine dose trial for an additional 7 days in either an inpatient or outpatient setting as determined by the investigator and the patient.[29] A total of 83 participants (13.8%) enrolled in the second open-label phase of the study and 70 (84.3%) of those subjects completed the open-label phase.[29]

The primary efficacy endpoints in Trial 3003 were the mean SOWS-Gossop total score on day 1 through 7 of treatment and the proportion of patients that completed 7 days of treatment.[29] The mean SOWS-Gossop scores for days 1 through 7 were 5.23, 4.07, and 3.8 for placebo, lofexidine 2.16 mg and lofexidine 2.88 mg, respectively.[29] The LSMD from placebo and lofexidine 2.16 mg was -0.21 (95% CI -0.37 to -0.04; p = 0.009) and the LSMD from placebo and lofexidine 2.88 was -0.26 (95% CI -0.44 to -0.09; p = 0.003).[29] The change in SOWS-Gossop scores between placebo and lofexidine was statistically significant for both dosing regimens of lofexidine. There was no significant difference observed between the two doses of lofexidine.[29] The proportion of 7-day treatment completers was significantly higher for both lofexidine arms compared to placebo. Twenty-eight percent of patients receiving placebo completed 7 day treatment compared to 42% of patients receiving lofexidine 2.16 mg (Odds Ratio (OR) 1.85; 95% CI 1.18 to 2.88; p=0.007) and 40% of patients receiving lofexidine 2.88 mg (OR 1.71; 955 CI 1.09 to 2.67; p=0.019).[29] There was no significant difference between the two doses of lofexidine in 7 day completion rates.[29]

Trial Limitations:

The published trial has a number of limitations which reduced the assessment of study quality to poor. The co-primary endpoints in the published trial showed a statistical difference in reducing withdrawal symptoms and time-to-dropout as measured in 6 hour time intervals. However, the clinical significance of the

change in SOWS-Gossop score did not meet the minimal clinically significant difference of 5 points. The time to study dropout revealed a difference of 3 hours which is not a clinically significant difference in time to withdrawal. Furthermore, there was substantial attrition (63-73%) from this trial due to patients requesting to withdraw from study either due to withdrawal symptoms or for reasons unrelated to withdrawal symptoms. Missing data were estimated using a multiple imputation technique. Conflict of interest for study authors was disclosed and 50% of the authors are either an employee or a consultant for US WorldMeds.

Since the data from Trial 3003 is unpublished, the methodological quality of the trial cannot be fully assessed. Both trials limited enrollment to subjects acutely withdrawing from heroin and short-acting prescription opioids. The efficacy of lofexidine in patients undergoing a taper of opioids or patients discontinuing long-acting opioids has not been evaluated. Furthermore, there are not adequate data to assess the risks of lofexidine beyond 7 days of consecutive use. For this reason, the FDA recommends a postmarketing study of lofexidine in patients discontinuing opioids using a slow taper dosing regimen beyond 7 days. Finally, no comparative data of lofexidine to other treatment options such as clonidine are available.

Clinical Safety:
In clinical trials the most commonly reported adverse reactions with lofexidine were orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.[10] Upon cessation of treatment with lofexidine, subjects were observed to experience rebound blood pressure elevations. These observed risks are consistent with the known effects of alpha-2 adrenergic agonists.[29] **Table 4** presents the incidence of adverse events that occurred in 10% or greater of patients treated with lofexidine and for which the incidence in patients treated with lofexidine was greater than in patients treated with placebo. Rates of serious and severe adverse effects requiring treatment discontinuation were relatively low. The incidence of treatment emergent adverse effects is outlined in **Table 5**.

Table 4 : **Adverse Reactions Reported by ≥ 10% of Lofexidine-Treated Patients and More Frequently than Placebo**[10]

Adverse Reaction	Lofexidine 2.16 mg/day, % (n=229)	Lofexidine 2.88 mg/day, % (n=222)	Placebo, % (n=151)
Insomnia	51	55	48
Orthostatic Hypotension	29	42	5
Bradycardia	24	32	5
Hypotension	30	30	1
Dizziness	19	23	3
Somnolence	11	13	5
Sedation	13	12	5
Dry Mouth	10	11	0

Table 5: Treatment Emergent Adverse Effects observed in clinical trials of lofexidine compared to placebo[10]

Treatment Emergent Adverse Effect (TEAE)	Lofexidine 2.16 mg/day, % (n=229)	Lofexidine 2.88 mg/day, % (n=222)	Placebo, % (n=151)
TEAE related to opioid withdrawal	79	80	85
TEAE not related to opioid withdrawal	77	79	40
TEAE leading to study discontinuation	19	25	29
Serious TEAE	0	2	1

Severe TEAE	4	8	7
Deaths	0	0.5	0

The approved label for lofexidine contains a warning about the risk of QT prolongation associated with lofexidine administration.[10] The observed increase in QT interval in the studies conducted by the manufacturer does not suggest that the effect is clinically significant and did not appear to be dose-related.[29] However, there is a publication in the literature that reports that three subjects had clinically significant QT prolongation while receiving concurrent lofexidine and methadone.[29] In addition, there is one postmarketing case of torsade de pointes in a patient that was receiving lofexidine.[29] Overall, the concern for QT prolongation with lofexidine appears to be mainly limited to settings in which it would be co-administered with other medications that lead to QT prolongation (e.g., methadone).[29]

Look-alike / Sound-alike Error Risk Potential: Nothing reported

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduction of opioid withdrawal symptoms
2) Completion of detoxification program
3) Serious adverse events
4) Study withdrawal due to an adverse event
5)Long term abstinence
6)Quality of life

Primary Study Endpoint:
1) Reduction of opioid withdrawal symptoms as assessed by SOWS-Gossop score on Day 3 of therapy

Table 5. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Alpha-2 adrenergic agonist
Oral Bioavailability	72% oral absorption: peak plasma levels observed 3-5 hour after administration
Distribution and Protein Binding	Mean volume of distribution = 480 liters; plasma protein binding = 55%
Elimination	Approximately 93.5% of the dose was recovered in urine post-dose. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.
Half-Life	12 hours
Metabolism	Primarily metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP2C19

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.Study 3002 Gorodetzky, et al[9] DB, PC, MC, PG N = 264 Three phases of treatment over 8 days: 1.Screening phase as an outpatient days -7 to -1 2. Inpatient treatment phase on days 1-5 3.Post-treatment inpatient phase on days 6-7 15 sites in the United States from 2006-2007	1. Lofexidine 2.88 mg/day (0.72 mg PO QID) on days 1-5, followed by placebo (4 tablets) on days 6-7 2. Placebo (4 tablets) PO QID on days 1-5, followed by placebo (4 tablets) PO QID on day 6-7 (Lofexidine supplied as 0.18mg tablets)	Demographics: -Mean age: 37 yo -Gender: 76% male -Ethnicity: White - 53% Black – 24% Hispanic – 23% -Primary Opioid Use: Heroin – 62% Oxycodone – 21% Hydrocodone – 15% Key Inclusion Criteria: -Age ≥18 yo -Opioid dependent according to DSM-IV criteria -Use of heroin, morphine or any opioid with a similar half-life for ≥21 of the past 30 days -OOWS score ≥2 at baseline -Positive urine toxicology screen for opiates and negative for methadone and buprenorphine Key Exclusion Criteria: -Serious medical or psychiatric illness (seizures, insulin-dependent diabetes, hepatic or renal disease)	ITT: 1.134 2.130 PP: 1.50 (37%) 2.35 (27%) Attrition: 1.84 (63%) 2.95 (73%)	Primary Endpoint: Mean SOWS-Gossop total score, day 3 1.6.32 2.8.67 LSMD = -2.24 95% CI -3.88 to -0.60 p=0.009 Mean time to Dropout (Number of 6 hour time quadrants) 1. 6.9 2. 6.4 p = 0.0034 95% CI NR Secondary Endpoints: SOWS-Gossop score from Day 1 through Day 5 1.8.31 2.10.64 LSMD -2.33 95% CI -3.42 to -1.25 p < 0.001 Number of treatment completers on Day 5 1.66 (49%) 2. 43 (33%) p=0.009 95% CI NR	NA NA NA NNT = 7	Outcome: Any TEAE 1.97% 2.94% p=0.25 Severe TEAE 1.23% 2.29% p value NR Study Withdrawal due to TEAE 1.4% 2.5% p value NR Insomnia 1.44% 2.42% p=0.80 Hypotension 1.25% 2.1% p<0.01 Dizziness 1. 22% 2.7% p<0.01 Bradycardia 1.10% 2.2% p<0.01 95% CI NR for all outcomes	NS NA NA NS 24/5 15/7 8/13	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized by centralized ITTRS. Patients were allocated in a 1:1 ratio. Demographics similar between groups at baseline. Performance Bias: Unclear. Placebo and lofexidine matched to maintain blinding. Study protocol not available in supplemental materials for assessment. Not clear if protocol was followed at all 15 sites. Detection Bias: Low. Quadruple blinded: participant, care provider, investigator, and outcomes assessor. Attrition Bias: High. High attrition rate (63-73%) due to patient request to withdraw from study. Missing data estimated using a multiple imputation technique Reporting Bias: Unclear. Study protocol not available in supplemental materials for assessment of outcome reporting. Other Bias: Study conducted by US WorldMeds, NIDA, and Department of Veterans Affairs. US WorldMeds funded the study, participated in study design, monitoring of study sites, administration of trial, writing the report and submission for publication. Conflict of interest for study authors disclosed. 50% of the authors are either an employee or a consultant for US WorldMeds. **Applicability**: Patient: High proportion of young adult, White males dependent on short acting opioids in acute withdrawal in an inpatient setting. Cannot extrapolate results to patients on long acting opioids or tapered withdrawal in an outpatient setting. Intervention: Used the higher dose of lofexidine as this trial was completed prior to dose-ranging trial.

		-Self reported AIDS, active tuberculosis, or active syphilis -Dependence on any psychoactive substance -Abnormal cardiovascular exam (prolonged QT, hypertension, hypotension, bradycardia, history of MI) -Use of methadone or buprenorphine within 14 days -Use of psychotropics, analgesics, anticonvulsants, anti-hypertensives, anti-arrhythmics, antitretroviral, or cholesterol lowering agents within 4 weeks prior to study enrollment						Comparator: Placebo used as comparator. May have been more helpful to compare lofexidine to clonidine. Outcomes: SOWS-Gossop score validated in other clinical trials. Minimal clinical difference defined as 5 points by the investigators. Time to dropout a co-primary endpoint. Double blind component of trial only conducted over 5 days, limiting assessment of risks of therapy over 14 days. Setting: 15 U.S. sites

Abbreviations : AIDS = Acquired Immune Deficiency Syndrome; ARR = absolute risk reduction; CI = confidence interval; COI = conflict of interest; DB = double blind; DSM-IV = Diagnostic and Statistical Manual for Mental Disorders Fourth Edition; ITT = intention to treat; ITTRS = interactive touch tone randomization system; LSMD = Least Squares Mean Difference; MC = multi-center; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NIDA = National Institute on Drug Abuse; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OOWS = Objective Opiate Withdrawal Scale; PBO = placebo; PC = placebo controlled; PG = parallel group; PO = oral; PP = per protocol; QID = four times a day; SOWS = short opiate withdrawal scale; TEAE = treatment emergent adverse event; YO = years old

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Appendix 1: Current Preferred Drug List

Route	Form	Brand	Generic	PDL
ORAL	TABLET DR	ACAMPROSATE CALCIUM	ACAMPROSATE CALCIUM	Y
INTRAMUSC	SUS ER REC	VIVITROL	NALTREXONE MICROSPHERES	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE-NALOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	FILM	SUBOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	ZUBSOLV	BUPRENORPHINE HCL/NALOXONE HCL	Y
ORAL	TABLET	NALTREXONE HCL	NALTREXONE HCL	Y
ORAL	TABLET	ANTABUSE	DISULFIRAM	N
ORAL	TABLET	DISULFIRAM	DISULFIRAM	N
SUBLINGUAL	TAB SUBL	BUPRENORPHINE HCL	BUPRENORPHINE HCL	N
BUCCAL	FILM	BUNAVAIL	BUPRENORPHINE HCL/NALOXONE HCL	N
SQ	SOLER SYR	SUBLOCADE	BUPRENORPHINE	N
IMPLANT	IMPLANT	PROBUPHINE	BUPRENORPHINE HCL	
ORAL	TABLET	LUCEMRYA	LOFEXIDINE	

Appendix 2: Abstracts of Comparative Clinical Trials

Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. Journal of Psychopharmacology. 2017; 31(8):1046-1055.

Buprenorphine/naloxone, methadone and lofexidine are medications with utility in the treatment of opiate withdrawal. We report the first randomised controlled trial to compare the effects of these two medications on withdrawal symptoms and outcome during opiate induction/stabilisation and detoxification. A double-blind randomised controlled trial was conducted in an outpatient satellite clinic of a specialist drug service. Eighty opiate dependent individuals meeting DSM-IV criteria for opiate dependence, using ⩽ ½ g heroin smoked/chased or ¼ g heroin injected or ⩽ 30mg methadone, with ⩽ 3 years of opioid dependency, underwent a short-term opiate treatment programme involving induction/stabilisation on methadone 30mg or buprenorphine/naloxone 4mg/1mg, followed by detoxification (where the methadone group was assisted by lofexidine). The main outcome measures were urine drug screens for opiates and withdrawal and craving questionnaires. There were no overall differences in positive urine drug screens and drop-outs during any phase of the study. During induction/stabilisation, withdrawal symptoms subsided more slowly for buprenorphine/naloxone than for methadone, and craving was significantly higher in the buprenorphine/naloxone group ($p<0.05$, 95% confidence interval –3.5, –0.38). During detoxification, withdrawal symptoms were significantly greater and the peak of withdrawal was earlier for the methadone/lofexidine group than the buprenorphine/naloxone group ($p<0.01$, 95% confidence interval 3.0, 8.3). Methadone/lofexidine and buprenorphine/naloxone had comparable outcomes during rapid outpatient stabilisation and detoxification in low dose opiate users.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 5 2018

1 exp Buprenorphine/	4617
2 exp Buprenorphine, Naloxone Drug Combination	211
3 exp Naltrexone/	7426
4 exp Prescription Drug Misuse	1314
5 exp Opioid-Related Disorders	23081
6 Substance-Related Disorders	88730
7 1 ore 2 or 3	11870
8 4 or 5 or 6	110018
9 7 and 8	3205

10 limit 5 to (English language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 123

11 Lofexidine.mp	164

Ovid MEDLINE(R) without Revisions 1996 to July Week 5 2018

1 acamprosate.mp.	740
2 exp Disulfiram/	3345
3 exp Naltrexone/	7426
4 exp Alcoholism/	72196
5 exp Substance-Related Disorders/	259680
6 exp Alcohol Deterrents/	4240
7 1 or 2	3983
8 4 or 5 or 6	261830
9 7 and 8	3901

10 limit 9 to (English language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 18

Appendix 4: Highlights of Prescribing Information

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

LUCEMYRA™ (lofexidine) tablets, for oral use
Initial U.S. Approval: 2018

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

LUCEMYRA is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. (1)

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

- The usual LUCEMYRA dosage is three 0.18 mg tablets taken orally 4 times daily at 5- to 6-hour intervals LUCEMYRA treatment may be continued for up to14 days with dosing guided by symptoms. (2.1)
- Discontinue LUCEMYRA with a gradual dose reduction over 2 to 4 days. (2.1)
- Hepatic or Renal Impairment: Dosage adjustments are recommended based on degree of impairment. (2.2, 2.3)

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

Tablets: 0.18 mg. (3)

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

None (4)

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

- Risk of Hypotension, Bradycardia, and Syncope: May cause a decrease in blood pressure, a decrease in pulse, and syncope. Monitor vital signs before dosing and advise patients on how to minimize the risk of these cardiovascular effects and manage symptoms, should they occur. Monitor symptoms related to bradycardia and orthostasis. When using in outpatients, ensure that patients are capable of self-monitoring signs and symptoms. Avoid use in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure, as well as in patients with marked bradycardia. (5.1)
- Risk of QT Prolongation: LUCEMYRA prolongs the QT interval. Avoid use in patients with congenital long QT syndrome. Monitor ECG in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, hepatic or renal impairment, or in patients taking other medicinal products that lead to QT prolongation. (5.2)
- Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs: LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. (5.3)
- Increased Risk of Opioid Overdose after Opioid Discontinuation: Patients who complete opioid discontinuation are at an increased risk of fatal overdose should they resume opioid use. Use in conjunction with comprehensive management program for treatment of opioid use disorder and inform patients and caregivers of increased risk of overdose. (5.4)
- Risk of Discontiuation Symptoms: Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy, reduce dose gradually. (5.5)

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

Most common adverse reactions (incidence ≥ 10% and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds at 1-833-LUCEMYRA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

- Methadone: Methadone and LUCEMYRA both prolong the QT interval. ECG monitoring is recommended when used concomitantly. (7.1)
- Oral Naltrexone: Comcomitant use may reduce efficacy of oral naltrexone. (7.2)
- CYP2D6 Inhibitors: Concomitant use of paroxetine resulted in increased plasma levels of LUCEMYRA. Monitor for symptoms of orthostasis and bradycardia with concomitant use of a CYP2D6 inhibitor. (7.4)

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

Revised: XX/2018

Lofexidine

Goal(s):

- Encourage use of substance use disorder medications on the Preferred Drug List.
- Restrict use of lofexidine under this PA to ensure medically appropriate use of lofexidine based on FDA-approved indications.

Length of Authorization:

- Up to 14 days

Requires PA:

- Lofexidine 0.18mg tablets

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication? (Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults)	**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 do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for up to 14 days of total therapy. Note: FDA approved indication is for up to 14 days of therapy

P&T/DUR Review: 11/18 (DM)
Implementation: TBD

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Encourage use of buprenorphine products on the Preferred Drug List.
- Restrict use of buprenorphine products under this PA to management of opioid use disorder.
- Restrict use of oral transmucosal buprenorphine monotherapy products (without naloxone) to pregnant patients or females actively trying to conceive.

Length of Authorization:

- Up to 6 months

Requires PA:

- Buprenorphine sublingual tablets
- Suboxone® and generics (buprenorphine/naloxone) film and sublingual tablets that exceed an average daily dose of 24 mg per day of buprenorphine
- Bunavail® (buprenorphine/naloxone buccal film)
- Zubsolv® (buprenorphine/naloxone sublingual tablets)
- Probuphine® (buprenorphine subdermal implants)
- Sublocade™ (buprenorphine extended-release subcutaneous injection)

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~~ Is the diagnosis ~~is being treated and is the requested treatment~~ funded by the OHP ~~for that condition~~? ~~Note: Treatments which appear on an unfunded line of the prioritized list are not funded by the OHP~~	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP

Approval Criteria		
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 prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system (e.g. individual and group counseling, intensive outpatient treatment, recovery support services, or 12-step fellowship)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Buprenorphine therapy must be part of a comprehensive treatment program that includes psychosocial support.
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com), ~~and has the prescriber verified~~ evaluated the PDMP at least once in the past 6 months, and verified that the patient is not currently ~~has not~~ ~~been~~ prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the requested medication a preferred agent?	**Yes:** Go to #8	**No:** Go to #7
7. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #8
8. Is the request for the buprenorphine implant system (Probuphine)?	**Yes:** Go to #9	**No:** Go to #10

Approval Criteria		
9. Has the patient been *clinically stable* on 8 mg daily or less of Suboxone or Subutex (or equivalent, see Table 1) for at least 6 months? Note: see Table 1 for definition of clinical stability and for equivalent dosing of other buprenorphine products.	**Yes:** If all criteria in Table 1 met, approve 4 implants for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for extended-release subcutaneous buprenorphine injection (Sublocade™)?	**Yes:** Go to #11	**No:** Go to # 13
11. Is the provider registered through the Sublocade™ REMS program? Note: Sublocade carries a boxed warning that stipulates healthcare settings and pharmacies that order and dispense Sublocade™ must be certified in the Sublocade™ REMS program and comply with the REMS requirements due to serious harm or death if this product is administered intravenously. Prescriber offices that only order Sublocade from a certified pharmacy for a specific patient are exempt from certification. Further information is available at www.SublocadeREMS.com or call 1-866-258-3905.	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
12. Has the patient been clinically stable on a transmucosal buprenorphine-containing product at a dose of 8 to 24 buprenorphine per day (or equivalent-see note below) for a minimum of 7 days? Note: One Suboxone® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one Subutex® (buprenorphine HCl) 8 mg sublingual tablet or one Bunavail® (buprenorphine and naloxone) 4.2mg/0.7 mg buccal film or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet	**Yes:** Approve 300mg once a month for 2 months followed by 100mg once a month for 6 months total Increasing the maintenance dose to 300mg once a month may be considered for patients who tolerate the 100mg dose but do not demonstrate a satisfactory clinical response as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use.	**No:** Pass to RPh. Deny; medical appropriateness.
13. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Is the prescribed product a buprenorphine monotherapy product (i.e., without naloxone)	**Yes:** Go to #15	**No:** Go to #17~~6~~
15. Is the patient pregnant or a female actively trying to conceive?	**Yes:** Go to #17	**No:** Go to #16
16. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria	
17. What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter.

Table 1. Criteria for Approved Use of Probuphine (buprenorphine implant).[1]

PROBUPHINE implants are only for use in patients who meet ALL of the following criteria:

• Patients should not be tapered to a lower dose for the sole purpose of transitioning to PROBUPHINE
• Stable transmucosal buprenorphine dose (of 8 mg per day or less of a sublingual Subutex or Suboxone sublingual tablet or its transmucosal buprenorphine product equivalent) for 3 months or longer without any need for supplemental dosing or adjustments:
  ○ Examples of acceptable daily doses of transmucosal buprenorphine include:
  ▪ Subutex (buprenorphine) sublingual tablet (generic equivalent) 8 mg or less
  ▪ Suboxone (buprenorphine and naloxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less
  ▪ Bunavail (buprenorphine and naloxone) buccal film 4.2 mg/0.7 mg or less
  ▪ Zubsolv (buprenorphine and naloxone) sublingual tablets 5.7 mg/1.4 mg or less

Consider the following factors in determining clinical stability and suitability for PROBUPHINE treatment: • no reported illicit opioid use • low to no desire/need to use illicit opioids • no reports of significant withdrawal symptoms • stable living environment • participation in a structured activity/job that contributes to the community • consistent participation in recommended cognitive behavioral therapy/peer support program • stability of living environment • participation in a structured activity/job
Reference: PROBUPHINE (buprenorphine implant for subdermal administration) [Prescribing Information]. Princeton, MJ: Braeburn Pharmaceuticals, Inc., May 2016.

Renewal Criteria		
1. Has the patient been assessed for the effectiveness of the treatment plan and overall progress that warrants continued treatment with buprenorphine?	**Yes:** Go to # 2.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com), and has the prescriber verified evaluated the PDMP at least once in the past 6 months, and verified that the patient is not currently has not been prescribed any opioid analgesics from other prescribers?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	Yes: Go to # 4	No: Pass to RPh. Deny; medical appropriateness
~~2.~~4. What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter. *Note: Probuphine® and Sublocade™ have only been studied for a total duration of 12 months	

P&T/DUR Review: *11/18 (DM); 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *TBD; 4/1/2017; 9/1/13; 1/1/10*

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Policy Evaluation: Substance Use Disorders

Purpose of the Review:
This goal of this review is to examine the impact of removing prior authorization (PA) requirements for preferred medication assisted therapy (MAT) for treatment of opioid use disorder (OUD).

Research Questions:

1. Has utilization of MAT for OUD increased since removal of PA criteria for preferred MAT products?
2. Did removal of the PA criteria appear to impact rates of long-term, clinical outcomes for patients with OUD (e.g., opioid overdose, use of naloxone, return to opioid use, or concomitant use of MAT and opioids)?
3. Did off-label use of MAT (e.g., for chronic pain or other substance abuse) change after removal of PA criteria?
4. Did utilization of psychosocial support systems change after removal of PA criteria?

Conclusions:

- Utilization of buprenorphine/naloxone and medical claims for MAT continue to increase. After removal of the PA criteria, approximately 83% of patients prescribed MAT had an initial paid claim compared to 40% of patients in the year prior to the PA removal. For patients with paid claims, 40% of the patients had claims for more than 120 days of continuous therapy in the 6 months following the index event (IE), and about 30% of the population had less than 30 days of continuous therapy following their first paid claim.
- After removal of PA criteria, approximately 93% of patients with a denied IE were prescribed products containing only buprenorphine. In 77% of patients, there was a subsequent paid claim for MAT. In the vast majority of patients without a subsequent paid MAT claim, a PA was never requested by the provider.
- Rates of long-term, clinical outcomes were similar before and after removal of the PA criteria.
    - In patients with claims for OUD, paid claims for naloxone have increased from 3.7% to 8.3%. However, 4% of patients prescribed MAT had a subsequent diagnosis of opioid overdose, acute intoxication, or medical claims for naloxone in the 6 months following the index event. More than 90% of these patients did not have a subsequent paid pharmacy claim for naloxone. Less than 1% of patients had 2 or more claims for naloxone.
    - Overall use of opioids was limited following an initial claim for MAT. After MAT initiation, 90-93% of patients had less than 7 days of opioid therapy in the following 6 months. Only 0.7% to 2.2% of patients had more than 30 days of concomitant opioid and MAT use.
- Off-label use of MAT appears to be limited. Approximately 85% of patients had a diagnosis of OUD based on available diagnoses or presence of medical claims for OUD. Rates were similar before and after removal of the PA criteria and upon comparison of patients with paid or denied claims.
- Utilization of non-pharmacological psychosocial support or enrollment in SUD treatment programs was limited. Only 39-40% of patients had at least one claim for non-pharmacological substance use disorder (SUD) services, and approximately 34% of patients had long-term utilization of non-pharmacological therapy after 3 months of treatment with MAT.

Author: Sarah Servid, PharmD November 2018

Recommendations:

- No PDL or PA criteria changes recommended based on utilization data.

Background:

In January 2017, in order to minimize barriers to care and provide increased access to medications for the treatment of opioid use disorder (OUD), the Pharmacy and Therapeutics Committee recommended removal of PA criteria for naltrexone extended release injection and preferred buprenorphine/naloxone sublingual tablets and film (unless the daily dose of buprenorphine exceeds 24 mg). This recommendation to increase access to treatment for opioid use disorder was part of a larger statewide initiative to address inappropriate opioid use and overdose. For example, in 2016 pharmacists in Oregon became legally able to prescribe naloxone, and in 2017 training requirements for pharmacists prescribing naloxone were removed in order to increase access to the medication. Similarly, starting in early 2017, nurse practitioners and physician assistants could become trained to prescribe and dispense buprenorphine.[1] Ongoing efforts also aim to increase access to behavioral treatments and provide prescribers guidance on medication assisted therapy (MAT) for treatment of OUD.

Upon removal of this PA criteria, several restrictions regarding use of MAT were removed. Previously, PA criteria had restricted buprenorphine use to diagnoses of OUD. Buprenorphine/naloxone is only indicated for OUD, but because it is a partial opioid agonist, it may be prescribed off-label for pain. In addition, with removal of the criteria, patients were no longer required to be enrolled in a treatment program which provides counseling and psychosocial support. Available literature demonstrates that enrollment in a treatment program has been correlated with better long-term outcomes. Removal of PA criteria would effectively increase access to medication treatment for those unable to access other non-pharmacological services, but may also result in less long-term success for patients without non-pharmacological support. Third, members were no longer required to fill their medications at a single pharmacy. In order to discourage concomitant prescribing with opioids, members receiving treatment for opioid use disorder had previously been required to be locked into a single pharmacy. Members who have claims at more than 4 or 5 pharmacies in the past year are still evaluated for the lock-in program, but it is currently unclear if concomitant opioid prescribing has increased since removal of the policy.

Current guidelines from the Veterans Administration and Department of Defense primarily recommend utilization of methadone (in the context of a treatment program), or buprenorphine/naloxone for patients with OUD (strong recommendation).[2] Buprenorphine alone may be considered for patients who are pregnant (weak recommendation), and extended-release injectable naloxone is recommended as an option for patients for whom opioid agonist therapy is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for at least 7 days without acute withdrawal symptoms (strong recommendation).[2]

This goal of this review is to examine the impact of removing PA requirements on preferred products for patients prescribed MAT. Products for OUD which are non-preferred and continue to require PA include Bunavail® (buprenorphine/naloxone film), Probuphine® (buprenorphine implant), buprenorphine sublingual tablets, and Sublocade® (buprenorphine extended-release injection).

Methods:

This is an observational retrospective analysis which compares utilization of treatments for OUD before removal of the PA criteria from preferred products (the control period from 3/1/2016 to 2/28/2017) and after removal of the PA criteria (the experimental period from 3/1/17 to 2/28/18). Drugs for which the PA was removed included preferred buprenorphine/naloxone products and injectable naltrexone (Vivitrol®). The patient population included FFS patients with an opioid use disorder. Patients were excluded if they had Medicare Part D coverage (identified with benefit packages BMM, MBD, MND, or MED) or if they had limited or no Medicaid drug benefit (identified with benefit packages CWM, SMF, SMB). Members were excluded if they were enrolled in Medicaid (based on combined FFS and CCO eligibility) for less than 75% of the time in the year prior to the index event in order to ensure complete medical records for their prior diagnoses. Patients were also required to have continuous Medicaid eligibility in the 3 months after the IE to capture more accurate information for subsequent therapy. Baseline characteristics were assessed at time of the IE.

The following definitions were used to classify groups of interest:

- The **index event (IE)** was defined as the first paid or denied FFS pharmacy claim for MAT. See **Table A1** for codes associated with MAT for opioid use disorder. Claims for MAT included pharmacy claims for buprenorphine/naloxone, buprenorphine, or naltrexone. Denied claims were defined as claims with an error code of 3002 (NDC requires PA), 3000 (units exceed authorized units on PA master file), 4167 (Drug quantity per day limit exceeded), 4026 (day supply limit exceeded for covered NDC), or 2603 (Recipient Locked in) and without any of the error codes listed in **Table A2**. If a patient had a paid and denied claim on the same day, the IE was classified as paid.
- Patients with **opioid use disorder** were defined as a diagnosis of opioid use disorder within 2 years prior to the index event (IE), medical claims with diagnosis indicating an opioid overdose, or medical claims for nonpharmacological alcohol or drug services. See **Appendix 1** for medical codes (**Table A3 and A4**) and diagnoses (**Table A5**) associated with opioid use disorder treatments.
- **Naloxone treatment** was defined as any paid claims for drugs in the Opioid Reversal Agents preferred drug list (PDL) class or medical claims for naloxone administration (J2310). Pharmacy claims for naloxone would be prescribed in order to prepare for the event of an overdose. Medical claims likely represent naloxone which was actually administered to the patient by a provider in a medical setting, but may also represent some providers who dispense naloxone to patients in the clinic for later use.
- **Duration of MAT** was defined using pharmacy claims. MAT may be billed using a variety of mechanisms (both pharmacy and medical), but only pharmacy claims were used to estimate covered days over the treatment period as days' supply is not available on medical claims. Covered days were estimated based on the days' supply submitted with the pharmacy claim. Oral therapies are administered daily, injectable naltrexone is typically administered every 4 weeks, and buprenorphine implants are administered every 6 months. Duration of treatment was defined as the period of covered days from the first paid claim to the first gap in coverage of at least 14 continuous days. Because the duration of time members were enrolled in FFS was limited, both CCO and FFS claims were used to estimate duration of treatment in the 6 months following the first paid claim. In patients with an initial denied claim, the duration was evaluated in the 6 months following the first paid claim for patients with a subsequent prescription and does not reflect patients without any paid claims.
- **Treatment discontinuation** was defined as a gap in coverage of MAT for 14 or more continuous days. Patients were evaluated for continuation of therapy in the 6 months following the IE.
- The proportion of days covered (PDC) for pharmacy FFS or CCO claims was also used to estimate **adherence to treatment**. The PDC was assessed for the 6 months following the index event. Short-term therapy over a period of 6 months would correspond to a PDC of up to 25% (≤45 days), intermediate therapy corresponds to PDC of 25-75% (46 to 135 days), and long-term therapy corresponds to a PDC greater than 75% (>135 days every 6 months). Short-term or intermediate therapy may be indicative of low adherence to treatment or early treatment discontinuation.
- **Return to opioid use** was defined as any paid or denied opioid claims following treatment discontinuation. Duration of opioid use was categorized using the total sum of covered days for paid claims in the 6 months following treatment discontinuation (including both CCO and FFS utilization). In order to approximate the proportion of patients potentially paying cash for opioid prescriptions, the sum of covered days was also estimated using both paid and denied opioid claims. If there were multiple denied claims for the same prescription, each prescription was only counted once on the date of the earliest

claim. Denied claims are only available for FFS patients and were included in estimates of duration if there was not a paid claim for the same prescription number. Error codes associated with included and excluded claims are listed in **Table A7**.

- Patients with **concomitant use of opioids** and MAT were identified based on paid pharmacy claims for MAT and paid claims for a medication within the following PDL classes: opioids, long-acting and opioids, short-acting. Concomitant use was categorized based on the duration of overlapping claims (≤30 days or >30 days). To approximate the proportion of patients potentially paying cash for opioid prescriptions, concomitant use was also estimated using both paid and denied opioid claims. If there were multiple denied claims for the same opioid prescription, each prescription was only counted once on the date of the earliest claim.

Results:

Figure 1 shows recent data for utilization of MAT before and after removal of prior authorization criteria for naltrexone and preferred buprenorphine/naloxone products. Utilization of buprenorphine/naloxone and administration of MAT through medical claims has continued to increase while pharmacy claims for naltrexone and buprenorphine-only products remain relatively constant. This is consistent with continued prior authorization requirements for buprenorphine-only products. In recent months there has also been a slight increase in prescribing of naloxone. Increased utilization is likely influenced by community-wide efforts to increase access to naloxone for patients prescribed opioids or MAT, and it is not clear from this data if increased prescribing corresponds to any trend in opioid overdose or poisoning.

Medical claims for MAT which are not impacted by any PA policies follow a similar trend with increasing utilization over time. Medical claims are often billed more frequently than pharmacy claims (with an average claim count of 46-61 claims per person over 6 months) and may include daily administration of buprenorphine/naloxone or methadone. Therefore, the claim count per member per month (as shown on the right axis of the graph) is higher for medical claims compared to pharmacy claims. Approximately, 5-7% of patients evaluated in this analysis have MAT claims billed through both pharmacies and medical clinics, but the focus of this analysis is on pharmacy claims impacted by the change in policy.

Figure 1. Utilization of paid FFS pharmacy claims for medications for OUD (per member per month [PMPM]) from 1/1/2016 to present. Prior authorization was removed for preferred MAT products on March 1, 2017. Utilization of medical claims for OUD is also included for context. Medical claims do not require PA and would not have been impacted by the policy. The count of pharmacy claims is shown on the left axis and the count of medical claims per member per month is measured on the right axis.

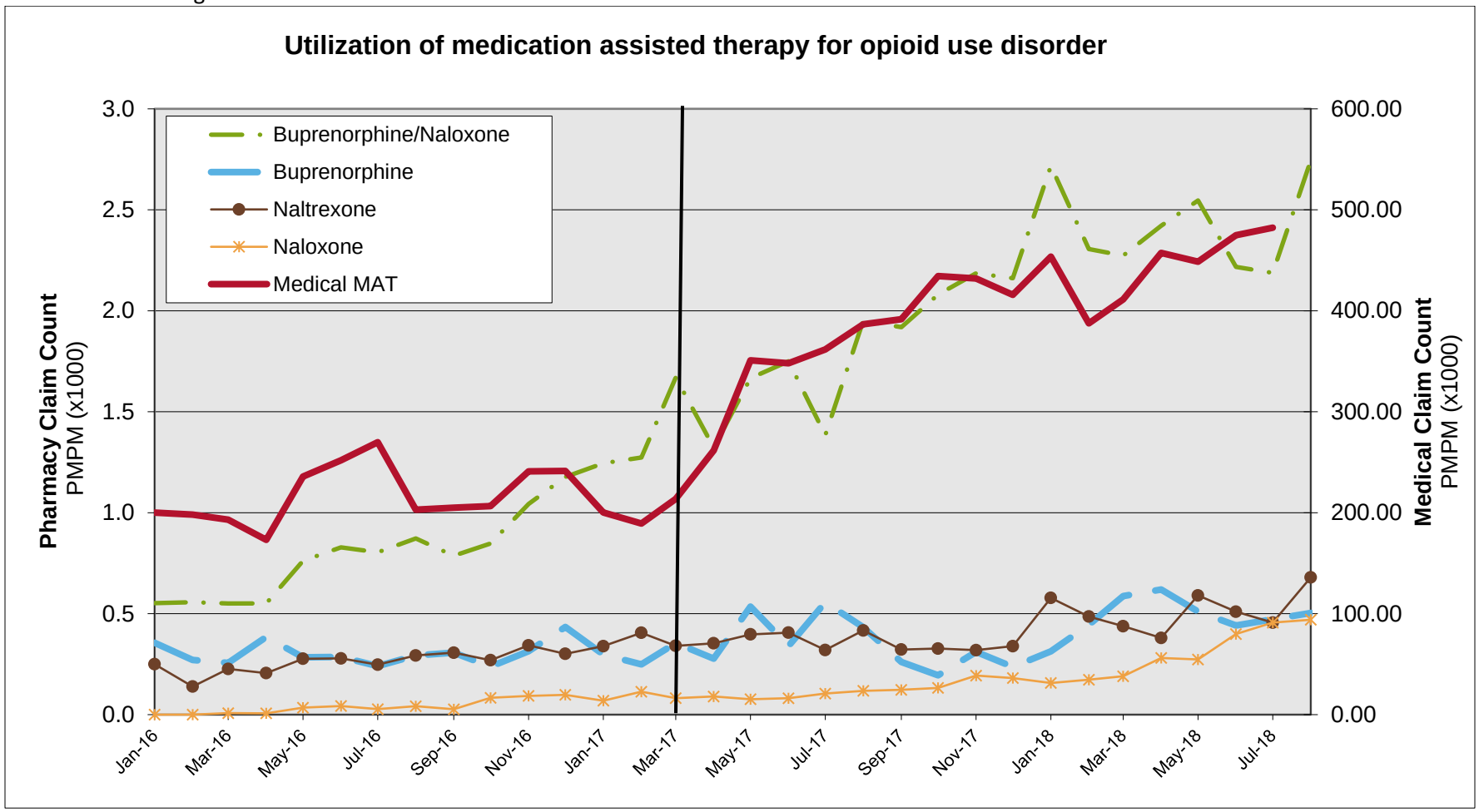

Table 1 lists basic demographics for patients with claims for MAT. Overall, demographics were similar before and after removal of the policy with the majority of claims prescribed to adult patients. Approximately 53-57% were female and 48-51% were white. On average, 17-19% of patients were prescribed doses over 24 mg/day of buprenorphine. Denied claims were slightly higher in patients on high dose buprenorphine (22-28%) compared to patients with an initial paid claim (14-15%). Overall rates were similar before and after removal of the PA criteria.

Table 1. Demographics before and after removal of the policy. Average PDC was evaluated in the 6 months following the index event.

	Before Group		After Group	
	All Index Events		All Index Events	
N=	**1,045**		**1,160**	
Mean age (range)	35	6-66	35	9-65
<13	2	0.2%	1	0.1%
13-18	8	0.8%	10	0.9%
19-60	1,019	97.5%	1,126	97.1%
>60	16	1.5%	23	2.0%
Female	596	57.0%	624	53.8%
White	529	50.6%	556	47.9%
Native American	107	10.2%	158	13.6%
Buprenorphine dose >= 24 mg/day	200	19.1%	197	17.0%
Average days to lost enrollment/CCO enrollment (min/max)	56	(0-184)	53	(0-184)

In patients with an initial paid claim, average duration of MAT was 192 days before removal of PA criteria and 151 days after removal of PA criteria (**Table 2**). Duration was defined as the time from the first paid claim to the first gap in coverage of at least 14 days. Over 40% of the population has claims for more than 120 days in the 6 months following the index event, and about 30% of the population had less than 30 days of continuous therapy following their first paid claim. Rates were similar both before and after removal of the PA criteria. If patients had an initial denied MAT claim but a subsequent paid claim, estimates of treatment duration and PDC were similar compared to patients who had an initial paid claim.

Table 2. Duration of treatment and proportion of days covered (PDC) estimates. In patients with an initial denied claim, the duration was evaluated in the 6 months following the first paid claim for patients with a subsequent prescription and does not reflect patients without any paid claims.

	Before Group						After Group					
	All Index Events		Index Event Paid Claim		Index Event Denied Claim		All Index Events		Index Event Paid Claim		Index Event Denied Claim	
N=	**1,045**		417	39.9%	628	60.1%	**1,160**		963	83.0%	197	17.0%
Mean duration of (MAT) treatment	217		192		224		152		151		154	
1-7 days	36	3.4%	10	2.4%	26	4.1%	66	5.7%	60	6.2%	6	3.0%
8-30 days	199	19.0%	127	30.5%	72	11.5%	256	22.1%	231	24.0%	25	12.7%
31-60 days	106	10.1%	52	12.5%	54	8.6%	147	12.7%	133	13.8%	14	7.1%
61-120 days	126	12.1%	62	14.9%	64	10.2%	135	11.6%	118	12.3%	17	8.6%
>120 days	465	44.5%	166	39.8%	299	47.6%	513	44.2%	421	43.7%	92	46.7%
Average PDC in 6 months after IE												
PDC <= 25%	297	28.4%	100	24.0%	197	31.4%	320	27.6%	253	26.3%	67	34.0%
PDC 26%-75%	273	26.1%	136	32.6%	137	21.8%	283	24.4%	242	25.1%	41	20.8%
PDC > 75%	475	45.5%	181	43.4%	294	46.8%	557	48.0%	468	48.6%	89	45.2%

Table 3 shows the number of patients with a paid or denied index event stratified by drug. After removal of prior authorization criteria, 83% of patients had an initial paid claim for MAT compared to 40% of patients in the year before the PA was removed. There was relatively little change in the number of patients with approved or denied claims for non-preferred products, and 93% of patients with denied claims were for buprenorphine-only products after removal of the PA criteria.

Table 3. Patients with pharmacy claims for MAT before and after implementation of the policy.

	Before Group						After Group					
	All Index Events		Index Event Paid Claim		Index Event Denied Claim		All Index Events		Index Event Paid Claim		Index Event Denied Claim	
N=	**1,045**		417	39.9%	628	60.1%	**1,160**		963	83.0%	197	17.0%
Index Event by Drug												
Naltrexone	198	18.9%	190	45.6%	8	1.3%	266	22.9%	264	27.4%	2	1.0%
Buprenorphine/naloxone	608	58.2%	180	43.2%	428	68.2%	646	55.7%	635	65.9%	11	5.6%
Buprenorphine only products	239	22.9%	47	11.3%	192	30.6%	248	21.4%	64	6.6%	184	93.4%
Naloxone in 6 months after IE	39	3.7%	16	3.8%	23	3.7%	96	8.3%	87	9.0%	9	4.6%

Diagnoses associated with claims for MAT are described in **Table 4**. Approximately 85% of patients were classified as having an OUD based on available diagnoses or presence of medical claims for OUD. Rate of diagnoses was similar before and after the policy, indicating that there was little change in off-label prescribing patterns despite reduced restrictions for preferred buprenorphine/naloxone products. Rates were similar between patients with paid and denied IE, and a large proportion of patients with a denied IE had a diagnosis of OUD.

Table 4. Diagnoses related to MAT use. Patients may have more than one opioid diagnosis or off-label diagnosis.

	Before Group						After Group					
	All Index Events		Index Event Paid Claim		Index Event Denied Claim		All Index Events		Index Event Paid Claim		Index Event Denied Claim	
N=	**1,045**		417	39.9%	628	60.1%	**1,160**		963	83.0%	197	17.0%
Total with OUD	892	85.4%	330	79.1%	562	89.5%	997	85.9%	834	86.6%	163	82.7%
Diagnosis of opioid use, dependence, or abuse	829	79.3%	274	65.7%	555	88.4%	909	78.4%	745	77.4%	164	83.2%
Other diagnoses or medical claims indicating OUD (poisoning or non-pharmacological claims for drug services)	591	56.6%	245	58.8%	346	55.1%	723	62.3%	626	65.0%	97	49.2%
Total patients without diagnoses of OUD	151	14.4%	87	20.9%	64	10.2%	162	14.0%	129	13.4%	33	16.8%
Other substance use disorders	73	7.0%	50	12.0%	23	3.7%	61	5.3%	54	5.6%	7	3.6%
Chronic pain	30	2.9%	9	2.2%	21	3.3%	37	3.2%	23	2.4%	14	7.1%

The disposition of patients with denied index events for MAT is shown in **Table 5.** Approximately 66-73% of patients had a subsequent paid claim for MAT within 30 days of the denial. In 19-23% of patients, a PA was never requested for the patient. The majority of patients (69-70%) without subsequent paid claims for MAT did have a diagnosis of OUD. OUD was defined based on diagnosis codes for opioid abuse, dependence, and use or based on medical claims indicating OUD (such as diagnoses of opioid poisoning or non-pharmacological claims for drug services).

Table 5. Disposition of denied pharmacy claims before and after removal of the PA criteria. Longer time between the initial denial and a paid claim may indicate barriers to treatment for appropriate use, whereas a large volume of PA denials may indicate use for inappropriate high dose of off-label treatment.

	Before Group		After Group	
	N	%	N	%
Index Event Denied Claim	628		197	
MAT pharmacy claim filled OR paid medical claim for MAT within 30 days	459	73.1%	131	66.5%
MAT pharmacy claim filled OR paid medical claim for MAT within 90 days	48	7.6%	20	10.2%
Never had a Medication Assisted Therapy (MAT) claim within 90 days of a denied claim	121	19.3%	46	23.4%
PA not requested in the 5 days before or 30 days after the denied claim	116	95.9%	43	93.5%
PA denied in the 5 days before or 30 days after the initial denied claim	0	0.0%	0	0.0%
Never received drug and had diagnosis of OUD	83	68.6%	32	69.6%

Table 6 evaluates impact of MAT on long-term outcomes. Overall, incidence of clinical outcomes was similar before and after the policy implementation. Approximately 4% of patients with claims for MAT had a subsequent diagnoses of opioid overdose, acute intoxication, or medical claims for naloxone in the 6 months following the index event. However, it is concerning that a large majority of these patients did not have a paid pharmacy claim for naloxone in that same timeframe. Less than 1% of patients had 2 or more claims for naloxone.

Use of concomitant or subsequent opioid use was also evaluated. Overall use of opioids was limited following an initial claim for MAT. After MAT initiation, 90-93% of patients had less than 7 days of opioid therapy in the following 6 months. Proportions were similar for all patients regardless of whether they had a paid or denied index event for MAT. Approximately 64-67% of patients discontinued MAT treatment in the 6 months following an initial claim. Of patients who discontinued MAT treatment (defined as a continuous gap coverage of at least 14 days), 28% and 19% of patients had a subsequent claim an opioid prescription in the before and after groups, respectively (data not shown). Similarly, few patients had concurrent utilization of MAT and concurrent utilization was generally for short durations. Only 10-13% of patient had concurrent paid claims for opioids and MAT, and duration on concomitant use exceeded 30 days in only 0.7%-2.2% of patients. Upon evaluation of both paid and denied opioid claims, there was very little change in duration of opioid use compared to analysis of only paid opioid claims (data not shown). This indicates that cash paying for opioids may be less of an issue for this population.

Table 6. Impact of MAT on long-term outcomes. Patients may be counted more than once in each category. All outcomes were evaluated in the 6 months following the index event.

	Before Group		After Group	
	All Index Events		All Index Events	
N=	**1,045**		**1,160**	
Patients with diagnosis of opioid overdose, acute intoxication, or medical claims for naloxone	40	3.8%	48	4.1%
Patients categorized above AND without a paid pharmacy claim for naloxone in the 6 months following the event	40	3.8%	45	3.9%
Patients with ≥2 paid claims for naloxone	2	0.2%	9	0.8%
Duration of opioid use in the following 6 months (paid claims)				
<=7 days	941	90.0%	1,080	93.1%
8-30 days	63	6.0%	55	4.7%
31-60 days	20	1.9%	10	0.9%
61-120 days	9	0.9%	8	0.7%
>120 days	12	1.1%	7	0.6%

Utilization of non-pharmacological services is shown in **Table 7**. With removal of the criteria, patients were no longer required to be enrolled in a treatment program with use of preferred products. However, utilization of counseling and non-pharmacological services was similar before and after removal of the PA criteria. Overall, 39-40% of patients had at least one claim for non-pharmacological SUD services, and approximately 34% of patients had long-term non-pharmacological therapy after 3 months of treatment with MAT.

Table 7. Utilization of non-pharmacological psychosocial support or enrollment in SUD treatment programs.

	Before Group						After Group					
	All Index Events		Index Event Paid Claim		Index Event Denied Claim		All Index Events		Index Event Paid Claim		Index Event Denied Claim	
N=	**1,045**		417	39.9%	628	60.1%	**1,160**		963	83.0%	197	17.0%
Patients with any medical claims for non-pharmacological SUD services (in 6 months after IE)	405	38.8%	187	44.8%	218	34.7%	467	40.3%	402	41.7%	65	33.0%
Patients with medical claims for non-pharmacological SUD services for more than 3 months after the IE (From 3 months after IE to 9 months after IE)	356	34.1%	162	38.8%	194	30.9%	396	34.1%	340	35.3%	56	28.4%

Discussion and limitations:

Several limitations exist as a result of the retrospective nature of this analysis. First, data is based on claims history which may not accurately reflect true patient diagnoses or correlate with actual medication adherence. For example, pharmacy claims for naloxone are typically prescribed as a precautionary measure in order to prepare for the event of an overdose and may not correlate to actual rates of overdose. Medical claims likely represent naloxone which was actually administered to the patient by a provider in a medical setting, but may also represent some providers who dispense naloxone to patients in the clinic for later use. Both medical claims and pharmacy claims may not capture administration of naloxone by friends, family, emergency medical technicians, or first responders. Both ICD-9 and ICD-10 diagnosis codes were used to identify diagnoses for patients. Though efforts were made to accurately identify comparable codes, there may be differences in diagnoses based on the ICD version for claims identified before and after October 2015 when the ICD-10 version was implemented. For example, ICD-10 diagnoses have 3 distinct codes for opioid dependence, abuse, or use whereas ICD-9 codes for OUD describe populations with opioid dependence/abuse and non-dependent opioid abuse.

In addition, use of proportion of days covered attempts to estimate the frequency which a patient takes a prescription, but accuracy of this method has not been validated and patients may not always be categorized appropriately. For example, a patient with PDC less than 25% over 6 months could have up to 45 days of continuous coverage in the reporting period and could be indicative of long-term therapy initiation or only a brief treatment duration. Similarly, treatment discontinuation as defined in this analysis (>14 days gap in coverage) may not accurately capture patients who have brief interruptions in therapy or discontinue but re-initiate therapy. Because many patients transition in and out of CCOs duration of therapy and PDC estimates included paid claims for both FFS and CCOs. However, policies surrounding MAT may be different between CCOs which may impact estimates of therapy duration.

This analysis does not evaluate use of MAT when administered in a clinical setting. MAT may be billed using a variety of mechanisms (both pharmacy and medical), but only pharmacy claims were included in this analysis. Medical claims are often billed with multiple mechanisms, and therefore, the number and duration of claims is often difficult to quantify. However, based on current estimates, only a small proportion of included patients (5-7%) had both medical and pharmacy claims for MAT.

Similarly, though the analysis included data on paid pharmacy claims from both CCO and FFS, data may still be incomplete. For example, in members with denied claims and no subsequent paid pharmacy claims for MAT, 93% of members did not have a PA request. However, some of these members may have paid medical

claims for MAT or transitioned into a CCO for which there may be different policies for MAT. In this population, the average number of days members were enrolled in FFS was 53-56 days, and continuity of care as members transition between FFS and CCOs may affect coverage of medications.

Removal of the PA criteria for preferred MAT products allowed increased access to MAT in the FFS population. However, ongoing national and state-wide efforts may have also enhanced access to or referral for treatment of OUD and may account for the increasing utilization of MAT. For example, factors which may impact utilization of MAT include changes in opioid prescribing patters, increased awareness and diagnoses of OUD, efforts to increase the number of prescribing providers for buprenorphine, and availability of medical clinics for treatment of OUD. Similarly, recent utilization trends for naloxone for prevention of overdose are likely influenced by increased awareness for risks of overdose, increased prescribing from available providers, and effort to enhance access to naloxone.

References:

1. SAMHSA: Substance Abuse and Mental Health Services Administration. Medication-Assisted Treatment (MAT). 2018; https://www.samhsa.gov/medication-assisted-treatment. Accessed October 15, 2018.
2. The Management of Substance Use Disorders Work Group. VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF SUBSTANCE USE DISORDERS. 2015; https://www.healthquality.va.gov/guidelines/MH/sud/. Accessed October 15, 2018.

Appendix 1: Coding for methods and definitions

Table A1. Pharmacy codes for MAT

GSN	Route	FormDesc	Generic	PDL
066635	SL	FILM	buprenorphine HCl/naloxone HCl	Y
066636	SL	FILM	buprenorphine HCl/naloxone HCl	Y
070259	SL	FILM	buprenorphine HCl/naloxone HCl	Y
070262	SL	FILM	buprenorphine HCl/naloxone HCl	Y
051640	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
051641	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
071189	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
071190	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
073424	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
073425	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
074685	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
076981	SL	TAB SUBL	buprenorphine HCl/naloxone HCl	Y
004518	PO	TABLET	naltrexone HCl	Y
060935	IM	SUS ER REC	naltrexone microspheres	Y
077999	SQ	SOLER SYR	buprenorphine	N
078000	SQ	SOLER SYR	buprenorphine	N
029312	SL	TAB SUBL	buprenorphine HCl	N
029313	SL	TAB SUBL	buprenorphine HCl	N
072449	BC	FILM	buprenorphine HCl/naloxone HCl	N

072450	BC	FILM	buprenorphine HCl/naloxone HCl	N
072451	BC	FILM	buprenorphine HCl/naloxone HCl	N
076145	IL	IMPLANT	buprenorphine HCl	

Table A2. Error Codes for denied OUD claims

Included Codes

Error Code	Description
4026	DAY SUPPLY LIMIT EXCEEDED FOR COVERED NDC
2603	Recipient Locked in
4167	DRUG QUANTITY PER DAY LIMIT EXCEEDED
3000	UNITS EXCEED AUTHORIZED UNITS ON PA MASTER FILE
3002	NDC REQUIRES PA

Excluded Codes

Error Code	Description
1017	NON-REBATABLE ELIGIBLE INDICATOR
505	THIRD PARTY PAYMENT AMOUNT MORE THAN CLAIM CHARGE
3343	Questionable TPL amount
628	Other Coverage Reject Code Required for OCC 3
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER
4007	NON-COVERED NDC DUE TO CMS TERMINATION
4890	Non covered drug class
4891	Not covered drug class
643	INVALID OTHER COVERAGE CODE
238	RECIPIENT NAME IS MISSING
2809	DOB IS INVALID
5001	EXACT DUPLICATE
513	RECIPIENT NAME AND NUMBER DISAGREE
4999	THIS DRUG IS COVERED BY MEDICARE PART D
4002	Non-Covered Drug
576	CLAIM HAS THIRD-PARTY PAYMENT
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE
2017	RECIPIENT SERVICES COVERED BY HMO PLAN

Table A3. Medical Codes for MAT

HCPCS	Description
H0020	Alcohol and/or drug services; methadone administration and/or service (provision of the drug by a licensed practitioner)
J3490, J3590	Include only if associated with any of the pharmacy drug codes for MAT (see Table A1) or with methadone (GSNs 004237 004238; 004239; 004240; 004242; 023767)

J0571	Buprenorphine oral 1mg
J0570	Buprenorphine implant 74.2mg (Probuphine)
Q9992	Buprenorphine XR over 100mg (Sublocade)
J0592	Buprenorphine hydrochloride
J0572	Buprenorphine/naloxone, oral, less than or equal to 3 mg buprenorphine
J0573	Buprenorphine/naloxone, oral, greater than 3 mg, but less than or equal to 6 mg buprenorphine
J0574	Buprenorphine/naloxone, oral, greater than 6 mg, but less than or equal to 10 mg buprenorphine
J0575	Buprenorphine/naloxone, oral, greater than 10 mg buprenorphine
J2310	Injection, naloxone hydrochloride, per 1 mg
J2315	Injection, naltrexone, depot form, 1 mg (Vivitrol)

Table A4. Medical codes for non-pharmacological drug abuse services

HCPCS	Description
H0005	Alcohol and/or drug services; group counseling by a clinician
H0006	Alcohol and/or drug services; case management
H0007	Alcohol and/or drug services; crisis intervention (outpatient)
H0008	Alcohol and/or drug services; sub-acute detoxification (hospital inpatient)
H0009	Alcohol and/or drug services; acute detoxification (hospital inpatient)
H0010	Alcohol and/or drug services; sub-acute detoxification (residential addiction program inpatient)
H0011	Alcohol and/or drug services; acute detoxification (residential addiction program inpatient)
H0012	Alcohol and/or drug services; sub-acute detoxification (residential addiction program outpatient)
H0013	Alcohol and/or drug services; acute detoxification (residential addiction program outpatient)
H0014	Alcohol and/or drug services; ambulatory detoxification
H0015	Alcohol and/or drug services; intensive outpatient (treatment program that operates at least 3 hours
H0016	Alcohol and/or drug services; medical/somatic (medical intervention in ambulatory setting)
H0050	Alcohol and/or drug services, brief intervention, per 15 minutes
S9475	Ambulatory setting substance abuse treatment or detoxification services, per diem
T1006	Alcohol and/or substance abuse services, family/couple counseling
T1007	Alcohol and/or substance abuse services, treatment plan development and/or modification
T1012	Alcohol and/or substance abuse services, skills development
H2034	Alcohol and/or drug abuse halfway house services, per diem
H0047	Alcohol and/or other drug abuse services, not otherwise specified
OR312	Alcohol and/or substance abuse services
H0029	Alcohol and/or drug prevention alternatives service (services for populations that exclude alcohol a
H0028	Alcohol and/or drug prevention problem identification and referral service (e.g., student assistance

H0026	Alcohol and/or drug prevention process service, community-based (delivery of services to develop ski
H0022	Alcohol and/or drug intervention service (planned facilitation)
H2035	Alcohol and/or other drug treatment program, per hour
H2036	Alcohol and/or other drug treatment program, per diem
4306F	Patient counseled regarding psychosocial and pharmacologic treatment options for opioid addiction (sud)

Table A5. Diagnosis codes for opioid use disorder and opioid overdose

Code	Description	ICD Version Code
F111x	Opioid abuse	10
F112x	Opioid dependence	10
F119x	Opioid use	10
3040x	Addiction or dependence heroin, opioids, opium	9
3047x	Combinations of opioid type drug with any other drug dependence	9
3055x	Nondependent opioid abuse	9
F1112x	Opioid abuse with intoxication	10
F1122x	Opioid dependence with intoxication	10
F1192x	Opioid use, unspecified with intoxication	10
T400xxx-T400X5x	Poisoning by, adverse effect of opium	10
T401xxx-T401X5x	Poisoning by, adverse effect of heroin	10
T402xxx-T402X5x	Poisoning by, adverse effect of other opioids	10
T403xxx-T403X5x	Poisoning by, adverse effect of methadone	10
T404xxx-T404X5x	Poisoning by, adverse effect of other synthetic narcotics	10
T4060xx-T40605x	Poisoning by, adverse effect of other and unspecified narcotics	10
T4069xx-T40695x	Poisoning by, adverse effect of other narcotics	10
9650x	Poisoning by opiates and related narcotics	9
E9350-E9352	Analgesics antipyretics and antirheumatics causing adverse effects in therapeutic use	9
E9802	Poisoning by other sedatives and hypnotics, undetermined whether accidentally or purposely inflicted	9
E9800	Poisoning by analgesics, antipyretics, and antirheumatics, undetermined whether accidentally or purposely inflicted	9

Table A6. Other Relevant diagnoses

Chronic pain diagnoses

CodeDiagCondMedl	TextDesc	ICD_Version_Code	Category
3078	Pain disorders related to psychological factors	9	Chronic Pain
30780	Psychogenic pain, site unspecified	9	Chronic Pain
30789	Other pain disorders related to psychological factors	9	Chronic Pain

338	Pain not elsewhere classified	9	Chronic Pain
3380	Central pain syndrome	9	Chronic Pain
3382	Chronic pain	9	Chronic Pain
33821	Chronic pain due to trauma	9	Chronic Pain
33822	Chronic post-thoracotomy pain	9	Chronic Pain
33828	Other chronic postoperative pain	9	Chronic Pain
33829	Other chronic pain	9	Chronic Pain
3383	Neoplasm related pain (acute) (chronic)	9	Chronic Pain
3384	Chronic pain syndrome	9	Chronic Pain
F454	Pain disorders related to psychological factors	10	Chronic Pain
F4541	Pain disorder exclusively related to psychological factors	10	Chronic Pain
F4542	Pain disorder with related psychological factors	10	Chronic Pain
G89	Pain, not elsewhere classified	10	Chronic Pain
G890	Central pain syndrome	10	Chronic Pain
G892	Chronic pain, not elsewhere classified	10	Chronic Pain
G8921	Chronic pain due to trauma	10	Chronic Pain
G8922	Chronic post-thoracotomy pain	10	Chronic Pain
G8928	Other chronic postprocedural pain	10	Chronic Pain
G8929	Other chronic pain	10	Chronic Pain
G893	Neoplasm related pain (acute) (chronic)	10	Chronic Pain
G894	Chronic pain syndrome	10	Chronic Pain
F10x	Alcohol related disorders	10	Other Substance Use Disorders
F12x	Cannabis related disorders	10	Other Substance Use Disorders
F13x	Sedative, hypnotic, or anxiolytic related disorders	10	Other Substance Use Disorders
F14x	Cocaine related disorders	10	Other Substance Use Disorders
F15x	Other stimulant related disorders	10	Other Substance Use Disorders
F16x	Hallucinogen related disorders	10	Other Substance Use Disorders
F19x	Other psychoactive substance related disorders	10	Other Substance Use Disorders
3050x-3054x	Nondependent drug abuse of various types	9	Other Substance Use Disorders
3056x-3059x	Nondependent drug abuse of various types	9	Other Substance Use Disorders
3041x-3046x	Drug dependence of various types (excluding opioid)	9	Other Substance Use Disorders
3048x-3049x	Drug dependence of various types (excluding opioid)	9	Other Substance Use Disorders
303x	Alcohol dependence syndrome	9	Other Substance Use Disorders

Table A7. Error Codes for denied opioid claims

Included Codes

Error Code	Description
2603	Recipient Locked in
7001	INFORMATIONAL PRODUR ALERT
628	Other Coverage Reject Code Required for OCC 3
505	THIRD PARTY PAYMENT AMOUNT MORE THAN CLAIM CHARGE
1040	PRESCRIBING PHYSICIAN NOT ENROLLED
3000	UNITS EXCEED AUTHORIZED UNITS ON PA MASTER FILE
4025	AGE IS NOT ALLOWED FOR NDC
6845	Narcotic Analgesics Duplication
1000	BILLING PROVIDER ID NOT ON FILE
643	INVALID OTHER COVERAGE CODE
3002	NDC REQUIRES PA
7002	CLAIM DENIED FOR PRODUR REASONS
4167	DRUG QUANTITY PER DAY LIMIT EXCEEDED
3022	Non-Pref Drug. Prior Authorization Required.
1026	PRESCRIBING PHYSICIAN ID NOT ON FILE
7000	CLAIM FAILED A PRODUR ALERT
6899	SHORT-ACTING OPIOID MAX 7-DAY SUPPLY EXCEEDED
4175	OPIATES DRUG QUANTITY PER DAY LIMIT EXCEEDED
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)
4165	DRUG QUANTITY PER DAY LIMIT EXCEEDED
4999	THIS DRUG IS COVERED BY MEDICARE PART D
576	CLAIM HAS THIRD-PARTY PAYMENT
2017	RECIPIENT SERVICES COVERED BY HMO PLAN

Excluded Codes

Error Code	Description
2808	DOB IS MISSING
219	QUANTITY DISPENSED IS MISSING
268	BILLED AMOUNT MISSING
222	DAYS SUPPLY INVALID
2804	CASE NUMBER NOT ON FILE
911	INTERNAL ERROR
221	DAYS SUPPLY MISSING
1017	NON-REBATABLE ELIGIBLE INDICATOR
502	DATE DISPENSED EARLIER THAN DATE PRESCRIBED
1016	NON-PARTICIPATING MANUFACTURER

4007	NON-COVERED NDC DUE TO CMS TERMINATION
4127	CANNOT PRIORITIZE RECIPIENT'S PROGRAMS
4026	DAY SUPPLY LIMIT EXCEEDED FOR COVERED NDC
351	REFILL NOT ALLOWED FOR NARCOTIC DRUGS
5000	POSSIBLE DUPLICATE
238	RECIPIENT NAME IS MISSING
2807	MATCH CODE INVALID
3343	Questionable TPL amount
2809	DOB IS INVALID
5001	EXACT DUPLICATE
513	RECIPIENT NAME AND NUMBER DISAGREE
4891	Not covered drug class
4890	Non covered drug class
4002	Non-Covered Drug
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE