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, February 6th, 2020 1:00 - 5:00 PM
DXC 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 in accordance with Oregon Revised Statute 183.333. This meeting also serves as the Rules Advisory Committee to the Oregon Health Plan for proposed changes to Oregon Administrative Rule 414-121-0111.

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Election of Chair & Vice Chair	R. Citron (OSU)
	D. Approval of Agenda and Minutes	Chair
	E. Department Update	T. Douglass (OHA)
1:40 PM	II. Oregon Administrative Rule Changes	
	A. Oregon Administrative Rule Changes	D. Weston (OHA)
	1. Proposed Language for OAR 414-121-0111	
	2. P&T Operating Procedures	
	3. Public Comment	
	4. Discussion of Recommendations to OHA	
1:55 PM	III. CONSENT AGENDA TOPICS	Chair
	A. P&T Methods for Quality Assessment of Evidence	
	B. Drug Class Reviews	
	1. Immunosuppressants Literature Scan	
	2. Diabetes, Insulins Literature Scan	
	3. Jeuveau™ (prabotulinumtoxinA-xvfs) Abbreviated Drug Review	
	4. Vyleesi™ (bremelanotide) Abbreviated Drug Review	
	5. Public Comment	

IV. DUR ACTIVITIES

2:00 PM	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (DXC)
	C. RetroDUR Report	R. Citron (OSU)
	D. Oregon State Drug Review	K. Sentena (OSU)
	1. Pearls and Pitfalls of Clinical Practice Guidelines	
	2. Update on Recent Guidance and Safety Alerts for Opioid Use in Non-Cancer Pain	

V. DUR NEW BUSINESS

2:15 PM	A. Orphan Drug Policy Proposal	S. Servid (OSU)
	1. Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
2:25 PM	B. Opioid Literature Scan and Prior Authorization Update	S. Servid (OSU)
	1. Literature Scan/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
2:40 PM	C. Febuxostat Prior Authorization Update	K. Sentena (OSU)
	1. Recommendations for Policy Changes	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

VI. PREFERRED DRUG LIST NEW BUSINESS

2:45 PM	A. Diabetes, Glucagon Class Review	K. Sentena (OSU)
	1. Class Review	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
2:55 PM	BREAK	
3:05 PM	B. Xenleta™ (lefamulin) New Drug Evaluation	M. Herink (OSU)
	1. New Drug Evaluation/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
3:20 PM	C. Biologics for Autoimmune Conditions Class Update	D. Moretz (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Skyrizi™ (risankizumab-rzaa) New Drug Evaluation	
	3. Rinvoq™ (upadacitinib) New Drug Evaluation	
	4. Public Comment	
	5. Discussion of Clinical Recommendations to OHA	

3:45 PM	D. Narcolepsy Agents Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Wakix® (pitolisant) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
4:05 PM	VII. EXECUTIVE SESSION	
4:50 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS	
	IX. ADJOURN	
	X. OHA RULES ADVISORY COMMITTEE 1. Public Comment	D. Weston (OHA)

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
Tracy Klein, PhD, FNP	Public	Nurse Practitioner	Portland	December 2020
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director	Coos Bay	December 2020
William Origer, MD	Physician	Residency Faculty	Albany	December 2020
James Slater, PharmD	Pharmacist	Pharmacy Director	Beaverton	December 2020
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021
Patrick DeMartino, MD, MPh	Physician	Pediatrician	Portland	December 2022
Dave Pass, MD	Physician	Medical Director	West Linn	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, November 21, 2019 1:00 - 5:00 PM

DXC Conference Room

4070 27th Ct. SE

Salem, OR 97302

MEETING AGENDA

MEETING MINUTES

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

Members Present: Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Tracy Klein, PHD, FNP; Caryn Mickelson, PharmD; William Origer, MD; Cathy Zehrung, RPh

Members Present by Phone: Dave Pass, MD; James Slater, PharmD; Kelley Burnett, DO;

Staff Present: Roger Citron, RPh; David Engen, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Dee Weston; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Jennifer Bowen

Staff Present by Phone: Kathy Sentena, PharmD

Audience:
Rick Frees, Vertex Pharmaceuticals; Tim McFerron, Alkermes; Hiten Patadia, Otsuka; Brandon Yip*, Sanofi; Sean Staff, Aimmune Therapeutics; Paul Thompson*, Alkermes; Trent Taylor, Johnson & Johnson; Mae Kwong, Johnson & Johnson*; Mario Aguiar*, Sanofi Genzyme ; Jie Ferg, Sanofi Genzyme; Ann Wheeler*, Indivior; Bobbi Jo Drum, BMS; Ellen Chow, BMS; Roy Lindfield, Sunovion; Duke Piyathasee*, Takeda; Andrea Willetts, Takeda; Devin Cram, Takeda; Lori McDermott, Supernus; Anna Breckeisler; Patrick Maxy, Horizion Pharmaceuticals; Holly Mousa; Ann Neilson, Tricida; Dennis Schaffer, Sanofi Genzyme; Amy Yang*, OHSU; Chi Kohlhoff, Vida pharmaceuticals;
(*) Provided verbal testimony
Written testimony provided: Posted to OSU Website

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I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.
B. Conflict of Interest Declaration - No new conflicts of interest were declared.
C. Approval of September 2019 minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd, all in favor
D. Department Update – Trevor Douglass

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Reports
B. Antifungal Class Update
C. Anticoagulant Class Update
Recommendation:
1. Make no changes to the preferred drug list (PDL) based on clinical evidence.
2. Evaluate comparative drug costs in executive session.

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

III. DUR ACTIVIES

A. ProDUR Report - Mr. Holsapple presented the ProDUR report
B. RetroDUR Report - Dr. Engen presented the RetroDUR Report
C. Oregon State Drug Reviews
1. Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG) Recommendations for Treatment of Schizophrenia
2. Stimulant Use in Excessive Somnolence Disorders

Dr. Sentena presented two recently published newsletters, thanked the Committee for reviewing the draft versions and solicited ideas for future newsletters.

IV. DUR NEW BUSINESS

A. Substance Use Disorders Literature Scan and Prior Authorization (PA) Update
Dr. Moretz presented the literature scan and proposal to:
1. Make no changes to the PDL or PA criteria based on the review of recent clinical evidence.

Dr. Servid presented the policy proposal and recommended PA criteria updates to:
2. Remove the PA requirement for all OUD products except for dose limit of 24 mg buprenorphine per day for transmucosal products.

3. Designate products as either preferred or voluntary non-preferred based on evaluation of costs in executive session.
4. Continue to monitor use of substance use disorder products to assess potential changes in medically appropriate use.

ACTION: The Committee recommended implementing the proposed changes to the PA criteria. As part of ongoing monitoring for this class the Committee recommended soliciting input from prescribers of MAT and to assess efficacy or treatment discontinuation between agents.
Motion to approve, 2nd, 7 in favor, 1 opposed

B. Antidepressant Use in Children Drug Use Evaluation (DUE)
Dr. Servid presented the proposal to:
1. Implement a safety edit for initiation of TCA therapy in children younger than the FDA-approved minimum age limit with the goal of preventing off-label use.
2. Automatically approve requests for:
    - Prescriptions identified as being written by a mental health specialist, or
    - Ongoing TCA therapy, or
    - Evidence of a recent trial of a SSRI.

ACTION: The Committee recommended implementing the proposed safety edit and to also implementing a retrospective DUR safety net program to identify patients with denied claims and no subsequent follow-up in order to minimize interruptions and delays in therapy
Motion to approve, 2nd, All in favor

C. Dupixent® (dupilumab) Prior Authorization Update
Dr. Moretz presented the proposal to:
1. Revise the dupilumab PA criteria to include chronic rhinosinusitis with nasal polyposis as an FDA-approved indication for dupilumab as add on therapy to standard of care

ACTION: The Committee recommended implementing the proposed changes to the dupilumab PA criteria after amending to specifying the duration of the required steroid course for step therapy and to change “inhaled” steroid in question #15 to “intranasal”.
Motion to approve, 2nd, All in favor

V. PREFERRED DRUG LIST NEW BUSINESS

A. Aemcolo™ (rifamycin) New Drug Evaluation
Dr. Sentena presented the proposal to:
1. Designate rifamycin as non-preferred on the PDL.

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2. Add rifamycin to PA criteria for rifaximin to ensure appropriate utilization of both medications.

ACTION: The Committee recommended implementing the proposed recommendations after amending the proposed PA criteria to add a question to approve only if there is a contraindication to azithromycin and fluoroquinolones.
Motion to approve, 2nd, 7 in favor – 1 opposed

B. Arikayce® (amikacin) New Drug Evaluation
Dr. Engen presented the proposal to:
1. Designate amikacin liposome inhalation suspension as non-preferred on the PDL.
2. Implementing the proposed clinical PA criteria.

ACTION: The Committee recommended implementing the proposed recommendations after modifying question #4 to confirm the patient has been adherent for the past 6 months to a 3-drug regimen.
Motion to approve, 2nd, All in favor

C. Drugs for Gaucher Disease Class Review
Dr. Servid presented the proposal to:
1. Create a class for lysosomal storage disorders and designate miglustat as non-preferred based on FDA labeling as second-line therapy and eliglustat as non-preferred based on need for additional enzymatic testing.
2. Recommend PA for all targeted therapies for Gaucher disease to ensure medically appropriate use.
3. Evaluate comparative costs in executive session.

ACTION: The Committee recommended adopting the proposals after amending to refer requests for Type 3 patients to the Medical Director for review.
Motion to approve, 2nd, 6 in favor, 2 opposed

D. Ruzurgi® and Firdapse® (amifampridine) New Drug Evaluations
Dr. Engen presented the proposal to:
1. Create a new PDL class for Lambert-Eaton Myasthenic Syndrome (LEMS) agents.
2. Implementing the proposed clinical PA criteria for amifampridine.
3. Evaluate comparative costs in executive session.

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

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E. Cholbam® (cholic acid) New Drug Evaluation
Dr. Moretz presented the proposal to:
1. Designate cholic acid as non-preferred on the PDL.
2. Implementing the proposed clinical PA criteria.

ACTION: The Committee recommended adopting the proposals after modifying the initial approval to 3 months and to include assessment of liver function tests (LFTs) in the renewal criteria.
Motion to approve, 2nd, All in favor

VI. EXECUTIVE SESSION

Members Present: Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Tracy Klein, PHD, FNP; Caryn Mickelson, PharmD; William Origer, MD; Cathy Zehrung, RPh

Members Present by Phone:
Dave Pass, MD; James Slater, PharmD; Kelley Burnett, DO;

Staff Present: Roger Citron, RPh; David Engen, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Dee Weston; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Jennifer Bowen;

Staff Present by Phone: Kathy Sentena, PharmD

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Antifungal Class Update
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

B. Anticoagulant Class Update
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

C. Substance Use Disorders
Recommendation: make buprenorphine injection (Sublocade™) preferred and buprenorphine sublingual tablets, disulfiram tablets, buprenorphine/naloxone film (Bunavail®) voluntary non-preferred on the PDL.

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

D. Drugs for Gaucher Disease
Recommendation: make taliglucerase alfa preferred all other agents for Gaucher disease as non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

E. Amifampridine New Drug Evaluations
Recommendation: make Ruzurgi® preferred and Firdapse® non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

IX. ADJOURN

X. OHA Rules Advisory Committee

PROPOSED changes to PDL rule

410-121-0030

Practitioner-Managed Prescription Drug Plan

(1) The Practitioner-Managed Prescription Drug Plan (PMPDP) is a plan that ensures that OHP fee-for-service clients have access to the most effective prescription drugs appropriate for their clinical conditions at the best possible price:

(a) Licensed health care practitioners, who are informed by the latest peer reviewed research, make decisions concerning the clinical effectiveness of the prescription drugs;

(b) Licensed health care practitioners also consider the client's health condition, personal characteristics, and the client's gender, race, or ethnicity.

(2) PMPDP Preferred Drug List (PDL):

(a) The PDL is the primary tool the Division uses to inform licensed health care practitioners about the results of the latest peer-reviewed research and cost effectiveness of prescription drugs;

(b) The PDL contains a list of prescription drugs that the Division, in consultation with the Drug Use Review (DUR)/Pharmacy & Therapeutics Committee (P&T Committee), has determined represent the most effective drugs available at the best possible price;

(c) The PDL shall include drugs that are Medicaid reimbursable and the Food and Drug Administration (FDA) has determined to be safe and effective.

(3) PMPDP PDL Selection Process:

(a) The Division shall utilize the recommendations made by the P&T Committee that result from an evidence-based evaluation process as the basis for selecting the most effective drugs. The recommendation and review process is described in OAR 410-141-0111;

(b) The Division shall ensure the drugs selected in section (3)(a) are the most effective drugs available for the best possible price and shall consider any input from the P&T Committee about other FDA-approved drugs in the same class that are available for a lesser relative price. The Division shall determine relative price using the methodology described in section (4);

(c) The Division shall evaluate selected drugs for the drug classes periodically:

(A) The Division may evaluate more frequently if new safety information or the release of new drugs in a class or other information makes an evaluation advisable;

(B) New drugs in classes already evaluated for the PDL shall be non-preferred until the new drug has been reviewed by the P&T Committee;

(C) The Division shall make all revisions to the PDL using the rulemaking process and shall publish the changes on the Division's Pharmaceutical Services provider rules website.

(4) Relative cost and best possible price determination:

(a) The Division shall determine the relative cost of all drugs in each selected class that are Medicaid reimbursable and that the FDA has determined to be safe and effective;

(b) The Division may also consider dosing issues, patterns of use, and compliance issues. The Division shall weigh these factors with any advice provided by the P&T Committee in reaching a final decision.

(5) Pharmacy providers shall dispense prescriptions in the generic form unless:

(a) The practitioner requests otherwise pursuant to OAR 410-121-0155;

(b) The Division notifies the pharmacy that the cost of the brand name particular drug, after receiving discounted prices and rebates, is equal to or less than the cost of the generic version of the drug.

(6) The exception process for obtaining non-preferred physical health drugs that are not on the PDL drugs shall be as follows:

(a) If the prescribing practitioner in their professional judgment wishes to prescribe a physical health drug not on the PDL, they may request an exception subject to the requirements of OAR 410-121-0040;

(b) The prescribing practitioner must request an exception for physical health drugs not listed in the PDL subject to the requirements of OAR 410-121-0060;

(c) Exceptions shall be granted when:

(A) The prescriber in their professional judgment determines the non-preferred drug is medically appropriate after consulting with the Division or the Oregon Pharmacy Call Center; or

(B) Where the prescriber requests an exception subject to the requirement of section (6)(b) and fails to receive a report of PA status within 24 hours, subject to OAR 410-121-0060.

(7) Table 121-0030-1, PMPDP PDL dated October 1, 2019 is adopted and incorporated by reference and is found at: www.orpdl.org.

Stat. Auth.: ORS 413.032, 413.042, 414.065, 414.325, 414.330 to 414.414, 414.312, 414.316

Stats. Implemented: ORS 414.065; 414.325, 414.334, 414.361, 414.369, 414.371, 414.353, 414.354

PROPOSED changes to P&T rule

410-121-0111 – Pharmacy & Therapeutics Committee

~~(1) Pursuant to Oregon Laws 2011, chapter 720 (HB 2100), the Drug Use Review Board (DUR Board) is abolished and the tenure of office for the members of the DUR Board expires. The legislature transferred the duties, functions and powers previously vested in the DUR Board to the Pharmacy and Therapeutics (P&T) Committee. This rule is retroactively effective on September 5, 2011, the date the P&T Committee was created and the DUR Board was abolished by HB 2100 and expires whenever the Oregon Health Authority (Authority) suspends the rule.~~

~~(2) Unless otherwise inconsistent with these administrative rules or other laws, any administrative rule or agency policy with reference to the DUR Board or a DUR Board volunteer, staff or contractor shall be considered to be a reference to the P&T Committee or a P&T Committee volunteer, staff or contractor. The current preferred drug list (PDL), prior authorization process, and utilization review process developed by the DUR Board remains in effect until such time as the Authority, after recommendations and advice from the P&T Committee, modifies them through the adoption of new administrative rules or policies and procedures.~~

(1) The Drug Use Review (DUR)/Pharmacy and Therapeutics Committee (P&T Committee) is composed of 11 individuals appointed by the director of the Oregon Health Authority (Authority) pursuant to ORS 414.353.

~~(3)~~(2)The P&T Committee shall advise the ~~Oregon Health Authority (~~Authority~~)~~ on the following:

(a) Implementation of the medical assistance program retrospective and prospective programs, including the type of software programs to be used by the pharmacist for prospective drug use review and the provisions of the contractual agreement between the state and any entity involved in the retrospective program;

(b) Implementation of the Practitioner Managed Prescription Drug Plan (PMPDP);

(c) Adoption of administrative rules pertaining to the P&T Committee;

(d) Development of and application of the criteria and standards to be used in retrospective and prospective drug use review and safety edit programs in a manner that ensures that such criteria and standards are based on compendia, relevant guidelines obtained from professional groups through consensus-driven processes, the experience of practitioners with expertise in drug therapy, data and experience obtained from drug utilization review program operations. The P&T Committee must have an open professional consensus process, establish an explicit ongoing process for soliciting and considering input from interested parties, and make timely revisions to the criteria and standards based on this input and scheduled reviews;

(e) Development, selection and application of and assessment for interventions being educational and not punitive in nature for medical assistance program prescribers, dispensers and patients.

~~(4)~~(3)The P&T Committee shall make recommendations to the Authority, subject to approval by the Director or the Director's designee, for drugs to be included on any PDL

adopted by the Authority and on the PMPDP. The P&T Committee shall also recommend all utilization controls, prior authorization requirements or other conditions for the inclusion of a drug on the PDL.

~~(5)~~(4)The P&T Committee shall, with the approval of the Director or designee, do the following:

(a) Publish an annual report;

(b) Publish and disseminate educational information to prescribers and pharmacists regarding the P&T Committee and the drug use review programs, including information on the following:

(A) Identifying and reducing the frequency of patterns of fraud, abuse or inappropriate or medically unnecessary care among prescribers, pharmacists and recipients;

(B) Potential or actual severe or adverse reactions to drugs;

(C) Therapeutic appropriateness;

(D) Overutilization or underutilization;

(E) Appropriate use of generic products;

(F) Therapeutic duplication;

(G) Drug-disease contraindications;

(H) Drug-drug interactions;

(I) Drug allergy interactions;

(J) Clinical abuse and misuse.

(K) Patient safety

(c) Adopt and implement procedures designed to ensure the confidentiality of any information that identifies individual prescribers, pharmacists or recipients and that is collected, stored, retrieved, assessed or analyzed by the P&T Committee, staff of the P&T Committee, contractors to the P&T Committee or the Authority.

[Propose new Ad Hoc portion based on ORS 414.353(3):]

~~(6)~~(5) The Director shall appoint an ad hoc expert to the P&T Committee when:

(a) The P&T Committee determines it lacks current clinical or treatment expertise with

respect to a particular therapeutic class; or

(b) An interested outside party requests appointment and demonstrates to the satisfaction of the Director that the P&T Committee lacks necessary clinical knowledge or treatment expertise with respect to a particular therapeutic class. All such requests must be made at least 21 calendar days before the P&T Committee meeting at which the class will be discussed.

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(6) An ad hoc expert as described in (5) above shall have full voting rights with respect to recommendations for drugs to be included on any PDL and on the PMPDP, and any utilization controls, prior authorization requirements or other conditions for the inclusion of a drug on the PDL. Ad hoc experts may participate but may not vote in any other activities of the committee.

[Propose new timeline portion; below is nearly verbatim from ORS 414.361(5) as amended by HB 2692:]

(7) P&T Committee recommendations shall be implemented as follows:

(a) No later than seven days after the date on which the committee makes a recommendation under (3) above, the Division shall publish the recommendation on the website of the Authority and shall submit the recommendation for Director review.

(b) As soon as practicable after the P&T Committee makes a recommendation, the Director shall decide whether to approve, disapprove or modify the recommendation. The Division shall publish the decision on the website and shall notify persons who have requested notification of the decision.

(c) Except as provided in subsection (d) of this subsection, a recommendation approved by the Director, in whole or in part, with respect to the inclusion of a drug on a PDL or the PMPDP may not become effective less than seven days after the date that the Director's decision is published on the website.

(d) The Director may allow the immediate implementation of a recommendation described in subsection (c) of this subsection if the Director determines that immediate implementation is necessary to protect patient safety or to comply with state or federal requirements.

(e) As provided by ORS 414.361, the Director shall reconsider any decision to approve, disapprove or modify a recommendation described in subsection (c) of this subsection upon the request of any interested person filed no later than seven days after the Director's decision is published on the website of the Authority. The Director's determination regarding the request for reconsideration shall be sent to the requester and posted to the website without undue delay. Upon receipt of a request for reconsideration, the Director may:

(A) Delay the implementation of the recommendation pending the reconsideration process; or

(B) Implement the recommendation if the director determines that delay could reasonably result in harm to patient safety or would violate state or federal requirements.

Stat. Auth.: ORS 413.042, 414.065, 414.355, 414.360, 414.365, 414.370, 414.380

Stats. Implemented: ORS 414.065, 414.353, 414.361

OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: January ~~2019~~2020

MISSION:

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

DUTIES:

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

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the OHA for drugs to be included on the preferred drug list (PDL).
    a. The P&T Committee may direct a Subcommittee to prepare these reviews.
2. Advise the OHA on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
3. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs, as well as the ability of Oregonians to access prescriptions that are appropriate for their clinical conditions.
4. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs.
5. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.
6. Guide and approve meeting agendas.
7. Periodically review and update operating procedures and evidence grading methods as needed.

AD-HOC EXPERT INVOLVEMENT:

1. The Director shall appoint an ad hoc expert to the P&T Committee when:
    a. The P&T Committee determines it lacks current clinical or treatment expertise with respect to a particular therapeutic class; or
    b. An interested outside party requests appointment and demonstrates to the satisfaction of the Director that the P&T Committee lacks necessary clinical knowledge or treatment expertise with respect to a

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particular therapeutic class. All such requests must be made at least 21 calendar days before the P&T Committee meeting at which the class will be discussed.

~~1. A medical expert may be chosen and appointed by the Director of the OHA to provide clinical or treatment expertise in response to a request by the P&T Committee or an interested outside party. The ad-hoc expert must be a licensed physician in Oregon who manages patients who would potentially receive the particular drug(s).~~

~~2. If an interested outside party requests that an ad-hoc expert be appointed for a particular drug, this request must be made 45 days before the scheduled Committee meeting to ensure adequate time for the appointment process.~~

~~3.~~2. The medical experts shall have full voting rights with respect to the PDL drugs for which they have been selected and appointed including all utilization controls, prior authorization requirements, review of confidential pricing information or other conditions for the inclusion of a drug on the PDL. The medical experts may participate but may not vote in any other activities of the committee.

~~4.~~3. P&T staff also may engage relevant health care professionals with clinical specialty to serve as expert reviewers, in addition to the ad-hoc experts, if needed.

CONDUCT OF MEETINGS:

1. All meetings and notice of meetings will be held in compliance with the Oregon Public Meetings Law.
2. The P&T Committee will elect a Chairperson and Vice Chairperson to conduct the meetings. Elections shall be held the first meeting of the calendar year.
3. Quorum consists of 6 permanent members of the P&T Committee. Quorum is required for any official vote or action to take place throughout a meeting.
4. All official actions must be taken by a public vote. Any recommendation from the Committee requires an affirmative vote of a majority of the Committee members.
5. The committee shall meet in executive session for purposes of reviewing the prescribing or dispensing practices of individual prescribers or pharmacists; reviewing profiles of individual patients; and reviewing confidential drug pricing information to inform the recommendations regarding inclusion of drugs on the Practitioner-Managed Prescription Drug Plan (PMPDP) or any preferred drug lists adopted by the OHA.
6. Meetings will be held at least quarterly but the Committee may be asked to convene up to monthly by the call of the OHA Director or a majority of the members of the Committee. DUR programs will be the focus of the meeting quarterly.
7. Agenda items for which there are no recommended changes based on the clinical evidence may be included in a consent agenda.
    a. Items listed under the consent agenda will be approved by a single motion without separate discussion. If separate discussion is desired, that item will be removed from the consent agenda and placed on the regular business agenda.
    b. Consent agenda items may include (but are not limited to) meeting minutes, drug class literature scans, and abbreviated drug reviews for unfunded conditions.

CONFLICT OF INTEREST POLICY:

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

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

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

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

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

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

PUBLIC COMMENT:

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

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

    a. Testimony can be submitted in writing or provided in-person

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

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

    c. Written testimony can be submitted by interested parties for the P&T Committee to consider on agenda items. Written testimony that includes clinical information should be submitted for evaluation by staff at least 2 weeks prior to the scheduled meeting through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management).

    d. Written documents provided during scheduled public testimony time of P&T Committee meetings will be limited to 2 pages of new information that was not included in previous reviews. Prescribing

Information is not considered new information; only clinically relevant changes made to Prescribing Information should be submitted.

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

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

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

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

DRUG AND DRUG CLASS REVIEWS:

1. Drug Class Reviews and New Drug Evaluations:

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

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

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

2. Drug Class Literature Scans and Abbreviated Drug Reviews:

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

Drug Use Research & Management Program
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Review Standards and Methods for Quality Assessment of Evidence

Updated: January 2020

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

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

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

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

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

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

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

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

    a. Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University (OHSU)
    b. U.S. Department of Veterans Affairs/Department of Defense
    c. Agency for Healthcare Research and Quality (AHRQ)
    d. Canadian Agency for Drugs and Technologies in Health (CADTH)
    e. National Institute for Clinical Excellence (NICE)
    f. BMJ Clinical Evidence

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

    a. Systematic reviews of randomized controlled trials
    b. Direct comparative randomized controlled trials (RCTs) evaluating clinically relevant outcomes
    c. FDA review documents
    d. Clinical Practice Guidelines developed using explicit evidence evaluation processes

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

    a. Observational studies, case reports, case series
        i. However, observational studies and systematic reviews of observational studies will be included to evaluate significant safety data beyond the FDA labeling information. Observational studies will only be included when there is not adequate data from higher quality literature.
    b. Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles) that do not include sufficient methodological details for quality evaluation, with the exception of FDA review documents

c. Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality compared to other relevant literature, or duplicate information in other materials under review.
d. Studies not designed to investigate clinically relevant outcomes
e. Systematic reviews identified with the following characteristics:
    i. Evidence is of poor or very poor quality
    ii. Evidence is of limited applicability to a US population
    iii. Systematic review does not meet defined applicability criteria (PICOTS criteria) for the topic
    iv. Systematic review is of poor methodological quality as evaluated by AMSTAR II criteria (see **Appendix B**)
    v. Evidence is based on indirect comparisons from network meta-analyses
    vi. Conflicts of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)
f. Guidelines identified with the following characteristics:
    i. There is no systematic guideline development method described
    ii. Strength of evidence for guideline recommendations are not provided
    iii. Recommendations are largely based on expert opinion
    iv. Poor methodological quality as assessed in **Appendix C** (AGREE II score is less than 113 points OR modified AGREE II-GRS score is less than 30 points)
    v. Conflict of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)

QUALITY ASSESSMENT

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

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

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

4. Clinical practice guidelines are considered for inclusion after assessment of methodological quality using the AGREE II global rating scale provided in **Appendix C**.

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

6. Emphasis of the review will be on clinically relevant outcomes. The following clinically relevant outcomes are graded for quality: mortality, morbidity outcomes, symptom relief, quality of life, functioning (physical, mental, or emotional), early discontinuation due to adverse events, and

severe adverse effects. Surrogate outcomes are considered if directly linked to mortality or a morbidity outcome. Clinically meaningful changes in these outcomes are emphasized.

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

    a. Evidence grades are defined as follows:
        i. High quality evidence: High confidence that the estimated effects produced in the studies reflect the true effect. Further research is very unlikely to change the estimated effect.
        ii. Moderate quality evidence: Moderate confidence that the estimated effects produced in the studies reflect the true effect. Further research may change the estimated effect.
        iii. Low quality evidence: Limited confidence that the estimated effects produced in the studies reflect the true effect. Further research is likely to change the estimated effect.
        iv. Insufficient evidence: Evidence is not available or too limited to permit any level of confidence in the estimated effect.

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

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

Table 1. DURM Conflict of Interest Analysis

Type of literature	"Fatal flaws"	If no "fatal flaws" exist, potential limitations to discuss when including the piece of literature	Other considerations- specific to the type of literature
Randomized controlled trial	• Conflict of interest not documented	• Authors or committee members have significant conflicts of interest • Concerning high dollar amounts of conflicts of interest are documented • Mitigation strategies (described in the article or journal/organization policies) are documented but could be more robust	• Higher risk of bias when the study sponsor is the pharmaceutical manufacturer and is included in data analysis and manuscript writing
Systematic review	• Conflict of interest not documented • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* persons with potential conflicts of interest are excluded from the assessment or review process, independent second review of articles considered for inclusion in SR that are reviewed first by their own author who is on the SR team		• May consider funding sources or conflicts of interest for both the systematic review and the included studies
Guideline	• Conflict of interest not documented • Chair has a conflict of interest • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* excluding persons with significant conflict of interest from the review process, recusing members with significant conflict of interest from voting on recommendations or having them leave the room during the discussion		• Guidelines with "fatal flaws" which are commonly used in practice may be included for clinical context but will not be considered when creating conclusions or recommendations

APPENDIX A. Methods to Assess Quality of Studies.

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

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

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

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

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

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

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

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

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

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

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

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

Table 3. PICOS Domains that Affect Applicability.

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

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

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

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

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

Table 4. Non-inferiority Trial Quality Scoring Template

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

15. Results are interpreted in relation to the noninferiority hypothesis.	□ Yes □ No □ Can't answer

References:

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

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

A measurement tool for the "assessment of multiple systematic reviews" (AMSTAR II) was developed and shown to be a validated and reliable measurement tool to assess the methodological quality of systematic reviews. There are 1~~1~~6 components addressed in the measurement tool below, and ~~each~~ questions can be scored in one of four ways: "Yes", "Partial Yes", "No", ~~"Can't Answer",~~ or "Not Applicable". The AMSTAR II is used as a guideline to identify high quality systematic reviews eligible for inclusion in DURM evidence summaries. High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#4~~3~~); characteristics of studies not provided (#~~6~~8); quality of studies were not assessed or considered when conclusions were formulated (#9~~7~~ and #13~~8~~)). Other areas identified as important domains in the AMSTAR II criteria include registration of a protocol (#2); justification for excluding individual studies (#7); appropriateness of meta-analysis methods (#11); and assessment of publication bias (#15). In general, a high quality systematic review will score a "yes" on most components presented in the AMSTAR II tool.

Ref. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.~~Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*. 2007;7:10. doi: 10.1186/1471-2288-7-10~~ .

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

	AMSTAR II Quality Scoring Template		
1)	**Did the research questions and inclusion criteria for the review include the components of PICO?** **For Yes:** □ Population □ Intervention □ Comparator group □ Outcome	Optional (recommended) □ Timeframe for follow-up	□ Yes □ No
2)	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**		

	For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: □ review question(s) □ a search strategy □ inclusion/exclusion criteria □ a risk of bias assessment	**For Yes:** As for partial yes, plus the protocol should be registered and should also have specified: □ a meta-analysis/synthesis plan, if appropriate, and □ a plan for investigating causes of heterogeneity □ justification for any deviations from the protocol	□ Yes □ Partial Yes □ No
3)	**Did the review authors explain their selection of the study designs for inclusion in the review?** **For Yes**, the review should satisfy ONE of the following: □ Explanation for including only RCTs □ OR Explanation for including only NRSI □ OR Explanation for including both RCTs and NRSI		□ Yes □ No
4)	**Did the review authors use a comprehensive literature search strategy?**		
	For Partial Yes (all the following): □ searched at least 2 databases (relevant to research question) □ provided key word and/or search strategy □ justified publication restrictions (e.g. language)	**For Yes**, should also have (all the following): □ searched the reference lists / bibliographies of included studies □ searched trial/study registries □ included/consulted content experts in the field □ where relevant, searched for grey literature □ conducted search within 24 months of completion of the review	□ Yes □ Partial Yes □ No
5)	**Did the review authors perform study selection in duplicate?** **For Yes,** either ONE of the following: □ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include □ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		□ Yes □ No
6)	**Did the review authors perform data extraction in duplicate?** **For Yes,** either ONE of the following: □ at least two reviewers achieved consensus on which data to extract from included studies □ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.		□ Yes □ No
7)	**Did the review authors provide a list of excluded studies and justify the exclusions?**		
	For Partial Yes: □ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	**For Yes, must also have:** □ Justified the exclusion from the review of each potentially relevant study	□ Yes □ Partial Yes □ No
8)	**Did the review authors describe the included studies in adequate detail?**		
	For Partial Yes (ALL the following): □ described populations □ described interventions □ described comparators □ described outcomes □ described research designs	**For Yes,** should also have ALL the following: □ described population in detail □ described intervention in detail (including doses where relevant) □ described comparator in detail (including doses where relevant) □ described study's setting □ timeframe for follow-up	□ Yes □ Partial Yes □ No
9)	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?**		
RCTs	**For Partial Yes,** must have assessed RoB from: □ unconcealed allocation, and □ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	**For Yes,** must also have assessed RoB from: □ allocation sequence that was not truly random, and □ selection of the reported result from among multiple measurements or analyses of a specified outcome	□ Yes □ Partial Yes □ No □ Includes only NRSI
NRSI	**For Partial Yes,** must have assessed RoB: □ from confounding, and □ from selection bias	**For Yes,** must also have assessed RoB: □ methods used to ascertain exposures and outcomes, and	□ Yes □ Partial Yes □ No

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

AMSTAR Quality Scoring Template	
1) Was an 'a priori' design provided? Note: the research question and inclusion criteria should be established before the conduct of the review and should be available.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2) Was there duplicate study selection and data extraction? Note: there should be at least two independent persons for study selection and data extraction; a consensus process for disagreements is in place; at least one person checks the other's work.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3) Was a comprehensive literature search performed? Note: at least 2 databases (eg, MEDLINE, CINAHL, Scopus) plus one supplementary source (ie, gray literature) are searched. The review must include years and names databases used. Key words and/or Medical Subject Headings (MeSH) are stated and, if feasible, the search strategy is provided. Current reviews, specialized registers, or experts in the field of study may also be consulted.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4) Was the status of publication (ie, gray literature) used as an inclusion criterion? Note: "gray literature" or "unpublished literature" was searched. Dissertations, conference proceedings, and trial registries are all considered "gray literature" for this purpose. If a database was used that contained both gray literature and published literature, it was specified that gray literature was specifically searched. The authors should state whether any studies were excluded from the systematic review based on publication status, language, etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5) Was a list of studies (included and excluded) provided? Note: a list of included and excluded studies should be provided or referenced. Alternatively, there is a live electronic link to the list.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6) Were the characteristics of the included studies provided? Note: in an aggregated form (eg, a table), data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed (eg, age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases) should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7) Was the scientific quality of the included studies assessed and documented? Note: methods of assessment were provided *a priori*. For example, a quality scoring tool or checklist was used or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is NOT acceptable).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8) Was the scientific quality of the included studies used appropriately in formulating conclusions? Note: interpretation and analysis of the methodological rigor and quality of the included studies should be clear stated in the conclusions and explicitly stated in formulating recommendations. For example, "results should be interpreted with caution due to poor quality of included studies" is a reasonable interpretation. Cannot score "yes" for this question if scored "no" for question #7.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9) Were the methods used to combine the findings of studies appropriate? Note: for the pooled results, a test should be performed to test for heterogeneity (ie, Chi squared test, I^2). If heterogeneity exists, a random effects model was used, an explanation for inability to combine study results due to heterogeneity was given, or the clinical appropriateness of combining individual study results was considered (i.e., is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10) Was the likelihood of publication bias assessed? Note: an assessment of publication bias was made and a graphical aid was provided (eg, funnel plot) and/or statistical tests (e.g., Egger regression test) were included. Alternatively, if few studies were included, the review mentions that publication bias could not be assessed.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11) Was the conflict of interest stated? Note: potential sources of support should be clearly acknowledged in both the systematic review AND is acknowledged for the included studies. Ideally, a high quality systematic review will not have significant conflicts of interest.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

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

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

Table 1. AGREE II Instrument.

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

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

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

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

APPENDIX D. GRADE Quality of Evidence.

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

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

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

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

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

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

QUALITY OF EVIDENCE GRADES:

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

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

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

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

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Drug Class Literature Scan: Immunosuppressants

Date of Review: February 2020

Date of Last Review: January 2016
Literature Search: 10/01/15 – 10/31/19

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

Conclusions:
- Two high quality systematic reviews, 4 clinical practice guidelines, one randomized controlled trial (RCT), 2 new indications and one safety alert were identified after literature review to update the evidence for this class.
- A Cochrane review in patients with Crohn's disease found clinical remission more effective in patients treated with infliximab compared to azathioprine (AZA) based on moderate strength of evidence, with an absolute risk reduction (ARR) of 16%. Combination therapy with AZA + infliximab was more effective compared to infliximab alone at inducing remission, with an ARR of 12%, based on moderate strength of evidence.[1]
- High quality evidence from a Cochrane review in patients undergoing kidney transplant found mycophenolate mofetil (MMF) to be more effective at preserving graft survival (ARR of 2.4%/number needed to treat [NNT] 42) and prevention of acute rejection (ARR 5.5%/NNT 18) compared to AZA; however, cytomegalovirus (CMV) was more common (approximately 1.7-fold increase) with MMF therapy.[2]
- High quality guidelines support the Oregon Health Plan (OHP) fee-for-service (FFS) preferred drug placement for the treatment of Crohn's disease, kidney transplant and ulcerative colitis.[3-6]
- Everolimus (Afinitor®) received an approval for the use as adjunctive treatment for adult and pediatric patients aged 2 years and older with tuberous sclerosis complex (TSC)-associated partial-onset seizures and for use in adults with renal angiomyolipoma and TSC not requiring immediate surgery.[4]
- Tacrolimus (Astagraf XL®) was approved for the use in pediatric patients in November of 2018.
- Caution should be used with everolimus (Afinitor®/Zortress) in patients of reproductive age due to evidence of fetal harm.[4,5]

Recommendations:
- No additional research is needed.
- No changes to the preferred drug list (PLD) are recommended based on the evidence. Consider making all therapies preferred due to high approval percentage of current prior authorization (PA) requests.
- Evaluate costs in executive session

Summary of Prior Reviews and Current Policy
- Previous review of immunosuppressants found no differences between cyclosporine or tacrolimus for the outcomes of acute rejection or morality in patients who had undergone a lung transplant. Adverse events were lower with tacrolimus.

Author:

- There is insufficient evidence to suggest differences in efficacy or harms between the immunosuppressants. Calcineurin inhibitors are used most commonly to prevent rejection after transplant.
- There were no changes made to the PDL after review of the evidence presented for this class in January of 2016.
- All therapies in the class are preferred with the exception of: azathioprine (Azasan), tacrolimus (Prograf), and tacrolimus extended release (Envarsus XR). Non-preferred therapies are subject to the non-preferred agent PA criteria. There are approximately 40-50 requests for non-preferred therapies each quarter, resulting in an approval rate of almost 100%.
- The immunosuppressant class is not a large portion of OHP medication expenditures. There was approximately 100% utilization of preferred immunosuppressant therapies.

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

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

New Systematic Reviews:

Cochrane – Azathioprine or 6-mercaptopurine for Induction of Remission in Crohn's Disease
A 2016 Cochrane report reviewed the efficacy and safety of AZA or 6-mercaptopurine (6-MP) compared to placebo or active treatment in adult patients with active (acute) Crohn's Disease.[1] Thirteen trials were included in the analysis: 9 placebo-controlled and 6 active treatment comparisons. Most trials were found to be at low risk of bias. Placebo-controlled trial durations ranged from 12-17 weeks and active treatment comparisons lasted up to 26 weeks. The main outcome studied was the proportion of patients with clinical remission, measured by a validated outcome (e.g., Crohn's Disease Activity Index score less than 150 points or a Harvey-Bradshaw Index score less than 3). Clinical improvement, remission, glucocorticoids (GCS) reduction (or not needed) and mucosal healing were important secondary outcomes. Results with high to moderate evidence will be discussed.

There was moderate strength of evidence, from placebo-controlled trials (n=5), of no difference in clinical remission rates between AZA or 6-MP and placebo, 458/1000 patients versus 372/1000 patients (RR 1.23; 95% CI, 0.97 to 1.55).[1] There were similar findings for the comparison of AZA or 6-MP to placebo for the outcome of clinical remission or improvement, based on moderate evidence, 452/1000 patients versus 359/1000 patients (RR 1.26; 95% CI, 0.98 to 1.62).[1] These findings are limited by the fact that GCS were allowed in the placebo group, therefore confounding the effect of AZA or 6-MP. Additionally, the authors felt that some of the study durations may not have been long enough to adequately represent treatment efficacy, suggesting a minimum of 17 weeks is needed for an immunosuppressant effect to be realized. There was a GCS sparing (prednisone dose less than 10 mg/day while maintaining remission) effect of AZA compared

to placebo, 64% versus 46% (RR 1.34; 95% CI, 1.02 to 1.77; moderate evidence).[1] Serious adverse events occurred in 14% of patients treated with AZA compared to 4% placebo.[1]

In active treatment comparisons, AZA was compared to infliximab for induction of remission in Crohn's disease. Azathioprine induced remission in 32% of patients compared to 48% of infliximab-treated patients (RR 0.66; 95% CI, 0.51 to 0.87; moderate evidence).[1] GCS free-remission occurred in 37% of AZA patients compared to 44% of infliximab-treated patients (RR 0.68; 95% CI, 0.51 to 0.90; 1 trial; moderate evidence). Mucosal healing was more common in infliximab-treated patients compared to AZA (28% vs. 16%).[1] Adverse events were similar between groups. Similar results were found for the combination of AZA plus infliximab compared to infliximab alone. Combination therapy was more effective in clinical remission induction compared to infliximab monotherapy (ARR 12%; RR 1.26; 95% CI, 1.03 to 1.54).[1] GCS-free clinical remission was more common in patients treated with combination treatment compared to monotherapy (60% vs. 48%; RR 1.23; 95% CI, 1.02 to 1.47).[1] Combination therapy of infliximab plus AZA was more effective at mucosal healing compared to infliximab (ARR 14%; RR 1.50; 95% CI, 1.02 to 2.19; moderate strength of evidence).[1]

In conclusion, the use of AZA or 6-MP may have a GCS-sparing effect, potentially reducing the impact of GCS-related adverse events. Infliximab was found to be more effective than AZA in patients with Crohn's disease. Strong conclusions on placebo-controlled comparisons cannot be made due to inherent limitations related to the duration of the studies. Additional active treatment comparisons would help to delineate the most effective treatment option for remission induction in patients with Crohn's disease.

<u>Cochrane – Mycophenolic Acid versus Azathioprine as Primary Immunosuppression for Kidney Transplant Recipients</u>

The use of MMF was compared to AZA in patients requiring immunosuppression due to kidney transplant in a 2015 Cochrane review.[2] Twenty-three trials (n=3,301) were included. Thirteen of the studies did not use any antibody induction therapy. Maintenance immunotherapy was used in all studies, most commonly calcineurin inhibitors (cyclosporine or tacrolimus) combined with GCS, in addition to AZA or MMF. Most studies had an unclear risk of bias. Mycophenolic acid was more effective at preserving graft survival and prevention of acute rejection compared to AZA; however, cytomegalovirus (CMV) was more common with MMF therapy (**Table 1).**[2] Adverse events more common with MMF treatment were gastrointestinal and thrombocytopenia. Elevated liver enzymes were associated more with AZA use.

Limitations to the findings include the lack of reporting of panel reactive antibodies (PRA) and previous loss of a kidney graft, which are indicative of baseline immunological risk. Adverse events were only reported in a small number of studies. The risk of bias was unclear in a majority of studies.

Table 1. Primary Immunosuppression in Kidney Transplant Recipients Treated with Mycophenolic Acid or Azathioprine[2]

Outcome	Result*	Strength of Evidence	Conclusion
All-cause Death	AZA: 49/1000 MMF: 47/1000 RR 0.95 (95% CI, 0.7 to 1.29)	Moderate	No difference in death between treatments
Graft loss (censored for death)	AZA: 11/100 MMF: 9/100 RR 0.78 (95% CI, 0.61 to 0.98)	High	MMF associated with an absolute reduction in graft loss of 9% compared to 11.4% for AZA (ARR 2.4%/NNT 42)
Acute rejection, steroid resistant/antibody treated	AZA: 11/100 MMF: 5/100 RR 0.48 (95% CI, 0.36 to 0.65)	High	MMF associated with an ARR of 5.5%/NNT 18 compared to AZA
Infection, CMV tissue invasive	AZA: 4/100 MMF: 7/100 RR 1.7 (95% CI, 1.1 to 2.61)	High	Increased risk of infection with MMF vs. AZA
Acute rejection	AZA: 35/100 MMF: 23/100 RR 0.65 (95% CI, 0.57 to 0.73)	High	MMF associated with a reduced risk of acute rejection.
Key: * Illustrative comparative risk Abbreviations: AZA = azathioprine; CMV = cytomegalovirus; MMF = mycophenolate mofetil; NNT = number needed to treat; RR = relative risk			

After review, 50 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

<u>NICE – Crohn's Disease: Management</u>
A 2019 NICE guidance evaluated the evidence for the surgical and pharmacological management of patients with Crohn's disease.[3] Drug therapy recommendations for inducing remission and maintenance will be discussed. Endoscopic relapse and clinical relapse are important outcomes in determining response to therapy. Conventional GCS are recommended for remission of disease. Azathioprine, 6-MP, or methotrexate are not recommended to be used as monotherapy to induce remission and should be combined with other therapies. Recommendations for the role of traditional immunosuppressants are presented in **Table 2**. Patients taking AZA should be monitored for neutropenia.

Table 2. NICE Recommendations for the Use of Immunosuppressants in Patients with Crohn's Disease[3]

Indication	Recommendation
Remission Induction Add-on Treatment Options	• Glucocorticoids (GCS) are recommended first-line • AZA or 6-MP added to conventional GCS or budesonide for remission induction* • Infliximab, adalimumab, ustekinumab and vedolizumab recommended for patients unresponsive to conventional therapy (immunosuppressants or GCS)
Maintaining Remission Options	• AZA or 6-MP as monotherapy to maintain remission when previously used with conventional GCS or budesonide to induce remission • AZA or 6-MP are recommended to those who have not previously used these treatments
Maintaining Remission in Crohn's Disease after Surgery	• AZA in combination with up to 3 months postoperative metronidazole in patients with ileocolonic Crohn's disease with complete macroscopic resection within the last 3 months • AZA monotherapy is appropriate for patients with metronidazole intolerance
Key: * Assess thiopurine methyltransferase (TPMT) activity prior to use. If TPMT is deficient do not use and use lower doses if TPMT activity is below normal. Abbreviations: AZA = azathioprine; GCS = glucocorticoids; 6-MP = mercaptopurine	

NICE – Immunosuppressive Therapy for Kidney Transplant in Adults

A 2017 review of immunosuppressants from NICE offered guidance for patients who are undergoing kidney transplantation.[6] Recommendations were for induction and maintenance therapies, which included the following: basiliximab, rabbit anti-human thymocyte immunoglobulin (rATG), tacrolimus (immediate-release and prolonged-release), mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus, and betacept.[6] Induction therapy consists of approximately 2 weeks of an intensive immunosuppressive regimen. Maintenance therapy is started right after transplant and continued for the duration of the patient's life.

Evidence for the recommendations was provided by an assessment group that performed a systematic review and critical appraisal. These current recommendations are related to therapy (induction and maintenance) used around the time of transplant (**Table 3**).[6] There was insufficient evidence to make strong conclusions on comparative efficacy between maintenance therapies. Initial treatment with r-ATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended.[6] Everolimus is associated with an increased risk of anemia and sirolimus may cause peripheral edema and bone marrow suppression contributing to intolerance. There was insufficient evidence to recommend options for preventing organ rejection in adults who are not able to tolerate therapies in Table 3 or standard triple therapy with CSA, AZA, and a GCS.

Table 3. NICE Recommendations for Kidney Transplant in Adults – Treatment Related to Immediate Transplant Phase.[6]

Initial Therapy	*Comments*
Basiliximab* (induction)	In conjunction with a calcineurin inhibitor. No statistical difference was identified between basiliximab and rabbit anti-human thymocyte immunoglobulin (rATG) with no evidence of a clinical difference between therapies.
Immediate release tacrolimus	As part of an immunosuppressive regimen
Mycophenolate mofetil	As part of an immunosuppressive regimen
Key:*Basiliximab is the most cost-effective treatment	

NICE- Immunosuppressive Therapy for Kidney Transplant in Children and Young People

An October 2017 guidance from NICE provided recommendations on immunotherapy for children and young people undergoing kidney transplant.[7] Drugs included in this review are: basiliximab, rATG, tacrolimus (immediate-release and prolonged-release), mycophenolate mofetil, mycophenolate sodium, sirolimus, and everolimus. Immunosuppressant recommendations for children and young people mirror those for adult kidney transplant recipients. These current recommendations are related to therapy (induction and maintenance) used around the time of transplant (**Table 4)**.[7] Initial treatment with rATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended. Overall, comparative evidence between immunosuppressants is limited in children and young people undergoing a kidney transplant.

Table 4. NICE Recommendations for Kidney Transplant in Children and Young People – Treatment Related to Immediate Transplant Phase.[7]

Initial Therapy	*Comments*
Basiliximab (induction)	In conjunction with a calcineurin inhibitor
Immediate-release tacrolimus	As part of an immunosuppressive regimen
Mycophenolate mofetil	As part of an immunosuppressive regimen

NICE – Ulcerative Colitis: Management

NICE updated the recommendations for the management of ulcerative colitis in 2019.[8] Most of the evidence related to studies of patients with mild to moderate ulcerative colitis. Immunosuppressants are usually reserved for more severe disease. Recommendations for the use of immunosuppressants in severe ulcerative colitis are presented in **Table 5**.

Table 5. NICE Recommendations for the use of Immunosuppressants in the Management of Ulcerative Colitis.[8]

Recommendation	*Comments*
Severe Ulcerative Colitis	
IV cyclosporine	For patients whom IV GCS are not appropriate
IV cyclosporine	In combination with IV GCS in patients who fail to respond within 72 hours of starting IV GCS or worsen during GCS treatment
Remission Maintenance	
AZA or 6-MP	After 2 or more inflammatory exacerbations in 12 months that require treatment with systemic GCS or if remission isn't maintained by aminosalicylates
Remission Maintenance After a Single Episode of Acute Ulcerative Colitis	
Azathioprine or mercaptopurine	Aminosalicylates can be considered if intolerant to other therapies
Abbreviations: AZA = azathioprine; GCS = glucocorticoids; IV = intravenous; 6-MP = mercaptopurine	

After review, 22 guidelines were excluded due to poor quality.[9–30]

New Formulations/Indications:

Everolimus (Afinitor®)

In 2018 everolimus received an approval for the use as adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures at a dose of 5 mg/m^2.[4] Evidence for this indication was provided by a phase 3 trial (EXIST-3) described below in **Table 7**.[31]

In 2016 everolimus was approved for use in adults with renal angiomyolipoma and TSC not requiring immediate surgery at a dose of 10 mg orally daily.[4] Evidence for the approval was based on one phase 3 trial (EXIST-2) described below in **Table 7**.[32]

Tacrolimus (Astagraf XL®)

The FDA approved tacrolimus for the use in pediatric patients in November of 2018.[33] Approval was based on pharmacokinetic studies demonstrating similar tacrolimus concentrations at 24 hours as immediate-release tacrolimus (Prograf) in pediatric de novo kidney transplant patients.

Tacrolimus (Envarsus XR®)

Envarsus XR was FDA approved in 2018 for the prophylaxis of organ rejection in de novo kidney transplant patients in combination with other immunosuppressants.[34] This formulation of tacrolimus was previously indicated for use in patients who had transitioned from immediate-release tacrolimus. The recommended dose is 0.14 mg/kg once daily.

New FDA Safety Alerts:

Table 6. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Everolimus[4, 5]	Afinitor®/Zortress	2015	Warnings	Can cause fetal harm. Patients should be advised of reproductive potential risk to a fetus and to use contraception if of reproductive potential.

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34. Envarsus XR Prescribing Information. Veloxis Pharmaceuticals, Inc.Cary, North Carolina. 2018.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
azathioprine	AZATHIOPRINE	TABLET	Y
azathioprine	IMURAN	TABLET	Y
cyclosporine	CYCLOSPORINE	CAPSULE	Y
cyclosporine	SANDIMMUNE	CAPSULE	Y
cyclosporine	SANDIMMUNE	SOLUTION	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	CAPSULE	Y
cyclosporine, modified	GENGRAF	CAPSULE	Y
cyclosporine, modified	NEORAL	CAPSULE	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	SOLUTION	Y
cyclosporine, modified	GENGRAF	SOLUTION	Y
cyclosporine, modified	NEORAL	SOLUTION	Y
everolimus	ZORTRESS	TABLET	Y
mycophenolate mofetil	CELLCEPT	CAPSULE	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	CAPSULE	Y
mycophenolate mofetil	CELLCEPT	SUSP RECON	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	SUSP RECON	Y
mycophenolate mofetil	CELLCEPT	TABLET	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	TABLET	Y
mycophenolate sodium	MYCOPHENOLIC ACID	TABLET DR	Y
mycophenolate sodium	MYFORTIC	TABLET DR	Y
sirolimus	RAPAMUNE	SOLUTION	Y
sirolimus	SIROLIMUS	SOLUTION	Y
sirolimus	RAPAMUNE	TABLET	Y
sirolimus	SIROLIMUS	TABLET	Y
tacrolimus	PROGRAF	CAPSULE	Y
tacrolimus	TACROLIMUS	CAPSULE	Y
azathioprine	AZASAN	TABLET	N
tacrolimus	ASTAGRAF XL	CAP ER 24H	N
tacrolimus	PROGRAF	GRAN PACK	N
tacrolimus	ENVARSUS XR	TAB ER 24H	N

Appendix 2: New Comparative Clinical Trials

A total of 549 citations were manually reviewed from the initial literature search. After further review, 547 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 7. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Bissler, et al[32] (EXIST-2) Phase 3, DB, MC, PC, RCT	Everolimus 10 mg daily Vs. Placebo daily Median exposure 36 weeks	Adult patients with renal angiomyolipoma 3 cm or larger and TSC diagnosis or sporadic lymphangioleio-myomatosis, not requiring immediate surgery4 (n=118)	Proportion of patients with confirmed angiomyolipoma response of at least a 50% reduction in total volume of target angiomyolipoma relative to baseline	<u>Response rate:</u> Everolimus: 42% Placebo: 0% MD 42% (95 CI, 24-58%) P < 0.0001
French, et al[31] (EXIST-3) Phase 3, DB, MC, PC, RCT	Everolimus 3-7 ng/mL (low exposure) Vs. Everolimus 9-15 ng/mL (high exposure) Vs. Placebo 18 week core phase (followed an 8 week baseline phase)	Patients with TSC and treatment-resistant seizures receiving 1-3 concomitant antiepileptic drugs (n=366)	Change from baseline in the frequency of seizures during the maintenance period defined as a response rate* and median percentage reduction in seizure frequency	<u>Response rate:</u> Everolimus low exposure: 28.2% Everolimus high exposure: 40% Placebo: 15.1% Everolimus low exposure vs. placebo P = 0.0077 Everolimus high exposure vs. placebo P < 0.001 <u>Reduced seizure frequency:</u> Everolimus low exposure: 29.3% Everolimus high exposure: 39.6% Placebo: 14.9% Everolimus low exposure vs. placebo P = 0.0028 Everolimus high exposure vs. placebo P < 0.0001

Key: * Response rate was defined as the proportion of patients achieving 50% or greater reduction in seizure frequency
Abbreviations: CR = complete response; DB = double-blind; DLBCL = diffuse large B-cell lymphoma; IPI = International Prognostic Index; MC = multi-center; PC = placebo controlled; RCT = randomized clinical trial; TSC = tuberous sclerosis complex.

Appendix 3: Abstracts of Comparative Clinical Trials

Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial.

Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, Whittemore VH, Chen D, Sahmoud T, Shah G, Lincy J, Lebwohl D, Budde K.

BACKGROUND:
Angiomyolipomas are slow-growing tumours associated with constitutive activation of mammalian target of rapamycin (mTOR), and are common in patients with tuberous sclerosis complex and sporadic lymphangioleiomyomatosis. The insidious growth of these tumours predisposes patients to serious complications including retroperitoneal haemorrhage and impaired renal function. Everolimus, a rapamycin derivative, inhibits the mTOR pathway by acting on the mTOR complex 1. We compared the angiomyolipoma response rate on everolimus with placebo in patients with tuberous sclerosis or sporadic lymphanioleiomyomatosis-associated angiomyolipomata.
METHODS:
In this double-blind, placebo-controlled, phase 3 trial, patients aged 18 years or older with at least one angiomyolipoma 3 cm or larger in its longest diameter (defined by radiological assessment) and a definite diagnosis of tuberous sclerosis or sporadic lymphangioleiomyomatosis were randomly assigned, in a 2:1 fashion with the use of an interactive web response system, to receive oral everolimus 10 mg per day or placebo. The primary efficacy endpoint was the proportion of patients with confirmed angiomyolipoma response of at least a 50% reduction in total volume of target angiomyolipomas relative to baseline. This study is registered with ClinicalTrials.gov number NCT00790400.
RESULTS: 118 patients (median age 31·0 years; IQR 18·0–61·0) from 24 centres in 11 countries were randomly assigned to receive everolimus (n=79) or placebo (n=39). At the data cutoff, double-blind treatment was ongoing for 98 patients; two main reasons for discontination were disease progression (nine placebo patients) followed by adverse events (two everolimus patients; four placebo patients). The angiomyolipoma response rate was 42% (33 of 79 [95% CI 31–53%]) for everolimus and 0% (0 of 39 [0–9%]) for placebo (response rate difference 42% [24–58%]; one-sided Cochran-Mantel-Haenszel test p<0·0001). The most common adverse events in the everolimus and placebo groups were stomatitis (48% [38 of 79], 8% [3 of 39], respectively), nasopharyngitis (24% [19 of 79] and 31% [12 of 39]), and acne-like skin lesions (22% [17 of 79] and 5% [2 of 39]).
INTERPRETATION: Everolimus reduced angiomyolipoma volume with an acceptable safety profile, suggesting it could be a potential treatment for angiomyolipomas associated with tuberous sclerosis.

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study.

French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, Curatolo P, de Vries PJ, Dlugos DJ, Berkowitz N, Voi M, Peyrard S, Pelov D, Franz DN
BACKGROUND:
Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been used for various benign tumours associated with tuberous sclerosis complex. We assessed the efficacy and safety of two trough exposure concentrations of everolimus, 3-7 ng/mL (low exposure) and 9-15 ng/mL (high exposure), compared with placebo as adjunctive therapy for treatment-resistant focal-onset seizures in tuberous sclerosis complex.

METHODS:

In this phase 3, randomised, double-blind, placebo-controlled study, eligible patients aged 2-65 years with tuberous sclerosis complex and treatment-resistant seizures (≥16 in an 8-week baseline phase) receiving one to three concomitant antiepileptic drugs were recruited from 99 centres across 25 countries. Participants were randomly assigned (1:1:1), via permuted-block randomisation (block size of six) implemented by Interactive Response Technology software, to receive placebo, low-exposure everolimus, or high-exposure everolimus. Randomisation was stratified by age subgroup (<6 years, 6 to <12 years, 12 to <18 years, and ≥18 years). Patients, investigators, site personnel, and the sponsor's study team were masked to treatment allocation. The starting dose of everolimus depended on age, body-surface area, and concomitant use of cytochrome 3A4/P-glycoprotein inducers. Dose adjustments were done to attain target trough ranges during a 6-week titration period, and as needed during a 12-week maintenance period of core phase. Patients or their caregivers recorded events in a seizure diary throughout the study. The primary endpoint was change from baseline in the frequency of seizures during the maintenance period, defined as response rate (the proportion of patients achieving ≥50% reduction in seizure frequency) and median percentage reduction in seizure frequency, in all randomised patients. This study is registered with ClinicalTrials.gov, number NCT01713946.

FINDINGS:

Between July 3, 2013, and May 29, 2015, 366 patients were enrolled and randomly assigned to placebo (n=119), low-exposure everolimus, (n=117), or high-exposure everolimus (n=130). The response rate was 15·1% with placebo (95% CI 9·2-22·8; 18 patients) compared with 28·2% for low-exposure everolimus (95% CI 20·3-37·3; 33 patients; p=0·0077) and 40·0% for high-exposure everolimus (95% CI 31·5-49·0; 52 patients; p<0·0001). The median percentage reduction in seizure frequency was 14·9% (95% CI 0·1-21·7) with placebo versus 29·3% with low-exposure everolimus (95% CI 18·8-41·9; p=0·0028) and 39·6% with high-exposure everolimus (95% CI 35·0-48·7; p<0·0001). Grade 3 or 4 adverse events occurred in 13 (11%) patients in the placebo group, 21 (18%) in the low-exposure group, and 31 (24%) in the high-exposure group. Serious adverse events were reported in three (3%) patients who received placebo, 16 (14%) who received low-exposure everolimus, and 18 (14%) who received high-exposure everolimus. Adverse events led to treatment discontinuation in two (2%) patients in the placebo group versus six (5%) in the low-exposure group and four (3%) in the high-exposure group.

INTERPRETATION:

Adjunctive everolimus treatment significantly reduced seizure frequency with a tolerable safety profile compared with placebo in patients with tuberous sclerosis complex and treatment-resistant seizures.

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to October Week 1 2019
Search Strategy:

#	Searches	Results
1	azathioprine.mp. or Azathioprine/	21289
2	cyclosporine.mp. or Cyclosporine/	43181
3	everolimus.mp. or Everolimus/	5880
4	mycophenolate mofetil.mp. or Mycophenolic Acid/	11137
5	sirolimus.mp. or Sirolimus/	19233
6	tacrolimus.mp. or Tacrolimus/	22267
7	1 or 2 or 3 or 4 or 5 or 6	96850
8	limit 7 to (english language and humans and yr="2015 -Current")	11564
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	549

Appendix 5: Key Inclusion Criteria

Population	Patients with an indication for immunosuppressants
Intervention	Immunosuppressant
Comparator	Active treatment or placebo
Outcomes	Mortality, graft loss, infection, clinical remission, induction, and withdrawals due to adverse events
Timing	Any duration
Setting	Inpatient or outpatient

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

Drug Class Literature Scan: Insulins

Date of Review: February 2020

Date of Last Review: September 2019
Literature Search: 05/01/19 – 12/31/19

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

Conclusions:
- Insulins were recently reviewed in September of 2019; therefore, minimal new evidence was available for review. Two randomized clinical trials, one new guideline (clinical context only), one systematic review and one new insulin formulation was identified.
- An intravenous formulation of insulin regular human, brand name Myxredlin®, was approved to be used in adults and children with diabetes mellitus for glucose control.
- No new evidence was identified that would result in changes to the preferred drug list (PDL).
- No additional research is needed.

Recommendations:
- No changes to the PDL are recommended based on the clinical review of efficacy and safety.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The last review in September 2019 found no clinically significant differences in glucose lowering between long-acting insulin products or between the short-acting insulin products.
- After executive session, insulin glulisine pens and vials, insulin regular U-500 pens, Humalog mix 75/25 and 50/50 KwikPens, and insulin detemir vials were designated as preferred products on the PDL.
- Newly approved products, Ademelog® and FIASP® were maintained as nonpreferred therapies.
- Non-preferred pens and cartridges require a prior authorization justifying the need for a non-preferred product.
- There is approximately 85% utilization of preferred insulin products; however, insulin costs are still substantial.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the

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

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

New Systematic Reviews:

CADTH – Clinical Review Report: Insulin degludec and liraglutide (Xultophy)

In 2019, CADTH reviewed the clinical effectiveness of combined insulin degludec (long-acting insulin product) and liraglutide (glucagon-like peptide 1 receptor agonists [GLP-1 RA]) for use in patients with type 2 diabetes mellitus (T2DM) to improve blood glucose levels.[1] Xultophy® has been previously reviewed and presented to the Pharmacy and Therapeutics Committee; therefore, only summary recommendations from CADTH will be provided. CADTH recommends insulin degludec/liraglutide, in combination with metformin (with or without a sulfonylurea) as an option for patients requiring basal insulin who have failed to meet target blood glucose goals on a GLP-1 RA, with or without other antidiabetic therapies. Benefit of therapy should be reassessed at 26 weeks.[1]

After review, three systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[2–4]

New Guidelines:

High Quality Guidelines: None identified

Additional Guidelines for Clinical Context:

American Diabetes Association – Standards of Medical Care in Diabetes -2020

The American Diabetes Association updates management standards for patients with diabetes mellitus on an annual basis.[5] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions.

New Formulations:

Insulin Regular human (Myxredlin®) – Myxredlin® is a short-acting insulin indicated for use to improve glycemic control in adults and pediatric patients with diabetes mellitus.[6] Myxredlin® is formulated in a sodium chloride injection for intravenous use only.

New Indications:

Insulin aspart (FIASP®) – Rapid-acting insulin aspart was approved for use in pediatric patients based on a 26-week, randomized controlled trial in 777 patients with type 1 diabetes mellitus (T1DM).[7] Rapid acting insulin aspart was compared to insulin aspart (Novolog®), in a blinded manner at mealtimes. The third arm was an open-label rapid acting insulin aspart given post-meal. All regimens were given with insulin degludec once daily. The primary outcome was HbA1c lowering. Both doses of rapid-acting insulin aspart were shown to be noninferior to insulin aspart.[7]

New FDA Safety Alerts: None identified.

References:

1. Canadian Agency for Drugs and Technologies in Health. Clinical review report: Xultophy. CADTH Common Drug Review. December 2019. Available at: https://www.cadth.ca/sites/default/files/cdr/clinical/sr0599-xultophy-clinical-review-report.pdf. Accessed 31 December, 2019.

2. Maiorino M, Chiodini P, Bellastella G, et al. The good comparisons: insulin and glucagon-like peptide-1 receptor agonist in type 2 diabetes. A systematic review and meta-analysis of randomized controlled trials. Diabetes Research and Clinical Practice. 2019;154:101-115.

3. Santos L, Leite J, Barbosa L, et al. Effectiveness of insulin analogs compared with human insulins in pregnant women with diabetes mellitus: systematic review and meta-analysis. Rev Bras Gineco Obstet. 2019;41:104-115.

4. Canadian Agency for Drugs and Technologies in Health. Long-acting insulin analogues versus human NPH insulin for adults with type 2 diabetes and unresponsiveness to non-insulin therapies: clinical effectiveness, cost-effectiveness, and guidelines. CADTH Rapid Response Report. 3 May 2019. Available at:https://www.cadth.ca/sites/default/files/pdf/htis/2019/RB1331%20LA%20Insulin%20versus%20NPH%20Final.pdf. Accessed 31 December 2019.

5. American Diabetes Association. Pharmacological approaches to glycemic treatment: standards of medical care in diabetes - 2020. Diabetes Care. 2020;43:S98-S110.

6. Myxredlin (insulin human in sodium chloride injection) [prescribing information]. Deerfield, IL: Baxter Healthcare Corporation. June 2019.

7. Fiasp (insulin aspart) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk, December 2019.

8. Dovc K, Piona C, Mutlu G, et al. Faster compared with standard insulin aspart during day-and-night fully closed-loop insulin therapies in type 1 diabetes: a double-blind randomized crossover trial. Diabetes Care. 2019. published ahead of print. doi:10.2337/dc19-0895/-/DC1.

9. Bode B, Iotova V, Kovarenko M, et al. Efficacy and safety of fast-acting insulin aspart compared with insulin aspart, both in combination with insulin degludec, in children and adolescents with type 1 diabetes: the onset 7 trial. Diabetes Care. 2019;42:1255-1262.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
insulin aspart	NOVOLOG	CARTRIDGE	SQ	Y
insulin aspart	NOVOLOG FLEXPEN	INSULN PEN	SQ	Y
insulin aspart	NOVOLOG	VIAL	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30	VIAL	SQ	Y
insulin detemir	LEVEMIR FLEXTOUCH	INSULN PEN	SQ	Y
insulin detemir	LEVEMIR	VIAL	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	INSULN PEN	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS	VIAL	SQ	Y
insulin glulisine	APIDRA SOLOSTAR	INSULN PEN	SQ	Y
insulin glulisine	APIDRA	VIAL	SQ	Y
insulin lispro	HUMALOG	VIAL	SQ	Y
insulin lispro	INSULIN LISPRO	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50 KWIKPEN	INSULN PEN	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25 KWIKPEN	INSULN PEN	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70/30 KWIKPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70-30	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30	VIAL	SQ	Y
insulin NPH human isophane	HUMULIN N	VIAL	SQ	Y
insulin NPH human isophane	NOVOLIN N	VIAL	SQ	Y
insulin regular, human	HUMULIN R U-500 KWIKPEN	INSULN PEN	SQ	Y
insulin regular, human	HUMULIN R	VIAL	IJ	Y
insulin regular, human	NOVOLIN R	VIAL	IJ	Y
insulin regular, human	HUMULIN R U-500	VIAL	SQ	Y
insulin aspart (niacinamide)	FIASP PENFILL	CARTRIDGE	SQ	N
insulin aspart (niacinamide)	FIASP FLEXTOUCH	INSULN PEN	SQ	N
insulin aspart (niacinamide)	FIASP	VIAL	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-100	INSULN PEN	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-200	INSULN PEN	SQ	N
insulin degludec	TRESIBA	VIAL	SQ	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	INSULN PEN	SQ	N
insulin glargine/lixisenatide	SOLIQUA 100-33	INSULN PEN	SQ	N

insulin lispro	HUMALOG	CARTRIDGE	SQ	N
insulin lispro	HUMALOG JUNIOR KWIKPEN	INS PEN HF	SQ	N
insulin lispro	ADMELOG SOLOSTAR	INSULN PEN	SQ	N
insulin lispro	HUMALOG KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	HUMALOG KWIKPEN U-200	INSULN PEN	SQ	N
insulin lispro	INSULIN LISPRO KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	ADMELOG	VIAL	SQ	N
insulin NPH human isophane	HUMULIN N KWIKPEN	INSULN PEN	SQ	N
insulin regular, human	AFREZZA	CART INHAL	IH	N
insulin regular in 0.9 % NaCl	MYXREDLIN	PLAST. BAG	IV	

Appendix 2: New Comparative Clinical Trials

A total of fifty citations were manually reviewed from the initial literature search. After further review, forty-eight 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 two trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Dovc, et al[8] DB, RCT, CO	Faster insulin aspart vs. Insulin aspart (both administered via a fully closed-loop insulin therapy)	Adult patients with T1DM on an insulin pump (n=20)	Difference in blood glucose levels based time in range (70-180 mg/dL) over 27 hours based on glucose sensor data	Time in range: Faster insulin aspart: 53.3% Insulin aspart: 57.9% P=0.170 *No significant difference between treatments.*
Bode, et al[9] MC, RCT, DB	Mealtime fast-acting insulin aspart* vs. Mealtime insulin aspart* or Post-meal open-label faster insulin aspart* * All with insulin degludec 26-week (with 12-week run in)	Children and adolescents (1 to <18 years) with T1DM (n=777)	Change in baseline HbA1c after 26 weeks	Mealtime fast acting insulin aspart: -0.2% Mealtime insulin aspart: 0.0% Post-meal fast acting insulin aspart: 0.1% <u>Mealtime fast acting aspart vs. mealtime insulin aspart</u> TD -0.17% (95% CI, -0.30 to -0.03) P < 0.001 for non-inferiority, p=0.007 for superiority <u>Open-label post-meal insulin aspart vs. mealtime insulin aspart</u> TD 0.13% (95% CI, -0.01 to 0.26) P < 0.001 for non-inferiority *Fast-acting insulin aspart was noninferior to insulin aspart. Mealtime fast-acting insulin aspart was also superior to mealtime insulin aspart.*

Abbreviations: CI = confidence interval; CO = crossover; DB = double-blind; MC = multi-center; RCT = randomized clinical trial; T1DM = type 1 diabetes mellitus; TD = treatment difference

Appendix 3: Abstracts of Comparative Clinical Trials

Faster Compared With Standard Insulin Aspart During Day-and-Night Fully Closed-Loop Insulin Therapy in Type 1 Diabetes: A Double-Blind Randomized Crossover Trial
Klemen Dovc , Claudia Piona , Gül Yeşiltepe Mutlu , Natasa Bratina , Barbara Jenko Bizjan , Dusanka Lepej , Revital Nimri , Eran Atlas , Ido Muller , Olga Kordonouri , Torben Biester , Thomas Danne , Moshe Phillip , Tadej Battelino

Objective: We evaluated the safety and efficacy of day-and-night fully closed-loop insulin therapy using faster (Faster-CL) compared with standard insulin aspart (Standard-CL) in young adults with type 1 diabetes.
Research design and methods: In a double-blind, randomized, crossover trial, 20 participants with type 1 diabetes on insulin pump therapy (11 females, aged 21.3 ± 2.3 years, HbA_{1c} 7.5 ± 0.5% [58.5 ± 5.5 mmol/mol]) underwent two 27-h inpatient periods with unannounced afternoon moderate-vigorous exercise and unannounced/uncovered meals. We compared Faster-CL and Standard-CL in random order. During both interventions, the fuzzy-logic control algorithm DreaMed GlucoSitter was used. Glucose sensor data were analyzed by intention-to-treat principle with the difference (between Faster-CL and Standard-CL) in proportion of time in range 70-180 mg/dL (TIR) over 27 h as the primary end point.
Results: The proportion of TIR was similar for both arms: 53.3% (83% overnight) in Faster-CL and 57.9% (88% overnight) in Standard-CL (P = 0.170). The proportion of time in hypoglycemia <70 mg/dL was 0.0% for both groups. Baseline-adjusted interstitial prandial glucose increments 1 h after meals were greater in Faster-CL compared with Standard-CL (P = 0.017). The gaps between measured plasma insulin and estimated insulin-on-board levels at the beginning, at the end, and 2 h after the exercise were smaller in the Standard-CL group (P = 0.029, P = 0.003, and P = 0.004, respectively). No severe adverse events occurred.
Conclusions: Fully closed-loop insulin delivery using either faster or standard insulin aspart was safe and efficient in achieving near-normal glucose concentrations outside postprandial periods. The closed-loop algorithm was better adjusted to the standard insulin aspart.

Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec, in Children and Adolescents With Type 1 Diabetes: The Onset 7 Trial
Bruce W Bode , Violeta Iotova , Margarita Kovarenko , Lori M Laffel , Paturi V Rao , Srikanth Deenadayalan , Magnus Ekelund , Steffen Falgreen Larsen , Thomas Danne

Objective: To confirm efficacy and safety of fast-acting insulin aspart (faster aspart) versus insulin aspart (IAsp), both with basal insulin degludec, in a pediatric population with type 1 diabetes.
Research design and methods: After a 12-week run-in, this treat-to-target, 26-week, multicenter trial randomized participants (1 to <18 years) to double-blind mealtime faster aspart (n = 260), mealtime IAsp (n = 258), or open-label postmeal faster aspart (n = 259). The primary end point was change from baseline in glycated hemoglobin (HbA_{1c}) after 26 weeks of treatment. All available information regardless of treatment discontinuation was used for the evaluation of treatment effect.
Results: At week 26, mealtime and postmeal faster aspart were noninferior to IAsp regarding change from baseline in HbA_{1c} (P < 0.001 for noninferiority [0.4% margin]), with a statistically significant difference in favor of mealtime faster aspart (estimated treatment difference -0.17% [95% CI -0.30; -0.03], -1.82 mmol/mol [-3.28; -0.36]; P = 0.014). Change from baseline in 1-h postprandial glucose increment significantly favored mealtime faster aspart versus IAsp at breakfast, main evening meal, and over all meals (P < 0.01 for all). No statistically significant differences in the overall rate of severe or blood glucose-confirmed hypoglycemia were observed. Mean total daily insulin dose was 0.92 units/kg for mealtime faster aspart, 0.92 units/kg for postmeal faster aspart, and 0.88 units/kg for mealtime IAsp.
Conclusions: In children and adolescents with type 1 diabetes, mealtime and postmeal faster aspart with insulin degludec provided effective glycemic control with no additional safety risks versus IAsp. Mealtime faster aspart provided superior HbA_{1c} control compared with IAsp.

Appendix 4: Medline Search Strategy
Database(s): Ovid MEDLINE(R) ALL 1946 to December 31, 2019
Search Strategy:

#	Searches	Results
1	insulin aspart.mp. or Insulin Aspart/	1118
2	Insulin Detemir/ or insulin detemir.mp.	820
3	insulin glargine.mp. or Insulin Glargine/	2585
4	Insulin Lispro/ or insulin lispro.mp.	1131
5	insulin NPH.mp. or Insulin, Isophane/	1092
6	insulin regular.mp. or Insulin/	185244
7	insulin degludec.mp.	541
8	1 or 2 or 3 or 4 or 5 or 6 or 7	187543
9	limit 8 to (english language and humans and yr="2019 -Current")	1045
10	limit 9 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	50

Appendix 5: Key Inclusion Criteria

Population	Patients with T1DM and T2DM
Intervention	Insulins
Comparator	Active treatment comparisons or placebo
Outcomes	Mortality, micro- and macrovascular complications, glucose lowering, hypoglycemia
Timing	New onset or established diabetes
Setting	Outpatient

Insulins

Goal:
Provide evidence-based and cost-effective insulin options to patients with diabetes mellitus.

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 glulisine (Apidra SoloSTAR®), insulin regular, human (Humulin R U-500 Kwikpen®) insulin lispro protamine-lispro (Humalog® Mix 75-25 Kwikpen), insulin lispro protamine-lispro (Humalog® Mix 50-50 Kwikpen) insulin aspart (Novolog Flexpen®), insulin detemir (Levemir® Flextouch), insulin glargine (Lantus SoloSTAR®)

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. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Go to #4
4. Is the request for an insulin pen or cartridge?	**Yes:** Go to #5	**No:** Approve for up to 12 months

Approval Criteria		
5. Has the patient tried and failed or have contraindications to any of the preferred pens or cartridges listed above?	**Yes:** Go to #6	**No:** Pass to RPh; deny and recommend a trial of one of the preferred insulin products
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:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness

P&T / DUR Review: *9/19 (KS); 11/18 (KS); 9/17; 3/16; 11/15; 9/10*
Implementation: *11/1/2019; 11/1/17; 10/13/16; 1/1/11*

Jeuveau (prabotulinumtoxinA-xvfs)[1,2]

Indications

- Indicated for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugate and/or procerus muscle activity in adults.

Dosage

- Injected intramuscularly in 4 unit (0.1 mL) aliquots into each of five designated sites across the brow line for a total dose of 20 units.
- Supplied as 100 unit, single-dose vial of vacuum-dried powder for reconstitution with preservative-free 0.9% sodium chloride.

Background

- This biosimilar product is a botulinum toxin type A produced through fermentation of *Clostridium botulinum*. It functions as an acetylcholine release inhibitor and neuromuscular blocking agent. Local injection produces a partial chemical denervation of the muscle, which reduces muscle activity.
- Potency is specific to the type of botulinum toxin product, and it is not interchangeable with other botulinum toxin products.
- Cosmetic conditions of skin are unfunded under Oregon Health Plan prioritized list (line 654).

Efficacy

Approval by the FDA was obtained with two randomized, multi-center, double-blind, placebo-controlled trials [EV-001 (NCT02334423) and EV-002 (NCT02334436)] with identical designs. Block randomization was 3:1; patients received a single treatment of 5 injections. Trial participants were healthy adults with moderate to severe glabellar lines at maximum frown. Those with ptosis, deep dermal scarring, or inability to lessen glabellar lines were excluded. Subjects had a mean age of 51 years with 68 (10%) being ≥65 years, and were primarily white (84%) and female (91%). The primary endpoint was proportion of patients with ≥2 grade improvement from baseline at maximum frown at day 30. This was assessed by both patient and investigator using a 4-point grading scale called the Glabellar Line Scale. The primary endpoint was assessed with an intent-to-treat analysis with multiple imputation for handling of missing data, and a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by site. The investigators noted a CMH test was not appropriate after unblinding due to low placebo response rates and additionally performed a *post-hoc* analysis using an exact unconditional test. A randomized, double-blind, placebo and active controlled trial (EV-003) was conducted for European and Canadian regulatory agencies; however, additional information regarding results of this study are not available.

	Trial EV-001			**Trial EV-002**		
	PrabotulinumtoxinA-xvfs N=246	**Placebo** N=84	**P-Value***	**PrabotulinumtoxinA-xvfs N=246**	**Placebo N=84**	**P-Value***
Primary efficacy endpoint	67%	1%	<0.001	71%	1%	<0.001

*Confidence intervals not reported

Safety

Common adverse reactions: headache (12%), upper respiratory tract infection (3%), eyelid ptosis (2%), and increase in white blood cell count (1%)
Contraindications: known hypersensitivity to any botulinum toxin preparation or component of the formulation, infection at injection site
Warnings and precautions: Spread beyond local injection site causing a variety of symptoms consistent with botulinum toxin, including life-threatening swallowing and breathing difficulties and death have been reported. These can appear hours to weeks post-injection and patients should seek immediate medical care if swallowing, speech, or respiratory difficulties occur. Product is not interchangeable with other botulinum toxin products. Serious adverse reactions have been associated with botulinum toxin injections when used for unapproved use. These include excessive weakness, dysphagia, and aspiration pneumonia. These reactions are not related to distant spread of toxin and some have been fatal. Use caution when using in patients with preexisting cardiovascular disease, neuromuscular disorders, dysphagia or breathing difficulties, or pre-existing conditions at injection site. Dry eye and other ophthalmic effects have been reported and may be persistent or require referral to an ophthalmologist. There is a small risk of transmission of viral disease secondary to use of human albumin in the product. Safety in pregnancy, lactation, and pediatrics have not been established. Use in geriatrics has been studied, but data remain insufficient to determine if response differs from younger patients.

Evidence Gaps/Limitations

No studies found to support evidence for use in the treatment of Oregon Health Plan (OHP) funded conditions or co-morbidities.

Recommendation

Restrict use for OHP-covered conditions through Prior Authorization.

References

1. Jeuveau (prabotulinumtoxinA-xvfs) for intramuscular injection [prescribing information]. Santa Barbara, CA, USA. Evolus Inc. 2019.
2. FDA Center for Drug Evalulation and Research. Clinical Review and Evaluation Memorandum Resubmission of BLA761085. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761085Orig1s000MultiR.pdf Accessed: 2 Dec 2019.

Trade name (generic)[1]

Vyleesi (bremelanotide) for subcutaneous (SC) use

Indications

- Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD). This is characterized by low sexual desire that causes marked distress or interpersonal difficulty and NOT due to: (1) a co-existing medical or psychiatric condition, (2) problems with the relationship, or (3) effects of a medication or drug substance.
- This indication is an excluded and unfunded condition based on Oregon Health Plan (OHP) prioritized list (line 521).

Dosage

- Inject 1.75 mg SC to the abdomen or thigh, as needed, at least 45 minutes before anticipated sexual activity. Optimal window for administration is not defined.
- Maximum of 1 dose/24 hours and 8 doses/month.
- Supplied as a single-dose, 1.75 mg/0.3 mL auto injector.

Background

- Mechanism of action for HSDD in women is unknown.
- Functions as a melanocortin receptor (MCR) agonist resulting in activation of multiple MCR subtypes.
- MC1R subtype is expressed on melanocytes (see warnings and precautions-focal hyperpigmentation).

Efficacy

FDA approval was obtained with two identical, phase 3, randomized, double-blind, placebo-controlled trials [Study 1 (NCT02333071) and Study 2 (NCT02338960)] of premenopausal women with at least 6 months of acquired, generalized HSDD. The studies were conducted over 24 weeks, followed by a 52-week uncontrolled, open-label extension. Study participants were primarily Caucasian (86%) or Black (12%) with a mean age of 39 years. Average duration in a monogamous relationship was 12 years with mean duration of HSDD of 4 years. The co-primary endpoints for these trials were (1) change from baseline to end of study (EOS) in the Desire domain from the Female Sexual Function Index (FSFI) (5 point scale for each of 2 questions with sum multiplied by 0.6) and (2) change from baseline to EOS in score for feeling bothered by low sexual desire in the Female Sexual Distress Scale (FSDS)(4 point scale). Both endpoints were evaluated using an unadjusted Wilcoxon rank-sum test in a modified intent-to-treat analysis.

	Endpoint (1): FSFI improvement in Desire domain				**Endpoint (2): FSDS improvement**			
	Study 1		Study 2		Study 1		Study 2	
	Bremelanotide (N=313)	Placebo (N=315)	Bremelanotide (N=282)	Placebo (N=288)	Bremelanotide (N=313)	Placebo (N=314)	Bremelanotide (N=282)	Placebo (N=285)
Mean Baseline (SD)	2.1 (0.9)	2.0 (0.8)	2.0 (0.8)	2.1 (0.8)	2.9 (1.0)	2.8 (0.9)	2.9 (0.9)	2.9 (0.9)
Mean change from baseline (SD)	0.5 (1.1)	0.2 (1.0)	0.6 (1.0)	0.2 (0.9)	-0.7 (1.2)	-0.4 (1.1)	-0.7 (1.1)	-0.4 (1.1)
P-value	0.0002		<0.0001		<0.0001		0.0053	

SD-standard deviation

Safety

Common adverse reactions: nausea (40%), flushing (20.3%), injection site reactions (13.2%), headache (11.3%), vomiting (4.8%), cough (3.3%), fatigue (3.2%), hot flush (2.7%), paresthesia (2.6%), dizziness (2.2%), nasal congestion (2.1%)

Contraindications: Uncontrolled hypertension or known cardiovascular disease

Warnings and Precautions: Transient increased blood pressure and reduced heart rate; focal hyperpigmentation, with or without resolution after discontinuation, which may involve face, gingiva, and breasts and is more common in dark skin; nausea sometimes requiring anti-emetic therapy

Special populations: Avoid use in postmenopausal women, men, pregnancy, pediatrics, and geriatrics. Use caution with severe renal (GFR < 30 ml/min/1.73m^2) and hepatic (Child-Pugh C; score 10-15) impairment as these patients have increased incidence and severity of adverse reactions, particularly nausea and vomiting.

Evidence Gaps/Limitations

- Initial publication on safety and efficacy was retracted after multiple journals retracted studies by the lead author due to questions about methods, results, and statistical interpretation.[2]
- No studies found to support evidence for use in the treatment OHP-covered conditions or co-morbidities.

Recommendation

Restrict use for OHP-covered conditions through Prior Authorization

References

1. Vyleesi (bremelanotide) for subcutaneous injection [Prescribing Information]. Waltham, MA, USA. AMAG Pharmaceuticals, Inc. 2019.
2. Safarinejad MR. RETRACTED: Evaluation of the safety and efficacy of bremelanotide, a melanocortin receptor agonist, in female subjects with arousal disorder: a double-blind placebo-controlled, fixed dose, randomized study. *J Sex Med.* 2008;5(4):887-897.

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Feb 2020

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Pharmacy Utilization Summary Report: July 2018 - June 2019

Eligibility	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
Total Members (FFS & Encounter)	962,205	964,077	963,131	964,428	966,366	965,956	970,009	973,211	979,795	981,514	979,468	979,316	970,790
FFS Members	120,682	119,156	121,522	115,577	120,900	125,681	118,919	119,390	125,420	113,342	112,672	115,232	119,041
OHP Basic with Medicare	34,887	35,039	35,293	35,249	35,494	35,531	33,066	33,109	33,374	28,706	29,057	29,456	33,188
OHP Basic without Medicare	11,917	11,827	11,956	11,702	11,714	11,824	11,916	11,789	11,811	11,739	11,877	12,010	11,840
ACA	73,878	72,290	74,273	68,626	73,692	78,326	73,937	74,492	80,235	72,897	71,738	73,766	74,013
Encounter Members	841,523	844,921	841,609	848,851	845,466	840,275	851,090	853,821	854,375	868,172	866,796	864,084	851,749
OHP Basic with Medicare	41,300	41,375	41,334	41,471	41,476	41,372	43,801	43,841	43,822	48,472	48,276	48,107	43,721
OHP Basic without Medicare	62,869	62,744	62,264	62,281	62,113	61,913	61,991	61,974	61,949	62,066	61,919	61,721	62,150
ACA	737,354	740,802	738,011	745,099	741,877	736,990	745,298	748,006	748,604	757,634	756,601	754,256	745,878

Gross Cost Figures for Drugs	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	YTD Sum
Total Amount Paid (FFS & Encounter)	$74,521,792	$78,481,313	$69,183,134	$79,428,041	$74,046,495	$71,010,682	$80,515,529	$72,521,705	$79,631,996	$83,867,412	$85,057,437	$77,117,872	$925,383,408
Mental Health Carve-Out Drugs	$7,681,806	$7,922,644	$7,131,531	$8,141,860	$7,652,260	$7,529,124	$8,182,004	$7,375,393	$7,876,497	$8,448,811	$8,520,505	$7,767,519	$94,229,952
OHP Basic with Medicare	$4,472	$6,085	$4,293	$5,584	$4,637	$5,502	$8,243	$6,479	$5,197	$5,313	$9,126	$19,499	$84,430
OHP Basic without Medicare	$3,198,935	$3,332,935	$2,944,347	$3,385,534	$3,132,603	$3,111,911	$3,308,623	$2,985,088	$3,108,591	$3,368,797	$3,367,896	$3,012,746	$38,258,006
ACA	$4,424,340	$4,521,248	$4,131,416	$4,694,528	$4,454,212	$4,358,178	$4,802,505	$4,318,745	$4,696,984	$5,009,848	$5,081,168	$4,686,551	$55,179,723
FFS Physical Health Drugs	$2,794,928	$3,068,155	$2,490,425	$3,068,268	$2,657,002	$2,672,525	$3,152,240	$2,630,546	$2,866,645	$2,878,110	$2,914,441	$2,651,962	$33,845,245
OHP Basic with Medicare	$228,289	$237,203	$213,639	$292,188	$244,574	$241,618	$255,721	$220,127	$257,059	$251,786	$203,319	$133,754	$2,779,277
OHP Basic without Medicare	$822,590	$961,926	$710,880	$936,448	$814,596	$777,955	$1,027,448	$877,313	$953,273	$912,730	$975,672	$985,395	$10,756,226
ACA	$1,611,972	$1,701,207	$1,444,055	$1,714,148	$1,468,189	$1,529,063	$1,746,484	$1,420,693	$1,541,691	$1,580,085	$1,593,824	$1,430,846	$18,782,256
FFS Physician Administered Drugs	$1,490,154	$1,725,587	$1,419,187	$1,828,747	$1,516,926	$1,321,010	$1,904,554	$1,957,823	$1,752,537	$1,440,603	$1,513,040	$1,838,888	$19,709,057
OHP Basic with Medicare	$342,660	$450,906	$413,223	$411,838	$441,697	$307,451	$553,228	$495,331	$496,081	$368,760	$395,137	$344,886	$5,021,197
OHP Basic without Medicare	$275,350	$386,587	$217,519	$601,074	$134,561	$129,854	$329,160	$520,022	$234,759	$248,847	$242,006	$562,049	$3,881,789
ACA	$500,278	$579,252	$482,368	$470,042	$586,221	$555,699	$607,730	$559,221	$567,890	$407,241	$451,058	$558,756	$6,325,757
Encounter Physical Health Drugs	$50,301,743	$53,180,614	$47,491,725	$54,156,833	$50,034,455	$48,435,990	$53,517,490	$48,759,525	$54,624,993	$57,473,795	$57,946,778	$52,020,086	$627,944,027
OHP Basic with Medicare	$190,629	$271,154	$228,192	$263,143	$235,652	$248,672	$321,215	$266,961	$307,839	$299,944	$358,877	$565,422	$3,557,700
OHP Basic without Medicare	$13,360,636	$14,027,407	$12,442,795	$14,203,038	$13,151,725	$12,793,753	$13,540,450	$11,980,310	$13,354,852	$14,403,458	$14,572,546	$13,231,865	$161,062,836
ACA	$36,131,606	$38,204,830	$34,144,531	$39,049,665	$36,026,994	$34,817,123	$38,884,638	$35,821,447	$40,291,442	$42,096,095	$42,372,553	$37,594,858	$455,435,785
Encounter Physician Administered Drugs	$12,253,161	$12,584,313	$10,650,267	$12,232,333	$12,185,853	$11,052,033	$13,759,242	$11,798,419	$12,511,322	$13,626,093	$14,162,674	$12,839,417	$149,655,127
OHP Basic with Medicare	$243,143	$253,746	$203,545	$266,195	$260,151	$228,754	$398,528	$301,159	$275,818	$308,288	$362,391	$302,101	$3,403,819
OHP Basic without Medicare	$3,026,000	$2,873,402	$2,549,848	$2,809,458	$2,914,800	$2,646,244	$2,917,061	$2,897,129	$2,827,422	$3,050,912	$3,338,582	$2,752,459	$34,603,317
ACA	$8,730,964	$9,328,855	$7,769,273	$8,965,004	$8,884,524	$8,040,755	$10,257,737	$8,471,708	$9,254,952	$10,060,950	$10,259,405	$9,630,737	$109,654,863

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

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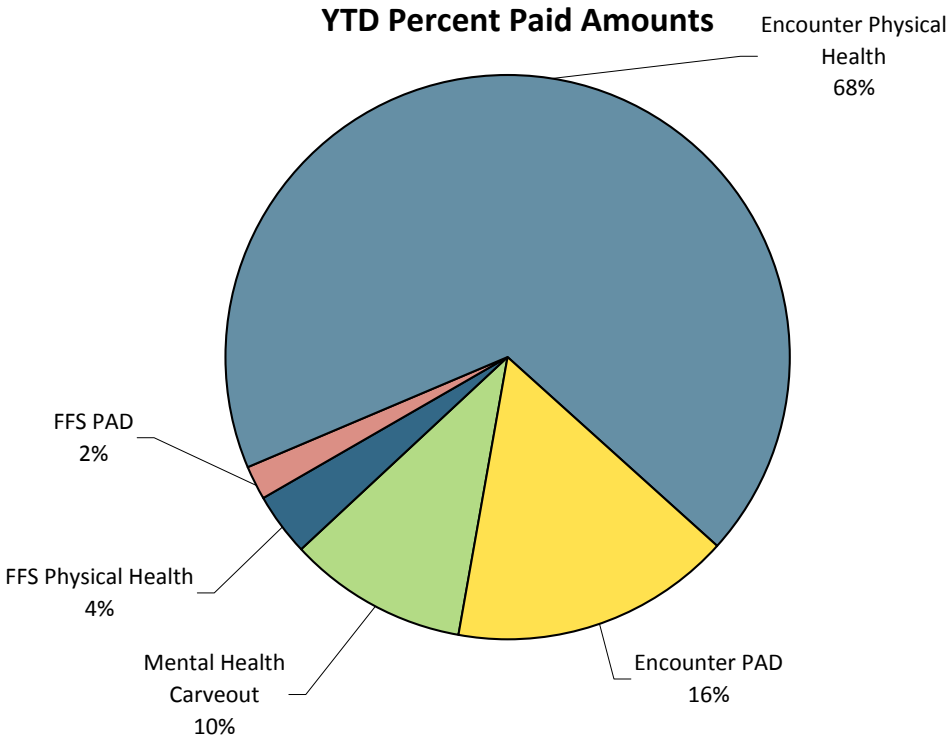

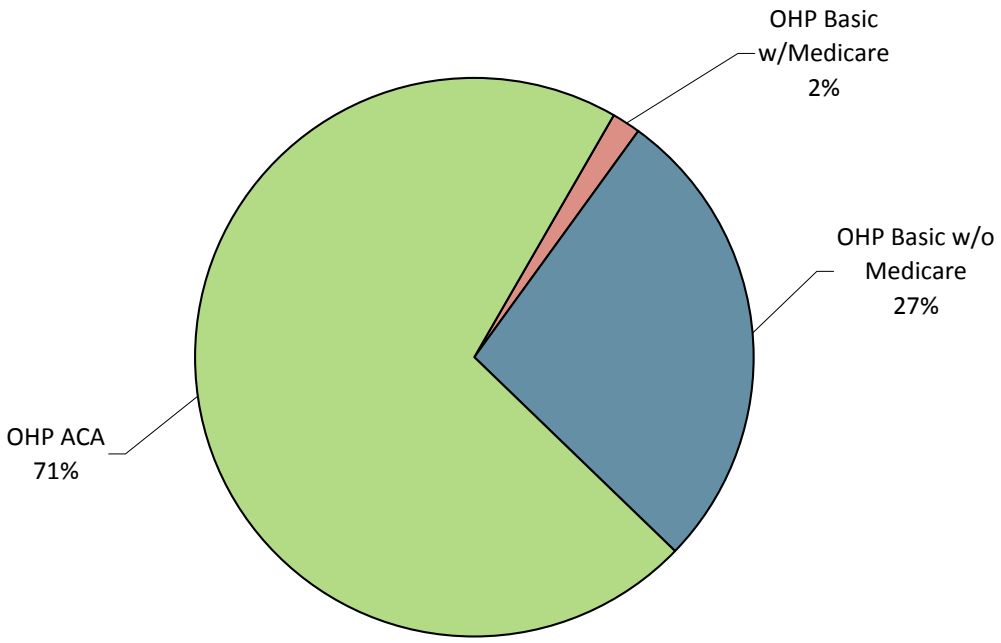

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee.
If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

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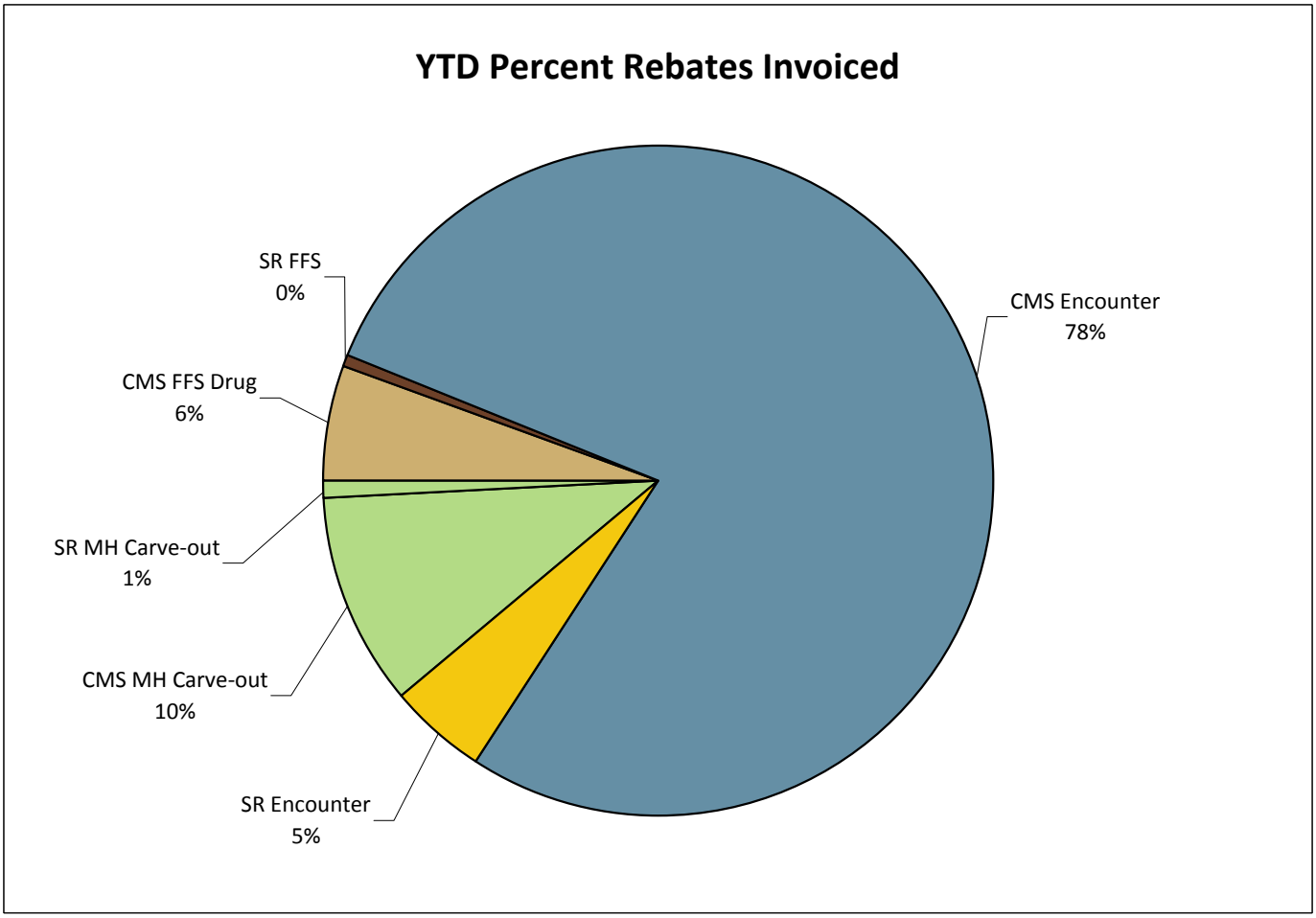
Pharmacy Utilization Summary Report: July 2018 - June 2019

Quarterly Rebates Invoiced	2018-Q3	2018-Q4	2019-Q1	2019-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$107,564,739	$101,192,193	$102,130,976	$105,957,133	$416,845,042
CMS MH Carve-out	$9,882,536	$10,078,062	$11,227,170	$11,538,192	$42,725,960
SR MH Carve-out	$573,570	$654,824	$1,065,433	$1,120,134	$3,413,962
CMS FFS Drug	$6,152,797	$5,411,275	$6,305,985	$6,023,675	$23,893,732
SR FFS	$372,775	$240,457	$259,357	$321,335	$1,193,924
CMS Encounter	$83,827,791	$82,090,312	$79,392,418	$80,907,385	$326,217,906
SR Encounter	$6,755,271	$2,717,263	$3,880,614	$6,046,412	$19,399,559

Quaterly Net Drug Costs	2018-Q3	2018-Q4	2019-Q1	2019-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$114,621,500	$123,293,024	$130,538,254	$140,085,588	$508,538,367
Mental Health Carve-Out Drugs	$12,279,875	$12,590,356	$11,141,291	$12,078,508	$48,090,030
FFS Phys Health + PAD	$6,462,864	$7,412,746	$7,699,003	$6,892,033	$28,466,647
Encounter Phys Health + PAD	$95,878,762	$103,289,922	$111,697,960	$121,115,046	$431,981,690



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

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Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$77.45	$81.41	$71.83	$82.36	$76.62	$73.51	$83.00	$74.52	$81.27	$85.45	$86.84	$78.75	$79.42
Mental Health Carve-Out Drugs	$7.98	$8.22	$7.40	$8.44	$7.92	$7.79	$8.43	$7.58	$8.04	$8.61	$8.70	$7.93	$8.09
FFS Physical Health Drugs	$23.16	$25.75	$20.49	$26.55	$21.98	$21.26	$26.51	$22.03	$22.86	$25.39	$25.87	$23.01	$23.74
FFS Physician Administered Drugs	$12.35	$14.48	$11.68	$15.82	$12.55	$10.51	$16.02	$16.40	$13.97	$12.71	$13.43	$15.96	$13.82
Encounter Physical Health Drugs	$59.77	$62.94	$56.43	$63.80	$59.18	$57.64	$62.88	$57.11	$63.94	$66.20	$66.85	$60.20	$61.41
Encounter Physician Administered Drugs	$14.56	$14.89	$12.65	$14.41	$14.41	$13.15	$16.17	$13.82	$14.64	$15.70	$16.34	$14.86	$14.63

Claim Counts	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
Total Claim Count (FFS & Encounter)	1,005,476	1,038,701	962,444	1,072,235	1,006,181	991,736	1,082,530	964,405	1,054,854	1,075,393	1,083,931	996,165	1,027,838
Mental Health Carve-Out Drugs	152,677	157,417	144,513	161,735	152,620	150,671	163,464	145,336	156,705	162,611	163,085	149,906	155,062
FFS Physical Health Drugs	55,350	57,641	52,425	58,552	54,932	53,777	60,219	53,732	58,688	56,928	56,150	48,039	55,536
FFS Physician Administered Drugs	14,803	15,637	14,127	15,134	13,812	14,237	16,043	13,306	14,748	13,860	14,463	13,089	14,438
Encounter Physical Health Drugs	674,584	697,498	648,529	723,919	679,589	668,544	729,075	650,857	712,773	727,086	733,541	675,414	693,451
Encounter Physician Administered Drugs	108,062	110,508	102,850	112,895	105,228	104,507	113,729	101,174	111,940	114,908	116,692	109,717	109,351

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$74.12	$75.56	$71.88	$74.08	$73.59	$71.60	$74.38	$75.20	$75.49	$77.99	$78.47	$77.41	$74.98
Mental Health Carve-Out Drugs	$50.31	$50.33	$49.35	$50.34	$50.14	$49.97	$50.05	$50.75	$50.26	$51.96	$52.25	$51.82	$50.63
FFS Physical Health Drugs	$50.50	$53.23	$47.50	$52.40	$48.37	$49.70	$52.35	$48.96	$48.85	$50.56	$51.90	$55.20	$50.79
FFS Physician Administered Drugs	$100.67	$110.35	$100.46	$120.84	$109.83	$92.79	$118.72	$147.14	$118.83	$103.94	$104.61	$140.49	$114.05
Encounter Physical Health Drugs	$74.57	$76.24	$73.23	$74.81	$73.62	$72.45	$73.40	$74.92	$76.64	$79.05	$79.00	$77.02	$75.41
Encounter Physician Administered Drugs	$113.39	$113.88	$103.55	$108.35	$115.80	$105.75	$120.98	$116.62	$111.77	$118.58	$121.37	$117.02	$113.92

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$19.10	$19.09	$18.80	$18.25	$18.03	$18.08	$18.30	$19.44	$19.57	$18.77	$18.88	$18.77	$18.76
Mental Health Carve-Out Drugs	$20.96	$20.76	$19.38	$19.52	$19.50	$18.47	$18.03	$18.18	$17.49	$17.96	$18.13	$18.16	$18.88
FFS Physical Health Drugs	$16.27	$16.15	$16.16	$16.42	$16.66	$15.89	$16.63	$16.86	$17.47	$17.94	$17.23	$17.91	$16.80
Encounter Physical Health Drugs	$18.81	$18.86	$18.84	$18.05	$17.74	$18.13	$18.50	$19.95	$20.23	$19.02	$19.18	$18.98	$18.86

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$360.23	$361.49	$337.88	$348.15	$356.67	$356.68	$365.87	$405.25	$448.76	$479.60	$486.76	$481.26	$399.05
Mental Health Carve-Out Drugs	$998.87	$993.03	$1,004.13	$1,016.88	$1,013.90	$1,021.50	$1,032.05	$1,041.90	$1,045.63	$1,068.49	$1,062.99	$1,061.59	$1,030.08
FFS Physical Health Drugs	$144.88	$152.10	$132.35	$152.16	$141.49	$149.11	$162.39	$154.06	$163.04	$171.63	$183.93	$204.44	$159.30
Encounter Physical Health Drugs	$362.47	$363.81	$337.68	$345.75	$355.89	$353.78	$362.12	$407.56	$455.61	$486.25	$491.81	$479.53	$400.19

Generic Drug Use Percentage	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
Generic Drug Use Percentage	85.4%	85.0%	84.7%	84.5%	85.2%	85.5%	85.7%	87.1%	88.1%	88.3%	88.5%	88.6%	86.4%
Mental Health Carve-Out Drugs	97.0%	97.0%	97.0%	96.9%	96.9%	96.9%	96.8%	96.8%	96.8%	96.8%	96.7%	96.8%	96.9%
FFS Physical Health Drugs	73.4%	72.7%	73.0%	73.5%	74.6%	74.6%	75.5%	76.6%	78.4%	78.8%	79.2%	80.0%	75.9%
Encounter Physical Health Drugs	83.8%	83.4%	82.9%	82.7%	83.5%	83.8%	84.0%	85.8%	87.0%	87.2%	87.3%	87.4%	84.9%

Preferred Drug Use Percentage	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Avg Monthly
Preferred Drug Use Percentage	86.41%	86.20%	86.07%	85.89%	85.81%	85.81%	85.82%	85.72%	85.72%	85.54%	85.51%	85.43%	85.8%
Mental Health Carve-Out Drugs	74.05%	73.87%	73.89%	73.82%	73.63%	73.67%	74.13%	73.91%	73.65%	73.66%	73.50%	73.22%	73.7%
FFS Physical Health Drugs	95.63%	95.76%	95.85%	95.68%	95.83%	95.79%	95.50%	95.43%	95.52%	95.23%	95.19%	95.24%	95.6%
Encounter Physical Health Drugs	88.44%	88.19%	88.02%	87.83%	87.77%	87.78%	87.66%	87.59%	87.59%	87.47%	87.46%	87.45%	87.8%

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

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2019

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,882,372	16.2%	4,951	$1,188	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,791,177	7.7%	1,468	$1,901	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$1,656,009	4.6%	1,434	$1,155	Y
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,518,746	4.2%	782	$1,942	Y
5	REXULTI	Antipsychotics, 2nd Gen	$1,451,796	4.0%	1,318	$1,102	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	$687,372	1.9%	118	$5,825	Y
7	BUPROPION XL	Antidepressants	$575,114	1.6%	26,346	$22	V
8	TRINTELLIX	Antidepressants	$566,563	1.6%	1,490	$380	V
9	SAPHRIS	Antipsychotics, 2nd Gen	$470,520	1.3%	753	$625	Y
10	VIIBRYD	Antidepressants	$467,184	1.3%	1,643	$284	V
11	FLUOXETINE HCL	Antidepressants	$460,080	1.3%	33,916	$14	Y
12	SERTRALINE HCL	Antidepressants	$454,456	1.3%	45,377	$10	Y
13	DULOXETINE HCL	Antidepressants	$445,168	1.2%	30,848	$14	V
14	TRAZODONE HCL	Antidepressants	$403,750	1.1%	39,631	$10	
15	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$401,535	1.1%	1,825	$220	V
16	ATOMOXETINE HCL*	ADHD Drugs	$391,003	1.1%	5,640	$69	Y
17	ARISTADA	Antipsychotics, Parenteral	$383,872	1.1%	189	$2,031	Y
18	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$348,770	1.0%	2	$174,385	
19	VENLAFAXINE HCL ER	Antidepressants	$343,655	0.9%	1,955	$176	V
20	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$339,651	0.9%	393	$864	Y
21	ESCITALOPRAM OXALATE	Antidepressants	$279,920	0.8%	27,227	$10	Y
22	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$272,151	0.8%	18,841	$14	
23	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$257,039	0.7%	23	$11,176	Y
24	LAMOTRIGINE	Antiepileptics (oral & rectal)	$250,351	0.7%	23,782	$11	Y
25	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$229,033	0.6%	14,816	$15	V
26	BIKTARVY	HIV	$225,371	0.6%	85	$2,651	Y
27	CONCERTA*	ADHD Drugs	$224,616	0.6%	784	$286	N
28	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$224,106	0.6%	2,119	$106	V
29	AMITRIPTYLINE HCL*	Antidepressants	$203,282	0.6%	14,485	$14	Y
30	VENLAFAXINE HCL ER	Antidepressants	$200,685	0.6%	15,124	$13	Y
31	LANTUS SOLOSTAR*	Diabetes, Insulins	$198,215	0.5%	559	$355	Y
32	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$190,412	0.5%	16,320	$12	Y
33	CITALOPRAM HBR	Antidepressants	$185,610	0.5%	20,945	$9	Y
34	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$179,615	0.5%	8	$22,452	Y
35	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$163,821	0.5%	9	$18,202	
36	FETZIMA	Antidepressants	$150,187	0.4%	376	$399	V
37	CHOLBAM*	Bile Therapy	$149,420	0.4%	2	$74,710	
38	LAMICTAL	Antiepileptics (oral & rectal)	$139,988	0.4%	142	$986	Y
39	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$137,665	0.4%	584	$236	V
40	BUPROPION HCL SR	Antidepressants	$134,957	0.4%	9,818	$14	Y
		Top 40 Aggregate:	**$24,035,235**		**366,128**	**$8,097**	
		All FFS Drugs Totals:	**$36,234,353**		**625,833**	**$596**	

*** Drug requires Prior Authorization**

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

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2019

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$348,770	3.3%	2	$174,385	
2	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$257,039	2.4%	23	$11,176	Y
3	BIKTARVY	HIV	$225,371	2.1%	85	$2,651	Y
4	CONCERTA*	ADHD Drugs	$224,616	2.1%	784	$286	N
5	LANTUS SOLOSTAR*	Diabetes, Insulins	$198,215	1.9%	559	$355	Y
6	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$179,615	1.7%	8	$22,452	Y
7	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$163,821	1.5%	9	$18,202	
8	CHOLBAM*	Bile Therapy	$149,420	1.4%	2	$74,710	
9	HYDROXYPROGESTERONE CAPROAT	Progestational Agents	$133,867	1.3%	51	$2,625	N
10	Etonogestrel Implant System	Physican Administered Drug	$130,160	1.2%	215	$605	
11	NOVOLOG FLEXPEN	Diabetes, Insulins	$127,481	1.2%	270	$472	Y
12	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$122,401	1.1%	543	$225	
13	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$115,581	1.1%	2,600	$44	Y
14	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$106,366	1.0%	28	$3,799	Y
15	NUVARING	STC 63 - Oral Contraceptives	$105,315	1.0%	397	$265	
16	Infliximab Not Biosimil 10mg	Physican Administered Drug	$104,094	1.0%	72	$1,446	
17	GENVOYA	HIV	$97,503	0.9%	34	$2,868	Y
18	FLOVENT HFA	Corticosteroids, Inhaled	$96,872	0.9%	558	$174	Y
19	VYVANSE*	ADHD Drugs	$96,845	0.9%	636	$152	Y
20	TRUVADA	HIV	$96,664	0.9%	79	$1,224	Y
21	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$95,642	0.9%	28	$3,416	
22	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$95,452	0.9%	13	$7,342	
23	AFINITOR	Antineoplastics	$93,859	0.9%	6	$15,643	
24	Factor Viii Recomb Novoeight	Physican Administered Drug	$88,572	0.8%	3	$29,524	
25	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$84,889	0.8%	1,613	$53	Y
26	Inj., Rituximab, 10 Mg	Physican Administered Drug	$84,780	0.8%	25	$3,391	
27	Mirena, 52 Mg	Physican Administered Drug	$84,344	0.8%	139	$607	
28	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$77,645	0.7%	289	$269	Y
29	Factor Viii Recombinant Nos	Physican Administered Drug	$77,419	0.7%	5	$15,484	
30	ELIQUIS	Anticoagulants, Oral and SQ	$76,316	0.7%	217	$352	Y
31	LANTUS	Diabetes, Insulins	$75,294	0.7%	257	$293	Y
32	VIMPAT	Antiepileptics (oral & rectal)	$74,356	0.7%	160	$465	Y
33	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$72,233	0.7%	19	$3,802	Y
34	Aflibercept Injection	Physican Administered Drug	$71,334	0.7%	135	$528	
35	SPIRIVA	Anticholinergics, Inhaled	$67,612	0.6%	171	$395	Y
36	Injection, Nivolumab	Physican Administered Drug	$66,768	0.6%	26	$2,568	
37	XIFAXAN*	Rifamycins	$66,477	0.6%	33	$2,014	
38	ENBREL*	Biologics for Autoimmune Conditions	$65,818	0.6%	11	$5,983	Y
39	Inj Pembrolizumab	Physican Administered Drug	$64,745	0.6%	44	$1,471	
40	Inj Trastuzumab Excl Biosimi	Physican Administered Drug	$63,605	0.6%	39	$1,631	
		Top 40 Aggregate:	**$4,627,177**		**10,188**	**$10,334**	
		All FFS Drugs Totals:	**$10,672,438**		**142,953**	**$612**	

*** Drug requires Prior Authorization**

Notes
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- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
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ProDUR Report for October through December 2019

High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	9	3	0	6	0.01%	33.3%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,352	284	1	1,066	1.23%	21.0%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	165	52	0	113	0.14%	31.5%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	70,783	12,519	91	58,165	68.17%	17.7%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	21,929	5,543	6	16,355	21.10%	25.3%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	711	113	0	597	0.67%	15.9%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	833	205	0	628	0.73%	24.6%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	485	152	1	331	0.43%	31.3%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	29	23	0	6	0.02%	79.3%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,460	2,052	0	5,386	7.17%	27.5%
		Totals	**103,756**	**20,946**	**99**	**82,653**	**99.68%**	**20.2%**

ProDUR Report for October through December 2019

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Diazepam	150	43	107	4,524	3.3%	28.7%
ER	Buprenorphine/Naloxone	89	23	66	2,117	4.2%	25.8%
ER	Lorazepam	388	100	288	11,762	3.3%	25.8%
ER	Seroquel (Quetiapine)	3,482	678	2,803	25,584	13.6%	19.5%
ER	Risperdal (Risperidone)	1,705	319	1,386	12,905	13.2%	18.7%
ER	Lamictal (Lamotrigine)	4,430	810	3,620	36,709	12.1%	18.3%
ER	Alprazolam	215	39	176	7,789	2.8%	18.1%
ER	Abilify (Aripiprazole)	2,632	450	2,181	20,957	12.6%	17.1%
ER	Zoloft (Sertraline)	5,390	921	4,469	55,753	9.7%	17.1%
ER	Wellbutrin (Bupropion)	4,363	743	3,619	48,881	8.9%	17.0%
ER	Buspirone (Buspar)	2,271	375	1,896	24,615	9.2%	16.5%
ER	Prozac (Fluoxetine)	3,994	642	3,352	42,645	9.4%	16.1%
ER	Trazodone	4,930	774	4,155	48,264	10.2%	15.7%
ER	Remeron (Mirtazapine)	1,357	210	1,147	11,955	11.4%	15.5%
ER	Lexapro (Escitalopram)	3,185	490	2,695	34,440	9.2%	15.4%
ER	Celexa (Citalopram)	2,070	263	1,807	24,718	8.4%	12.7%

ProDUR Report for October through December 2019

Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence	CC-Other
ER	October	3,496	118	311	941	6	2,018	1	101
ER	November	2,874	141	262	747	1	1,578	1	144
ER	December	2,810	190	250	736	5	1,517	0	112
	Total =	**9,180**	**449**	**823**	**2,424**	**12**	**5,113**	**2**	**357**
	Percentage of total overrides =		**4.9%**	**9.0%**	**26.4%**	**0.1%**	**55.7%**	**0.0%**	**3.9%**

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified	637			
		Unique Patients Identified	891			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	353			
		Total Faxes Successfully Sent	517			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$94,358			
	Lamotrigine ER to IR	Unique Prescribers Identified	363			
		Unique Patients Identified	652			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	130			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$94,002			

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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	88	101	81	102
		Total Faxes Successfully Sent	35	48	30	34
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	29	29	10	10
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	26	12	9
		Prescriptions Unchanged after 3 Months of Fax Sent	50	42	51	7
		Safety Monitoring Profiles Identified	3	2	7	4
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$71,052	$62,021	$21,682	$12,573

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Antipsychotic Use in Children	Total patients identified				1099
		Profiles sent for expert review				67
		Prescribers successfully notified				60
		Patients with change in antipsychotic drug in following 90 days				3
		Patients with continued antipsychotic therapy in the following 90 days				41

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipyschotics for Schizophreniacs	Total patients identified			22	84
		Total prescribers identified			22	82
		Prescribers successfully notified			22	81
		Patients with claims for the same antipsychotic within the next 90 days			6	31
		Patients with claims for a different antipsychotic within the next 90 days				3

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

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	46	77	87	76
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	9	5	16	7
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	85	110	120	134
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5	7	14	16
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed		10		
	High Risk Patients - Asthma	RetroDUR_Profiles Reviewed			12	
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed	19	12	12	38
		RetroDUR_Letters Sent To Providers	5	6	3	1
		Provider Responses	2	1	0	0
		Provider Agreed / Found Info Useful	2	1	0	0
	Lock-In	RetroDUR_Profiles Reviewed	52	5	31	20
		RetroDUR_Letters Sent To Providers	3			1
		Provider Responses	0			0
		Provider Agreed / Found Info Useful	0			0
		Locked In	3	0	0	0
	Polypharmacy	RetroDUR_Profiles Reviewed	16	18	168	55
		RetroDUR_Letters Sent To Providers	5	9	22	13
		Provider Responses	0	0	2	3
		Provider Agreed / Found Info Useful	0	0	2	3

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Combination Opioid-Sedative	Total patients identified				138
		Total prescribers identified				132
		Prescribers successfully notified				132
		Patients with discontinuation of therapy within next 90 days				27
		Patients with new prescription for naloxone within next 90 days				1
		Average number of sedative drugs dispensed within next 90 days				0
		Average number of sedative prescribers writing prescriptions in next 90 days				0
	ICS/LABA	Disqualified	24	20	29	12
		Disqualified - Erroneous denial	23	20	29	12
		Disqualified - No Provider Info	1			
		Faxes Sent	7	9	8	2
		Fax Sent - Combination Inhaler	6	7	5	
		Fax Sent - Controller	1		1	
		Fax Sent - SABA		1	1	1
		No Subsequent Pulmonary Claims		1	1	1

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Pearls and Pitfalls of Clinical Practice Guidelines

Rachel Proteau, PharmD Candidate and Megan Herink, Pharm.D, Drug Use Research & Management, Oregon State University College of Pharmacy

Clinical practice guidelines play an important role in optimizing patient care. They assist with interpretation of research, provide guidance for standard practice, and have the potential to improve patient outcomes. However, guidelines must also be critically evaluated. Commonly encountered limitations of guidelines include recommendations with low level of supporting evidence, potential bias due to conflicts of interest (COIs), and limited generalizability to real-world patients. These limitations must be considered when interpreting and applying guidelines in clinical practice.

Over recent decades, practice has moved increasingly towards evidence-based medicine. The quality of clinical practice guidelines has been a topic of increasing interest since the 1990's.[1] In 2011, the National Academy of Sciences Institute of Medicine (IOM) published a set of standards to promote development of guidelines with stronger, more transparent methodology (Table 1).[2] While these standards offer a useful framework, it is unclear how this has influenced development of recent guidelines. Evidence suggests that specialist society guidelines may be more concerning due to decreased transparency regarding guideline development and COI.[3,4]

The purpose of this newsletter is to review the level of evidence (LOE) supporting current cardiovascular (CV) guidelines, explore the potential effects of COI, and provide tips for primary care clinicians to critically assess guidelines and their application to individual patients.

Table 1: Summary of IOM Standards for Developing Trustworthy Guidelines[2]

• Standardize guideline development methodology	• Establish evidence-based systems for rating strength of recommendations
• Establish transparency and strategies for management of COI	• Articulate recommendations to reflect the supporting LOE and need for action
• Consider COI when establishing guideline development groups	• Seek external review of proposed guidelines by relevant stakeholders
• Maintain an ongoing interactive relationship between systematic review teams and guideline developers	• Monitor literature and update guidelines when new evidence suggests need for clinically important modification

Abbreviations: COI: conflict of interest; LOE: level of evidence

Level of Evidence Supporting Major Cardiovascular Recommendations

In March of 2019, a review published in the Journal of the American Medical Association *(JAMA*) examined the LOE supporting 51 current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines.[5] The primary outcome was the percentage of recommendations supported by evidence graded as LOE A (i.e. multiple randomized controlled trials [RCTs] or a single large RCT). Among the 26 ACC/AHA guidelines examined, only 8.5% of recommendations had LOE A support. Fifty percent of recommendations were graded LOE B (observational studies or a single smaller RCT), and 41.5% were based on expert opinion alone (LOE C). An analysis of CV guidelines from the ESC was similar, with slightly more of the recommendations coming from LOE A (15%).

Publication of the 2011 IOM evidence standards has not changed the quality of evidence in the ACC/AHA guidelines. Comparing current guidelines to previous versions in 2009, the number of LOE A recommendations did not significantly differ (9% vs. 11.7%, respectively). However, the proportion of LOE B recommendations increased, corresponding to a decrease in LOE C support.[6] A dearth of high quality evidence to inform guideline recommendations is evident in other fields as well, including infectious disease, liver, and cancer.[7-9]

An additional classification of recommendations (Class I-III) conveys both level of consensus and benefit versus harm. ACC/AHA defines a Class I recommendation as a strong recommendation that the medication or therapeutic test is indicated and should be performed or administered, as the benefit greatly outweighs the risk. Yet among Class I recommendations in the examined ACC/AHA guidelines, only 14.2% were supported by LOE A, and 37% were based on expert opinion alone (LOE C).[5] Making these recommendations based solely on expert opinion without real data remains controversial. These recommendations are more subject to bias and more likely to be reversed. An example of this comes from past CV guideline recommendations regarding perioperative beta blockers.[10] In the late 1990's, two small trials were published that suggested pre-operative initiation of beta-blockers could reduce post-operative cardiac complications.[10] These results were quickly adopted into recommendations in the ACC/AHA guidelines. However, larger trials were unable to replicate these benefits and ultimately the recommendations were reversed.

Conflict of Interest in Clinical Guidelines

A COI is a set of conditions in which professional judgement concerning a primary interest may be unduly influenced by a secondary interest. This may be intellectual or financial. Commercial COI seems to have the most potential to influence guideline recommendations and introduce bias.[11] COIs within guidelines may arise from any level of industry involvement, such as contributions to organizations authoring guidelines, and/or significant funding of pivotal trials. It is important to consider COI during guideline development, as bias in clinical practice guidelines can have a widespread negative effect on patient care.

COIs are common among guideline authors and vary significantly.[11-13] A study concluded that 56% of individuals involved in the ACC/AHA guidelines reported a COI.[14] This is problematic since it is known that a substantial number of ACC/AHA guideline recommendations are based on expert opinion. COIs appear to be particularly prevalent in guidelines considering expensive specialty medications.[15]

Ideally, authors of clinical guidelines would not have any COIs. Since that is a difficult standard to meet, IOM standards include strategies for managing COIs. These include, at a minimum, full disclosure of COIs for all potential members of the guideline development group.[2] Additional strategies include: excluding members with COIs from leadership roles (chair, vice-chair), limiting the proportion of members with any commercial COI to less than 50%, and fully excluding members with COI from panel participation and/or limiting their participation to very few, specific recommendations. Lastly, industry sponsors should not be involved in guideline development.

A recent evaluation of the ACC/AHA cholesterol management guidelines and a hepatitis C guideline found that neither guideline fully met the IOM standards for COI management.[11] Three-fourths (72%) of the hepatitis C virus guideline committee members and two-thirds of the co-chairs disclosed commercial COIs.[11] Although the ACC/AHA cholesterol guideline performed better, there remained discordance between COIs reported by authors during guideline publication and those disclosed by the same authors in other articles published around the same time.

Generalizability of Guidelines to Real World Patients

Guidelines are often viewed with a one-size-fits-all approach, but the translation of guideline recommendations to the care of an individual patient is complex. Clinical trial populations are more likely to include "ideal patients" – often younger, healthier, and more adherent than the average primary care patient. A 2014 review of 22 National Institute for Health and Care Excellence (NICE) primary care guidelines found that only 38% of the recommendations cited research derived from a primary care or community-based population.[16] In the real world, patients have co-morbidities and other factors (social, cultural, financial, etc.) that influence care decisions. These situations are under-represented or ignored in practice guidelines.

Table 2: Tips for Applying Guidelines to Clinical Practice

- Look for the level of evidence supporting guideline recommendations
  - RCTs and meta-analyses provide the highest LOE
  - Observational studies can be helpful when RCTs are not available, however recommendations based on observational data are not as reliable
  - Expert opinion is the lowest LOE. In the absence of any data these statements can provide helpful perspective, but should not be treated as evidence-based medicine
- Consider, "Are these recommendations appropriate to my patient?"
  - Do the guidelines offer any information on age, comorbidities, or contraindications that make the recommendations less applicable?
  - What modifications to guideline care are necessary for each individual patient?
- Look for a clear COI policy and try to determine if there are significant COIs, particularly when recommendations support the use of high-cost or specialty medications
  - All COIs should be disclosed. Committee chairs and co-chairs should not have any commercial COIs
  - Only a minority of committee members (<50%) should have a commercial COI.
  - If COIs are present, consider that bias may be present and critically evaluate the evidence behind the guideline recommendations

Conclusions

Clinical practice guidelines provide a needed resource to approach complex medical decision-making, enhance healthcare quality and safety, and accelerate the translation of research into clinical practice. Progress has been made since the IOM released standards for guideline methodology and transparency. Many organizations have since moved towards increased COI transparency and improvement in policies and procedures to manage COIs.[5,16]

Nevertheless, guideline reliability varies, and many suffer from significant methodological flaws, limitations in scientific evidence, and presence of COIs, making the recommendations difficult to apply to clinical practice. Tools are available to help guideline users assess the quality of guidelines, including the AGREE instrument (https://www.agreetrust.org/). However, these tools can be too time intensive to incorporate into a busy clinical practice. General awareness of fatal flaws in clinical practice guidelines and application of simple tips (Table 2) when reading guidelines can help clinicians quickly assess and apply guidelines more appropriately.

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Update on Recent Guidance and Safety Alerts for Opioid Use in Non-cancer Pain

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Introduction

In 2016, the Centers for Disease Control (CDC) released guidelines for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, or end-of-life care.[1] The goal of these guidelines was to promote patient care and safety in light of the rapidly increasing amount of reported opioid overdoses in the previous decade.[2] Multiple guidelines emphasized opioid dosage ceilings, avoiding concomitant benzodiazepines, limiting durations for acute pain, and treating opioid use disorder.[2-4] In addition to these guidelines, the Food and Drug Administration (FDA) has published safety alerts regarding the risks of abrupt discontinuation and rapid tapering of opioids in opioid dependent patients.[5] This newsletter will summarize recent guideline updates and FDA safety alerts.

Guideline Recommendations

With the publication of the 2016 CDC guidelines, multiple national and statewide organizations followed suit, including the American Society of Interventional Pain Physicians (ASIPP), the Department of Veterans Affairs (VA) and the Department of Defense (DoD). Guideline recommendations for chronic pain are outlined in **Table 1**. If opioids are prescribed for acute pain, they should be initiated at the lowest effective dose and patients should be re-evaluated after 3-5 days to assess appropriateness of continuing therapy.[4]

Table 1. Opioid Guideline Prescribing Recommendations

Recommendations	Monitoring
VA/DoD Guideline[4]	
● Use of non-opioid therapy preferred over opioids for chronic pain management ● If opioid is used, use lowest dose and shortest treatment duration ● Avoid concurrent use of benzodiazepines and opioids.	● Evaluate continuation of opioids every 3 months ● Taper opioids to lowest effective dose or discontinue when medication risks exceed benefit
ASIPP Guideline[3]	
● Establish appropriate physical and psychological diagnosis ● Stratify patients substance abuse risk (high/medium/low) prior to initiating opioid ● Initiate opioid therapy with low dose, short-acting drugs ● Reserve long-acting therapy for severe intractable pain not relieved by short-acting opioids	● Monitor for adherence and abuse by urine drug testing ● Assess improvement based upon analgesia relief and patient activity ● Periodically reassess for pain relief and/or functional status improvement of > 30% without adverse consequences

All opioid prescribing guidelines recommend close monitoring and tapering whenever possible. Tapering opioids to the lowest effective dose or discontinuation of therapy is recommended when patient risks exceed benefits. However, careful and slow tapering is essential in patients who are opioid tolerant and/or physically dependent on opioids. Recently, the US department of Health and Human Services published recommendations for dose reduction or discontinuation of long-term opioid analgesics. This document provides guidance for deciding when to taper, how to individualize the taper, how to treat symptoms of withdrawal, how to provide behavioral support, and guidance for tapering in special populations.[6] Emphasis is placed on the avoidance of tapering opioids when the benefits outweighs the risk and advising patients on the risk of overdose when there is a rapid return to a previously prescribed dose.[6]

Oregon Health Authority Task Force Guidelines

Chronic Pain

The Oregon Health Authority (OHA) recruited a task force of Oregon-based practitioners in 2016 to develop guidelines for prescribing opioids for acute and chronic pain, for both medical providers and dentists. The guidelines adopted the CDC Guidelines as the foundation for the recommendations while also addressing Oregon-specific concerns.[7] For management of chronic pain, the task force recommends documentation of clinical justification for doses higher than 50 mg of morphine milligram equivalence (MME) per day and to avoid doses greater than 90 MME.[7] The guideline also recommends a documented referral for pain management. This can include evaluation by a colleague, discussion with a peer group or multi-disciplinary pain consult team, or referral to a pain and/or addiction mental health specialist.[7] Providers are also encouraged to use the prescription drug monitoring program (PDMP) to assess for opioid misuse and abuse. If misuse or abuse is identified, the importance of engaging in a discussion with the patient about potential taper plans rather than patient dismissal is emphasized. If substance use disorder is a concern, treatment options and potential referral to a specialist should be explored.[7]

The recommendations strongly advise against co-prescribing opioids and central nervous system (CNS) depressants. Examples of CNS depressants are benzodiazepines, first and second generation antipsychotics, sedatives, and muscle relaxants.[7] If they are both prescribed, a pain specialist and/or pharmacist should be part of the care team. When misuse, abuse, or co-prescribing are of concern, it is recommended to use clinical tools, such as the PDMP and urine drug screens at least annually. The legalization of recreational marijuana in the state of Oregon and the limited available data for the interaction of marijuana with opioids is also of concern.

Clinicians should prioritize patient safety when patients use cannabinoids and opioids concurrently.[7]

Acute Pain

The goal of the acute pain prescribing recommendations is to improve patient safety while emphasizing effective and compassionate treatment in patients who have had limited exposure to opioids.[8] In general, opioids should NOT be considered as first-line therapy for mild to moderate pain. Mild to moderate pain can often be treated without opioids by recommending over-the-counter medications, and physical treatments such as ice and immobilization. **Table 2** outlines recommended over the counter (OTC) pain medications. If non-opioid interventions are ineffective, the lowest effective dose of short-acting opioids should be prescribed for less than 3 days. In cases of more severe acute pain, the initial prescription should be limited to less than 7 days.[8]

Table 2: Over-the-counter Pain Medication Options[9-11]

Medication	Dosing
Acetaminophen	650-1000 mg every 4-6 hours as needed Max 3000 mg per day[9]
Ibuprofen	200-400 mg every 6 hours as needed Max 1200 mg per day[10]
Naproxen	220 mg every 8-12 hours as needed Max 1200 mg per day[11]

Opioid Tapering

Beginning in March 2019, the OHA convened an expert panel to address guidelines for tapering opioids. This guidance should be publically available in late 2019.

FDA Safety Alerts:

In April of this year, the FDA released a safety statement identifying harm from abrupt discontinuation and/or rapid tapering of opioids in patients who are opioid dependent.[5] The FDA received reports of rapid opioid discontinuations leading to serious withdrawal symptoms, psychological distress, and suicide.[5] When patients are tapered off opioids due to a suspicion for substance use disorder, they should have medication assisted therapy (MAT) available. Additionally, a CDC advisory warned that applying the 2016 opioid guidelines to patients with chronic pain associated with cancer or sickle cell anemia increases the risk for harm.[2]

Federal Legislation

In response to the FDA recommendation to avoid the use of opioids with benzodiazepines and other CNS depressants, the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act was signed into federal law in October of 2018.[12] This law requires state Medicaid programs to develop a safety review process to monitor opioid doses prescribed in excess of state defined limits (90 MME per day in Oregon) and monitor concurrent use of opioids with benzodiazepines or antipsychotics. Although the evidence is limited to describe the risks of combining antidepressants and antipsychotics with opioids, it is required that Medicaid agencies monitor these combinations and they should be started at the lowest effective dose if they must be combined. Antidepressants and antipsychotics are frequently involved in opioid overdose. However, underlying mental health conditions increase the risk for opioid and other substance abuse. Evidence related to drug overdoses, highlights that opioid analgesics play a predominant role in pharmaceutical overdose deaths, alone or combined with other therapies.[13]

Oregon Policy Updates

In response to OHA opioid prescribing guidelines, the fee-for-service prior authorization criteria for long-acting opioids has been updated to include new indications and safety considerations. Important policy updates are highlighted below.

OHA Opioid PA Policy Updates

- Approve use of opioids for chronic pain associated with sickle cell disease
- Patient education requirement if opioid is to be used concurrently with a benzodiazepine or CNS depressant
- Restrict use of tramadol or codeine in patients less than 19 years of age based on FDA safety data

Conclusion

CDC guidelines regarding opioid prescribing set a precedent in 2016 to promote care and safety in response to rising opioid abuse and overdoses. Strict enforcement of these guidelines resulted in harm for some patients leading to FDA safety communications to help guide providers to safely manage opioid prescribing. These FDA alerts were accompanied by guideline updates from other major organizations including VA/DoD and OHA task forces. While there are slight differences between the reports from each organization, the overall message of providing safe yet effective pain management is clear. In general, opioids should be reserved for moderate-to-severe pain and in short-term situations whenever possible. It is also important to consider concurrent CNS depressants, especially benzodiazepines, when initiating opioids. Taper schedules should be developed on an individualized basis and should be done slowly for most patients. Overall, the recent changes to guidelines and FDA safety announcements emphasize safe and effective use of opioid medications for only essential indications.

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Policy Proposal: Orphan Drugs

Policy Proposal:

In the past several years, approval of orphan drugs by the Food and Drug Administration (FDA) has become more frequent. Orphan drugs are defined by the FDA as drugs and biologics intended for the safe and effective treatment, diagnosis or prevention of rare diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people but are not expected to recover the costs of developing and marketing a treatment.[1] Over the past 3 years, the fee-for-service (FFS) Pharmacy and Therapeutics (P&T) committee has reviewed 40 drugs with orphan drug status. However, due to the rare incidence of these conditions, there are few FFS patients prescribed these medications and estimated savings as a result of these policies is limited. The majority of requests for these orphan drugs meet currently developed prior authorization (PA) criteria. Recommendation of a more comprehensive policy for orphan drugs may improve bandwidth for topics at P&T meetings and support medically appropriate use of these therapies based on information in the FDA label. Table 1 in the prior authorization criteria could be updated at subsequent P&T meetings to incorporate newly approved orphan drugs as necessary.

Recommendation:

- Implement PA to support medically appropriate use of orphan drugs based on FDA labeling.

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1. Office of Orphan Products Development. Food and Drug Administration. Available at: https://www.fda.gov/about-fda/office-clinical-policy-and-programs/office-orphan-products-development. Updated November 18, 2019. Accessed January 7, 2020.

Orphan Drugs

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

Length of Authorization:
Up to 6 months

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

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

Table 1. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**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. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	**Yes:** Approve for up to 6 months Document benefit	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	**Yes**: Approve for up to 6 months Document benefit and provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

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Drug Class Literature Scan: Opioids

Date of Review: February 2020

Date of Last Review: September 2019
Literature Search: 04/01/19 – 01/03/20

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

Purpose for Review:
To review current best practice standards for appropriate dosage reduction or discontinuation of chronic opioid therapy. New guidance from United States Department of Health and Human Services (HHS) has been published on appropriate dosage reduction of long-term opioid analgesics and the Oregon Opioid Tapering Task Force has voted to approve clinical guidelines on opioid tapering.

Conclusions:
- One systematic review[1] and one new comparative randomized controlled trial (RCT)[2] was identified. Current evidence supports quantity and dose limits for acute conditions.
- Two new guidelines from HHS and draft guidance from the Oregon Opioid Tapering Task force were available for review.[3,4] Guidelines review best practice standards for opioid tapers in patients with chronic use and include recommendations for an individualized, patient-centered approach for initiation of opioid tapers for patients where risks of opioid use outweigh benefits.

Recommendations:
- Update PA criteria for short- and long-acting opioids to better address patients already established on long-term opioids (**Appendix 6**). The goal of these changes is to prevent harm from abrupt discontinuation of opioids and reinforce a shared patient and provider decision for appropriate dosage reduction.

Summary of Prior Reviews and Current Policy
- Current evidence supports modest improvements in pain and function with use of opioids for acute pain or chronic non-cancer pain compared to placebo (high quality evidence). Compared to other analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or nortriptyline, there is no difference in pain or functional status compared to opioids for chronic non-cancer pain (low to moderate quality evidence). Overall, evidence is limited by short follow-up and exclusion of patients at high risk for adverse events. Current high quality guidelines recommend opioid therapy be reserved for patients who with proven medical necessity and those who have failed non-opioid analgesic therapy. Chronic opioid therapy should only be considered with documented improvement in pain and function, thorough assessment of risks and benefits of therapy, and with appropriate ongoing monitoring.
- Currently FFS prior authorization (PA) criteria limits all short-acting opioid prescriptions to 7 days and no more than 90 milligram morphine equivalents (MME) per day. Quantity limits allow up to 2 prescriptions every 90 days without a PA. All prescriptions for long-acting opioids require a PA. Prior to implementation

of this policy, patients already prescribed opioids for chronic use were grandfathered at their current dose to avoid interruptions in care for patients already established on long-term therapy. For authorization of chronic therapy, providers are required to document sustained improvement from treatment, review the PDMP to verify appropriate prescribing, conduct a recent urine drug screen to assess for illicit drugs, and assess risk of concurrent central nervous system depressants.

- In May 2019, HERC guidelines were updated to remove required taper plans for patients using chronic short-acting opioids for back and spine conditions. Language was revised to state: "For patients receiving long-term opioid therapy (>90 days) for conditions of the back and spine, continued coverage of opioid medications requires an individual treatment plan which includes a taper plan *when clinically indicated*." Subsequently, HHS has released guidance for clinicians on appropriate dosage reduction and new guidance has been approved by the Oregon Opioid Tapering Task Force. Recommendations from these organizations are reviewed below.

Methods:

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

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

New Systematic Reviews:

A Cochrane systematic review evaluated efficacy and safety of tramadol for treatment of osteoarthritis.[1] This summary will focus on the available direct comparative evidence. Only 11 trials were included which compared tramadol to other active treatments.[1] Tramadol doses ranged from 37.5 to 400 mg per day and trials had a mean duration of 2 months.[1] Overall, evidence was limited by unclear risk for selective reporting, allocation concealment and blinding of providers.[1] About half of the included studies had high risk of reporting bias based on incomplete outcome data.[1] There was insufficient evidence to compare efficacy or safety of tramadol to acetaminophen.[1] There was moderate quality evidence that tramadol was slightly less effective than NSAIDs at pain reduction (standardized mean difference [SMD] 0.21, 95% confidence interval [CI] 0.07 to 0.36) and no different compared to other opioids (SMD –0.11, 95% CI –0.33 to 0.12).[1] Upon analysis of tramadol/acetaminophen compared to NSAIDs or opioids, there was no statistical difference in pain reduction. Differences in physical functioning compared to NSAIDs or other opioids were small. Tramadol therapy resulted in slightly worse physical functioning compared to NSAIDs (average worsening of 5 points [95% CI 2 to 8] on a 0 to 100 scale) and slightly better functioning compared to other opioids (67% vs. 51% of patients who defined their treatment as good or better; number needed to treat [NNT] of 7).[1] There was low quality evidence that participants treated with tramadol had a greater risk of withdrawing due to adverse events compared to NSAIDs (21% vs. 11%; relative risk [RR] 1.88, 95% CI 1.27 to 2.76) or other opioids (31% vs. 14%; RR 2.26, 95% CI 1.52 to 3.37).[1]

After review, 8 systematic reviews were excluded due to poor quality,[5] wrong study design of included trials (e.g., observational),[6-8] setting (e.g., inpatient),[9] comparator (e.g., no control or placebo-controlled),[10-13] or outcome studied (e.g., non-clinical).[14]

New Guidelines:
High Quality Guidelines: No new high quality guidelines were identified.

Additional Guidelines for Clinical Context:
HHS Guidelines for appropriate dosage reduction or discontinuation of long-term opioid analgesics were published in October 2019.[3] Methods for the development of this guideline were unavailable and the quality of recommendations could not be assessed. These guidelines emphasize the importance of care coordination and individualized patient care during initiation of an opioid taper plan in order to avoid risks associated with rapid discontinuation.[3] Risks of abrupt or rapid tapers can include withdrawal symptoms, worsening pain, psychological stress/suicidality, seeking opioids from high-risk sources, and loss of patient trust.[3] Required tapering should be avoided, particularly when benefits of opioid therapy continue to outweigh risks. Instead, the decision to taper opioids should be based on a shared decision between the patient and provider.[3] Use of shared decision making when developing tapers helps to establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations.[3]

HHS guidelines recommend tapering to a reduced dose or discontinuation of opioid therapy be *considered* in the following circumstances:[3]

- When pain improves
- When pain and function are not meaningfully improved
- Upon receipt of higher doses without documented benefit from higher dose
- When there is evidence of opioid misuse
- With significant adverse effects which affect quality of life or function
- When the patient experiences an overdose or with warning signs for overdose of confusion, sedation or slurred speech
- With co-prescribing of sedating medications or comorbid conditions that increase risk for adverse events
- With long-term prescribing and current risk-benefit assessment is unclear

A variety of tools and methods are recommended to support dosage reduction and include the following:

- Dosage reduction should be individualized based on patient history and goals.[3]
    - Commonly, a dose reduction of 5% to 20% per month is used in practice.
    - Use of slower tapers which may be better tolerated especially in patients with a history of long-term opioid use.
    - Faster tapers may be considered if safety concerns associated with opioid use are identified or with shorter-term use (weeks to months rather than years).
    - Development of flexible taper plans with routine evaluation and options to pause tapering may increase changes of success and decrease patient symptoms.
- Use of supporting therapy and a multidisciplinary treatment approach may improve patient outcomes.[3]
    - Integrate non-pharmacological and non-opioid pharmacological treatments into the therapy plan.
    - Provide behavioral health support and address and treat comorbid mental health conditions.

- Referral to a specialist is recommended if an imminent patient safety concern is identified or for unique populations such as patients with comorbid severe mental illness, other substance use disorders, or pregnancy.
- If there is evidence of misuse guidelines recommend assessment for opioid use disorder with evidence-based medication-assisted treatment when clinically indicated. Consider transition to buprenorphine for patients who are unsuccessful with even slow tapers.
- Manage symptoms of opioid withdrawal by slowing or pausing the taper and adding appropriate symptomatic treatment when indicated
- Reassess plan and symptoms at least quarterly for all patients. Close monitoring is recommended in patients who are unable or unwilling to taper and continue to be prescribed a high-risk regimen.

The Oregon Opioid Tapering Guidelines were approved by the Oregon Opioid Tapering Task Force in October 2019.[4] The methodology for the guideline development was unavailable. A draft of the Oregon guideline was available for review and includes many of the same best practices as outlined in the national HHS recommendations for opioid dose reduction. The goal of these guidelines is to reduce harms associated with opioid use and promote patient-centered care. Recommendations focus on individualized, shared decision making between patients and their provider regarding opioid tapers. Recommendations for health systems include support for a team-based, integrated approach to opioid tapering while ensuring access to multidisciplinary supports, non-opioid pharmacotherapy, and non-pharmacologic treatments.

After review, 1 guideline was excluded due to poor quality.[15]

New Formulations:
No new formulations were identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Month / Year of Change	Labeling Addition or Change	Addition or Change and Mitigation Principles (if applicable)
All opioid formulations[16]	10/2019	Warnings/Precautions	Modifications to label to emphasize the risk for life-threatening respiratory depression in patients with sleep-related breathing disorders including sleep apnea and sleep-related hypoxemia. Additional warnings added for withdrawal symptoms associated with abrupt discontinuation. Gradual taper is recommended to minimize withdrawal syndrome.

References:

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15. Bennett MI, Eisenberg E, Ahmedzai SH, et al. Standards for the management of cancer-related pain across Europe-A position paper from the EFIC Task Force on Cancer Pain. *European journal of pain (London, England).* 2019;23(4):660-668.
16. Food and Drug Administration. Drug Safety-related Labeling Changes (SrLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed January 3, 2020.

Appendix 1: Current Preferred Drug List

Long-Acting Opioids

Generic	Brand	Form	Route	PDL
fentanyl	DURAGESIC	PATCH TD72	TRANSDERM	Y
fentanyl	FENTANYL	PATCH TD72	TRANSDERM	Y
morphine sulfate	MORPHINE SULFATE ER	TABLET ER	ORAL	Y
morphine sulfate	MS CONTIN	TABLET ER	ORAL	Y
buprenorphine	BUPRENORPHINE	PATCH TDWK	TRANSDERM	N
buprenorphine	BUTRANS	PATCH TDWK	TRANSDERM	N
buprenorphine HCl	BELBUCA	FILM	BUCCAL	N
fentanyl	FENTANYL	PATCH TD72	TRANSDERM	N
hydrocodone bitartrate	ZOHYDRO ER	CAP ER 12H	ORAL	N
hydrocodone bitartrate	HYSINGLA ER	TAB ER 24H	ORAL	N
hydromorphone HCl	EXALGO	TAB ER 24H	ORAL	N
hydromorphone HCl	HYDROMORPHONE ER	TAB ER 24H	ORAL	N
levorphanol tartrate	LEVORPHANOL TARTRATE	TABLET	ORAL	N
methadone HCl	METHADONE HCL	ORAL CONC	ORAL	N
methadone HCl	METHADONE INTENSOL	ORAL CONC	ORAL	N
methadone HCl	METHADOSE	ORAL CONC	ORAL	N
methadone HCl	METHADONE HCL	SOLUTION	ORAL	N
methadone HCl	DOLOPHINE HCL	TABLET	ORAL	N
methadone HCl	METHADONE HCL	TABLET	ORAL	N
methadone HCl	METHADONE HCL	TABLET SOL	ORAL	N
methadone HCl	METHADOSE	TABLET SOL	ORAL	N
morphine sulfate	KADIAN	CAP ER PEL	ORAL	N
morphine sulfate	MORPHINE SULFATE ER	CAP ER PEL	ORAL	N
morphine sulfate	MORPHINE SULFATE ER	CPMP 24HR	ORAL	N
morphine sulfate	MORPHABOND ER	TAB ER 12H	ORAL	N
morphine sulfate/naltrexone	EMBEDA	CAP ER PO	ORAL	N
oxycodone HCl	OXYCODONE HCL ER	TAB ER 12H	ORAL	N
oxycodone HCl	OXYCONTIN	TAB ER 12H	ORAL	N
oxycodone myristate	XTAMPZA ER	CAP SPR 12	ORAL	N
oxymorphone HCl	OPANA ER	TAB ER 12H	ORAL	N
oxymorphone HCl	OXYMORPHONE HCL ER	TAB ER 12H	ORAL	N
tapentadol HCl	NUCYNTA ER	TAB ER 12H	ORAL	N
tramadol HCl	CONZIP	CPBP 17-83	ORAL	N
tramadol HCl	TRAMADOL HCL ER	CPBP 17-83	ORAL	N
tramadol HCl	CONZIP	CPBP 25-75	ORAL	N

tramadol HCl	TRAMADOL HCL ER	CPBP 25-75	ORAL	N
tramadol HCl	TRAMADOL HCL ER	TAB ER 24H	ORAL	N
tramadol HCl	TRAMADOL HCL ER	TBMP 24HR	ORAL	N

Short-Acting Opioids

Generic	Brand	Form	Route	PDL
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	ELIXIR	ORAL	Y
acetaminophen with codeine	CAPITAL W-CODEINE	ORAL SUSP	ORAL	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	SOLUTION	ORAL	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	TABLET	ORAL	Y
acetaminophen with codeine	TYLENOL-CODEINE NO.3	TABLET	ORAL	Y
acetaminophen with codeine	TYLENOL-CODEINE NO.4	TABLET	ORAL	Y
butorphanol tartrate	BUTORPHANOL TARTRATE	SPRAY	ORAL	Y
codeine sulfate	CODEINE SULFATE	TABLET	ORAL	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	SOLUTION	ORAL	Y
hydrocodone/acetaminophen	LORTAB	SOLUTION	ORAL	Y
hydrocodone/acetaminophen	HYDROCODONE/ACETAMINOPHEN	TABLET	ORAL	Y
hydrocodone/acetaminophen	LORCET	TABLET	ORAL	Y
hydrocodone/acetaminophen	LORCET HD	TABLET	ORAL	Y
hydrocodone/acetaminophen	LORCET PLUS	TABLET	ORAL	Y
hydrocodone/acetaminophen	NORCO	TABLET	ORAL	Y
hydromorphone HCl	HYDROMORPHONE HCL	SUPP.RECT	RECTAL	Y
hydromorphone HCl	DILAUDID	TABLET	ORAL	Y
hydromorphone HCl	HYDROMORPHONE HCL	TABLET	ORAL	Y
morphine sulfate	MORPHINE SULFATE	SOLUTION	ORAL	Y
morphine sulfate	MORPHINE SULFATE	SUPP.RECT	RECTAL	Y
morphine sulfate	MORPHINE SULFATE	TABLET	ORAL	Y
opium/belladonna alkaloids	BELLADONNA & OPIUM	SUPP.RECT	RECTAL	Y
opium/belladonna alkaloids	BELLADONNA-OPIUM	SUPP.RECT	RECTAL	Y
oxycodone HCl	OXYCODONE HCL	SOLUTION	ORAL	Y
oxycodone HCl	OXYCODONE HCL	TABLET	ORAL	Y
oxycodone HCl	ROXICODONE	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	OXYCODONE W/ACETAMINOPHEN	CAPSULE	ORAL	Y
oxycodone HCl/acetaminophen	ENDOCET	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	NALOCET	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	OXYCODONE-ACETAMINOPHEN	TABLET	ORAL	Y
oxycodone HCl/acetaminophen	PERCOCET	TABLET	ORAL	Y
tramadol HCl	TRAMADOL HCL	TABLET	ORAL	Y

tramadol HCl	ULTRAM	TABLET	ORAL	Y
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	CAPSULE	ORAL	N
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	TABLET	ORAL	N
acetaminophen/caff/dihydrocod	DVORAH	TABLET	ORAL	N
acetaminophen/caff/dihydrocod	PANLOR	TABLET	ORAL	N
butalbit/acetamin/caff/codeine	BUTALB-ACETAMINOPH-CAFF-CODEIN	CAPSULE	ORAL	N
butalbit/acetamin/caff/codeine	BUTALB-CAFF-ACETAMINOPH-CODEIN	CAPSULE	ORAL	N
butalbit/acetamin/caff/codeine	FIORICET WITH CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	ASA-BUTALB-CAFFEINE-CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	ASCOMP WITH CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	BUTALBITAL COMPOUND-CODEINE	CAPSULE	ORAL	N
codeine/butalbital/ASA/caffein	FIORINAL WITH CODEINE #3	CAPSULE	ORAL	N
fentanyl	SUBSYS	SPRAY	SUBLINGUAL	N
fentanyl citrate	ACTIQ	LOZENGE HD	BUCCAL	N
fentanyl citrate	FENTANYL CITRATE	LOZENGE HD	BUCCAL	N
fentanyl citrate	LAZANDA	SPRAY/PUMP	NASAL	N
fentanyl citrate	ABSTRAL	TAB SUBL	SUBLINGUAL	N
fentanyl citrate	FENTORA	TABLET EFF	BUCCAL	N
hydrocodone/acetaminophen	HYDROCODONE W/ACETAMINOPHEN	ELIXIR	ORAL	N
hydrocodone/acetaminophen	ZAMICET	SOLUTION	ORAL	N
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	TABLET	ORAL	N
hydrocodone/acetaminophen	VERDROCET	TABLET	ORAL	N
hydrocodone/acetaminophen	VICODIN	TABLET	ORAL	N
hydrocodone/acetaminophen	VICODIN ES	TABLET	ORAL	N
hydrocodone/acetaminophen	VICODIN HP	TABLET	ORAL	N
hydrocodone/ibuprofen	HYDROCODONE-IBUPROFEN	TABLET	ORAL	N
hydrocodone/ibuprofen	IBUDONE	TABLET	ORAL	N
hydrocodone/ibuprofen	REPREXAIN	TABLET	ORAL	N
hydrocodone/ibuprofen	XYLON 10	TABLET	ORAL	N
hydromorphone HCl	DILAUDID	LIQUID	ORAL	N
hydromorphone HCl	HYDROMORPHONE HCL	LIQUID	ORAL	N
ibuprofen/oxycodone HCl	OXYCODONE HCL-IBUPROFEN	TABLET	ORAL	N
meperidine HCl	MEPERIDINE HCL	SOLUTION	ORAL	N
meperidine HCl	DEMEROL	TABLET	ORAL	N
meperidine HCl	MEPERIDINE HCL	TABLET	ORAL	N
morphine sulfate	MORPHINE SULFATE	SYRINGE	ORAL	N
morphine sulfate	ARYMO ER	TAB PO ER	ORAL	N
oxycodone HCl	OXYCODONE HCL	CAPSULE	ORAL	N
oxycodone HCl	OXYCODONE HCL	ORAL CONC	ORAL	N
oxycodone HCl	OXYCODONE HCL	SYRINGE	ORAL	N

oxycodone HCl	OXAYDO	TABLET ORL	ORAL	N
oxycodone HCl	ROXYBOND	TABLET ORL	ORAL	N
oxycodone HCl/acetaminophen	OXYCODONE-ACETAMINOPHEN	TABLET	ORAL	N
oxycodone HCl/acetaminophen	PRIMLEV	TABLET	ORAL	N
oxycodone HCl/acetaminophen	ROXICET	TABLET	ORAL	N
oxycodone HCl/aspirin	OXYCODONE HCL-ASPIRIN	TABLET	ORAL	N
oxymorphone HCl	NUMORPHAN	SUPP.RECT	RECTAL	N
oxymorphone HCl	OPANA	TABLET	ORAL	N
oxymorphone HCl	OXYMORPHONE HCL	TABLET	ORAL	N
pentazocine HCl/naloxone HCl	PENTAZOCINE-NALOXONE HCL	TABLET	ORAL	N
propoxyphene nap/acetaminophen	PROPOXYPHENE NAPSYLATE W/APAP	TABLET	ORAL	N
tapentadol HCl	NUCYNTA	TABLET	ORAL	N
tramadol HCl/acetaminophen	TRAMADOL HCL-ACETAMINOPHEN	TABLET	ORAL	N
tramadol HCl/acetaminophen	ULTRACET	TABLET	ORAL	N
aspirin/codeine phosphate	ASPIRIN W/CODEINE	TABLET	ORAL	

Appendix 2: New Comparative Clinical Trials

A total of 204 citations were manually reviewed from the initial literature search. After further review, all except one trial was excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). This trial is summarized in the table below and the full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome(s)	Results
Yousef, et al.[2] DB, AC, RCT N=100 Duration: 30 days	1. Fentanyl 200 µg sublingual tablet 2. Piroxicam 20 mg fast-dissolving tablets Dose was titrated over 2 weeks to achieve a 50% reduction in pain episodes. Average dose after titration was not reported.	Patients with breakthrough cancer pain related to bone metastases on stable long-term analgesia Location: Egypt	Reduction in pain intensity using the VAS (range 0-10) Frequency of breakthrough pain attacks per day Onset of pain relief	Mean VAS at 1 month 1. 3.37 (SD 0.74) 2. 3.47 (SD 0.76) P=0.510 Breakthrough pain attacks at 1 month 1. 21.74 (SD 5.34) 2. 22.16 (SD 4.97) P=0.685 Mean onset of pain relief 1. 6.10 (SD 1.23) 2. 17.14 (SD 3.76) P<0.001

Abbreviations: AC = active comparator; DB = double blind; RCT = randomized clinical trial; VAS = visual analog scale

Appendix 3: Abstracts of Comparative Clinical Trials

Yousef AA, Alzeftawy AE. The efficacy of oral piroxicam fast-dissolving tablets versus sublingual fentanyl in incident breakthrough pain due to bone metastases: a double-blinded randomized study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2019;27(6):2171-2177.

PURPOSE: Breakthrough pain (BTP) is a transient exacerbation of pain occurring in a patient with chronic, persistent pain. The most common type is incident pain that is mostly related to bone metastases. The oral mucosa is an attractive route for drug delivery. Sublingual fentanyl preparations are a very attractive agent in controlling attacks of BTP due to its rapid absorption through the oral mucosa. Non-steroidal anti-inflammatory drugs (NSAIDs) play a key role as a first step in treatment of cancer pain; piroxicam sublingual formulations could be a useful alternative in controlling incident pain. Our study hypothesis is to evaluate the efficacy of sublingual fentanyl versus oral piroxicam fast-dissolving tablets in patients with incident pain and its impact on functional status.
PATIENTS AND METHODS: A cohort of 100 adults of both genders suffering from bone metastases. Patients were assigned to receive either sublingual fentanyl tablet (group 1) or oral piroxicam fast-dissolving tablets (group 2). The pain intensity reduction on a 0-10 visual analog scale (VAS), frequency of BTP attacks, and onset of pain relief. Secondary end points included the functional interference items of the Brief Pain Inventory (BPI).
RESULTS: There is no significant difference between the two groups regarding the patients' demographics. Significant decline of the VAS in each group in comparison to the pretreatment values (p = 0.001). Non-significant changes of the VAS, duration of pain attacks, and number of rescue doses in comparing both groups were measured. There was significant reduction in group 2 BPI regarding the relation with others, sleep pattern and enjoyment of life parameters at 2 and 4 weeks (p = 0.001).
CONCLUSION: Our study demonstrated that oral piroxicam fast-dissolving tablet is an analgesic alternative to sublingual fentanyl in patients with bone metastasis to control incidental BTP attacks with more favorable cost-benefit values.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 02, 2020

1	exp Analgesics, Opioid/ae, po, tu, to [Adverse Effects, Poisoning, Therapeutic Use, Toxicity]	45855
2	limit 1 to yr="2019 -Current"	977
3	limit 2 to (english language and humans)	884
4	limit 3 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")	204

Appendix 5: Key Inclusion Criteria

Population	Patients needing analgesia management
Intervention	short-acting or long-acting oral opioids
Comparator	Other opioids or analgesics
Outcomes	Improved pain control, symptoms, function, quality of life, or adverse events
Timing	Follow-up of at least 30 days
Setting	Outpatient

Long-acting Opioid Analgesics

Goals:

- Restrict use of long-acting opioid analgesics to OHP-funded conditions with documented sustained improvement in pain and function and with routine monitoring for opioid misuse and abuse.
- Restrict use of long-acting opioid analgesics for conditions of the back and/or spine due to evidence of increased risk vs. benefit.
- Promote the safe use of long-acting opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.

Length of Authorization:

Initial: 90 days (except 12 months for end-of-life, sickle-cell disease, severe burn, or cancer-related pain)
Renewal: Up to 6 months

Covered Alternatives:

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

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain, or pain associated with sickle cell disease or severe burn injury are exempt from this PA.

Table 1. Daily Dose Threshold (90 Morphine Milligram Equivalents per Day) of Opioid Products.

Opioid	90 MME/day	Notes
Fentanyl (transdermal patch)	37.5 mcg/hr	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	

Tapentadol	225 mg	
Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

Table 2. Specific Long-acting Opioid Products Subject to ~~Quantity~~ Frequency Limits per FDA-approved Labeling.

Drug Product	Quantity Limit
AVINZA	1 dose/day
BELBUCA	2 doses/day
BUTRANS	1 patch/7 days
EMBEDA	2 doses/day
EXALGO	1 dose/day
Fentanyl patch	1 dose/72 hr

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
MS CONTIN	3 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day
OXYCONTIN	2 doses/day

Drug Product	Quantity Limit
TROXYCA ER	2 doses/day
XARTEMIS XR	4 doses/day
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the request for a patient already established on any opioid treatment for >6 weeks (long-term, chronic treatment)?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #3

~~2.~~3. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, neuropathy, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #~~3~~4	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
~~3.~~4. Is the requested medication a preferred agent?	**Yes:** Go to #~~5~~6	**No:** Go to #~~4~~5
~~4.~~5. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #~~5~~6
~~5.~~6. Is the patient being treated for pain associated with sickle cell disease, severe burn injury, cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #~~6~~7
~~Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 3 months that opioid prescribing is appropriate?~~	~~**Yes:** Go to #7~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

~~6.~~7. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
~~7.~~8. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9
9. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past month that opioid prescribing is appropriate?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
~~8.~~10. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #11~~0~~

~~9.~~11. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Go to # 12~~1~~	**No:** Go to #13~~2~~
~~10.~~12. Has the prescriber provided documentation that the opioid and sedating medication will not be prescribed concurrently ~~of counseling the patient on the potential harms of concurrent use of opioids with a benzodiazepine or other central nervous system (CNS) depressant and determined that benefit outweighs risks~~?	**Yes:** Go to #13~~2~~	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~13. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14~~3~~
~~12.~~14. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #15~~4~~ Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

~~13.~~15. Has the patient had a urinary drug screen (UDS) within the past ~~year~~ 3 months to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

Renewal Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?	**Yes**: Go to #3	**No**: Go to **Approval Criteria**
3. Does the request document a taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #4
4. Is there documentation indicating it is **unsafe** to initiate a taper at this time?	**Yes:** Go to #5 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 1 month that opioid prescribing is appropriate?	**Yes:** Go to #6	**No:** Pass to RPh. Deny. Medical appropriateness
6. Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #7	**No:** Pass to RPh. Deny. Medical appropriateness

7. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #9 Document tool used and score vs. baseline: _____	**No:** Go to #8
8. Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny. Medical appropriateness
9. Is the request for an increased cumulative dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #10	**No:** Go to #13
10. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #13	**No:** Pass to RPh; deny; medical appropriateness

13. Does the patient have any of the following risk factors for overdose? a. Concomitant CNS depressants (benzodiazepines, muscle relaxants, sedating antipsychotics, etc) b. Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2 c. Recent urine drug screen indicating illicit or non-prescribed opioids d. Concurrent short- and long-acting opioid use	**Yes:** Go to #14 Document number of risk factors	**No:** Go to #15
14. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #15	**No:** Pass to RPh. Deny. Medical appropriateness
15. Does the patient have a pain contract on file with the prescriber?	**Yes:** Approved duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less): Risk factors: >=3: 2 month 1-2: 4 months 0: 6 months	**No:** Pass to RPh. Deny; medical appropriateness

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Prioritized-List.aspx

**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.

Citation of the original publication:

Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the following guidelines on opioid prescribing:

- The Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.

Selecting the optimal timing and approach to tapering depends on multiple factors. The decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids or with significant long-term use, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations, allowing for pauses during the taper, and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish ~~the~~an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:
    a. Assess for substance use disorder and transition to appropriate medication assisted treatment ~~Immediate discontinuation~~ if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. May consider ~~S~~starting with a taper of ≤10% of the original dose per ~~week~~ month and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid pharmacological and non-pharmacological options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.

11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.
Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *2/20 (SS), 9/19 (DM), 3/17 (MH); 11/16; 05/16*
Implementation: *TBD, 10/1/19*

Short-acting Opioid Analgesics

Goals:
- Restrict use of short-acting opioid analgesics for acute conditions funded by the OHP.
- Promote use of preferred short-acting opioid analgesics.

Length of Authorization:
Initial: 7 to 30 days (except 12 months for end-of-life, sickle cell disease, severe burn injury, or cancer-related pain)
Renewal: Up to 6 months

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

Requires a PA:

- Non-preferred short-acting opioids and opioid combination products.
- All short-acting products prescribed for more than 14 days. Each prescription is limited to 7 days in treatment-naïve patients. Patients may fill up to 2 prescriptions every 90 days without prior authorization. ~~patients with new opioid starts or prescribed more frequently than 2 prescriptions every 90 days.~~
- All codeine and tramadol products for patients under 19 years of age

Note:
- Patients on palliative care with a terminal diagnosis or with cancer-related pain or with pain associated with sickle cell disease or severe burn injury are exempt from this PA.

Table 1. Daily Dose Threshold (90 morphine milligram equivalents per day (MME/day) of Oral Opioid Products.

Opioid	90 MME/day Dose	Notes
Benzhydrocodone	73.5 mg	
Codeine	600 mg	Codeine is not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism, placing certain populations at risk for overdose.
Dihydrocodeine	360 mg	
Hydrocodone bitartrate	90 mg	
Hydromorphone	22.5 mg	
Levorphanol tartrate	8 mg	
Meperidine	900 mg	Meperidine is not recommended for management of chronic pain due to potential accumulation of toxic metabolites.
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	400 mg	400 mg/day is max dose and is not equivalent to 90 MME/day. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.

Approval Criteria	
1. What is the patient's diagnosis?	Record ICD10

2. Has the patient been prescribed any opioid analgesics (short or long-acting) for more than 6 weeks?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis funded by the OHP? Note: Currently, conditions such as fibromyalgia, TMJ, pelvic pain syndrome, neuropathy, and tension headache are not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.
4. Is the requested medication a preferred agent?	**Yes:** Go to #6	**No:** Go to #5
5. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Is the patient being treated for pain associated with sickle cell disease, severe burn injury or cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months.	**No:** Go to #7
7. Is the prescription for a product containing codeine or tramadol in a patient less than 19 years of age? Note: Cold symptoms are not funded on the prioritized list	**Yes:** Deny for medical appropriateness	**No:** Go to #8

8. Is the prescription for a short-acting fentanyl product? Note: Short-acting transmucosal fentanyl products are designed for breakthrough cancer pain only. This PA does not apply to transdermal fentanyl patches.	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9
9. Is the opioid prescribed for pain related to migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber reviewed at least once in the past ~~3~~ months~~s~~ and verified that opioid prescribing is appropriate?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
~~10.~~11. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Go to # 12~~0~~	**No:** Go to #13~~1~~

~~11.~~12. Has the prescriber provided documentation that the opioid and sedating medications will not be prescribed concurrently? ~~of counseling the patient on the potential harms of concurrent use of opioids with a benzodiazepine or other central nervous system (CNS) depressant and determined that benefit outweighs risks?~~	**Yes:** Go to #13~~1~~	**No:** Pass to RPh. Deny; medical appropriateness
~~Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber reviewed at least once in the past 3 months and verified that opioid prescribing is appropriate?~~	~~**Yes:** Go to #12~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~Did the patient's pain originate from acute injury, flare, or surgery that occurred in the last 6 weeks?~~	~~**Yes:** Go to #13~~	~~**No:** Go to #18~~
~~12.~~13. Within ~~this time period~~the past 6 weeks, has a 5-day trial of at least one non-opioid analgesic (e.g., NSAID, acetaminophen, and/or muscle relaxant) been tried for this indication at its maximum effective dose and found to be ineffective or are contraindicated?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
~~13.~~14. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #15	**No:** Approve for up to 30 days
~~14.~~15. Has the prescriber also developed a plan with the patient to stay active (home or prescribed exercise regimen) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, weight loss, massage therapy, or acupuncture?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness

~~15.~~16. Is this the first opioid prescription the patient has received for this pain condition?	**Yes:** Approve for up to 7 days not to exceed 90 MME	**No:** Go to #17
~~16.~~17. Can the prescriber provide documentation of sustained improvement in function of at least 30% compared to baseline with prior use of opioid analgesics (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, 3-item PEG scale, and MSPQ)?	**Yes:** Approve for up to 7 days not to exceed 90 MME	**No:** Pass to RPh. Deny; medical appropriateness.
18. ~~Has the patient been prescribed opioid analgesics for more than 6 weeks?~~	~~**Yes:** Go to #19~~	~~**No:** Go to #11~~
~~17. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline?~~ ~~18.~~19. ~~Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.*~~	~~**Yes:** Document tool used to measure pain and/or function. Go to #20~~	~~**No:** Pass to RPh. May approve for up to 30 days one time. For future claims without documentation: deny; medical appropriateness.~~ ~~Note: Management of opioid dependence is funded by the OHP.~~
~~19.~~20. ~~Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?~~	~~**Yes:** Go to #21~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Note: Management of opioid dependence is funded by the OHP.~~
~~20.~~21. ~~Is the opioid prescription for pain associated with a back or spine condition?~~	~~**Yes:** Go to #22~~	~~**No:** Go to #23~~

21.22. ~~Have any of the following therapies also been prescribed and utilized by the patient: spinal manipulation, physical therapy, yoga or acupuncture?~~	~~**Yes:** Document additional therapy. Approve for up to 7 days not to exceed 90 MME.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
22.23. ~~Does the total daily opioid dose exceed 90 MME (Table 1)?~~	~~**Yes:** Pass to RPh. May approve one time. For future claims: deny; medical appropriateness.~~ ~~For patients with a history of chronic opioid use, short-term approval may be considered if a patient-specific taper plan is documented or for up to 30 days to allow providers time to develop a taper plan. Subsequent approvals must document progress toward the taper.~~ ~~Note: Management of opioid dependence is funded by the OHP.~~	~~**No:** Approve for up to 30 days.~~

Renewal Criteria	
1. What is the patient's diagnosis?	Record ICD10 code

2. Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?	**Yes**: Go to #3	**No**: Go to **Approval Criteria**
3. Does the request document a taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #4
4. Is there documentation indicating it is **unsafe** to initiate a taper at this time?	**Yes:** Go to #5 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 1 month that opioid prescribing is appropriate?	**Yes:** Go to #6	**No:** Pass to RPh. Deny. Medical appropriateness
6. Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #7	**No:** Pass to RPh. Deny. Medical appropriateness
7. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. *	**Yes:** Go to #9 Document tool used and score vs. baseline:_____	**No:** Go to #8

8. Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny. Medical appropriateness
9. Is the request for an increased cumulative daily dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #10	**No:** Go to #12
10. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #12	**No:** Pass to RPh; deny; medical appropriateness
12. Does the patient have any of the following risk factors for overdose? a. Concomitant CNS depressants (benzodiazepines, muscle relaxants, sedating antipsychotics, etc) b. Total daily opioid dose > 90 MME or prescribed concurrent short- and long-acting opioids c. Recent urine drug screen indicating illicit or non-prescribed opioids	**Yes:** Go to #13 Document number of risk factors	**No:** Go to #14
13. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #14	**No:** Pass to RPh. Deny. Medical appropriateness

14. Does the patient have a pain contract on file with the prescriber?	**Yes:** Approved duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less): Risk factors: >=3: 2 month 1-2: 4 months 0: 6 months	**No:** Pass to RPh. Deny; medical appropriateness

*The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.
Citation of the original publication:
Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738

Clinical Notes:

How to Discontinue Opioids.

Adapted from the following guidelines on opioid prescribing:

- The Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.

Selecting the optimal timing and approach to tapering depends on multiple factors. The decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids or with significant long-term use, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations, allowing for pauses during the taper, and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish ~~the~~an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:

a. Assess for substance use disorder and transition to appropriate medication assisted treatment ~~Immediate discontinuation~~ if there is diversion or non-medical use,
b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
c. Slow taper for patients with no acute safety concerns. May consider ~~S~~starting with a taper of ≤10% of the original dose per ~~week~~ month and assess the patient's functional and pain status at each visit.

4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
   a. Assess the patient behaviors that may be suggestive of a substance use disorder
   b. Address increased pain with use of non-opioid pharmacological and non-pharmacological options.
   c. Evaluate patient for mental health disorders.
   d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

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Prior Authorization Criteria Update: Gout

Date of Review: February 2020

Purpose of the Update:
In 2017, a safety study showed an increased risk of heart-related death in patients randomized to febuxostat compared to allopurinol.[1] In 2018 results from the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial were made available and were analyzed by the Food and Drug Administration (FDA). Labeling was changed in 2019 with the addition of a boxed warning to febuxostat prescribing information which identified an increase in risk of heart-related deaths and death from all-causes with febuxostat use.[2]

The CARES trial was a multicenter, double-blind, noninferiority trial in patients (n=6190) with gout and cardiovascular (CV) disease.[3] There were 15 heart-related deaths per 1000 patients treated with febuxostat compared to 11 deaths per 1000 patients treated with allopurinol over one year.[3] All-cause death was 26 per 1000 patients treated with febuxostat compared to 22 per 1000 patients treated with allopurinol for one year. The primary composite endpoint (CV death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization) was similar between febuxostat and allopurinol, 10.8% versus 10.4%.[3] Subgroup analysis demonstrated no clear evidence of patients that may benefit or be at increased risk of harm from febuxostat therapy. It is recommended that febuxostat should be reserved for those who failed or cannot take allopurinol.

Boxed warning: Cardiovascular death
- Gout patients with established cardiovascular (CV) disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study.[4]
- Consider the risks and benefits of febuxostat when deciding to prescribe or continue patients on therapy. Febuxostat should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.[4]

Utilization: In quarter 3 of 2019, there were 2 claims for febuxostat. Allopurinol and cholchicine/probenecid are the preferred treatments for the class.

Recommendation:
1. Consider adding a requirement to febuxostat prior authorization (PA) criteria that the patient has been accessed for CV risk and the benefits outweigh the risks (**Appendix 1**).

References:

1. Food and Drug Administration. FDA to evaluate increased risk of heart-related death and death from all causes with the gout medicine febuxostat (Uloric). 15 November 2017. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluate-increased-risk-heart-related-death-and-death-all-causes. Accessed 8 November 2019.
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3. White W, Saag K, Becker M, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. NEJM 2018;378:1200-10.
4. Uloric (febuxostat) [product information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc., February 2019.

Appendix 1. Proposed Prior Authorization Criteria

Agents for Gout

Goal(s):

- To provide evidenced-based step-therapy for the treatment of acute gout flares, prophylaxis of gout and chronic gout.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the provider switch to a preferred product? Note: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee. Preferred products are available without a PA	**Yes:** Inform prescriber of covered alternatives in the class	**No:** Go to #3
3. Is the request for colchicine?	**Yes:** Go to #4	**No:** Go to #5
4. Has the patient tried and failed NSAID therapy or have contraindications to NSAIDs or is a candidate for combination therapy (i.e., multiple joint involvement and severe pain)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; recommend trial of NSAID
5. Is the request for febuxostat?	**Yes:** Go to #6	**No:** Go to #9
6. Has the patient tried and failed allopurinol or has contraindications to allopurinol?	**Yes:** Go to #7~~Approve for 12 months~~	**NO:** Pass to RPh. Deny; recommend trial of allopurinol
7. Is the patient at high risk for cardiovascular disease or have established cardiovascular disease?	**Yes:** Go to #8	**NO:** Approve for 12 months.
8. Has the provider documented a risk/benefit assessment?	**Yes:** Approve for 12 months. Document provider attestation	**NO:** Pass to RPh. Deny; medical appropriateness
~~7.~~9. Is the request for lesinurad?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; Medical appropriateness

Approval Criteria		
~~8.~~10. Is the patient concomitantly taking a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat)?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
~~9.~~11. Is the estimated CrCl < 45 mL/min?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months at a maximum daily dose of 200 mg

P&T/DUR Review: *1/17 (KS)*
Implementation: *4/1/2017*

Appendix 2: Search Strategy

1. FDA boxed warnings from 1/01/2015 – 11/14/2019
2. FDA drug safety communications 1/01/2015 – 11/14/2019

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Drug Class Review: Diabetes, Glucagon

Date of Review: February 2020 **End Date of Literature Search:** 11/26/2019

Purpose for Class Review:
The purpose of this class review is to create a glucagon class on the preferred drug list (PDL) and evaluate evidence for glucagon products to determine PDL status.

Research Questions:
1. What is the comparative efficacy and effectiveness of different glucagon formulations to reverse severe hypoglycemia in patients with diabetes mellitus?
2. What is the comparative tolerability and harms of different glucagon formulations when used to treat severe hypoglycemia in patients with diabetes mellitus?
3. Are there subpopulations of patients based on demographics (e.g., age, gender, race) or comorbidities (e.g., drug-disease interactions, obesity) with diabetes mellitus for which a specific glucagon formulation may be more effective or associated with less harm?

Conclusions:
- There is a paucity of high-quality evidence for any of the glucagon products used for the treatment of hypoglycemia. There is insufficient comparative evidence between the different glucagon formulations. One high-quality clinical practice guideline and 2 randomized controlled trials (RCT) were included in the review.
- A guideline from the National Institute for Health and Care Excellence (NICE) for the management of type 1 diabetes (T1DM) recommends intramuscular (IM) glucagon for the treatment of severe hypoglycemia (intranasal glucagon was not available at the time of the NICE review).[1]
- Glucagon nasal powder was found to be non-inferior to IM glucagon in a study of adult patients with T1DM (n=75).[2] Treatment success (defined as an increase in plasma glucose to 70 mg/dL or more, or an increase of at least 20 mg/dL from glucose nadir within in 30 minutes of receiving glucagon) was experienced by 98.7% of patients randomized to intranasal glucagon compared to 100% of patients given IM glucagon.[2]

Recommendations:
- Create a PDL class for the glucagon products.
- Evaluate costs in executive session.

Background:
Hypoglycemia requiring treatment is most commonly experienced in patients with T1DM and type 2 diabetes (T2DM) who use antidiabetic therapies to normalize glucose levels.[3] The prevalence of severe hypoglycemia is thought to be as high as 3 episodes a year in patients with T1DM, but infrequent in patients with T2DM. Hypoglycemia is associated with many symptoms, including tremor, palpitations, anxiety, sweating, hunger and, in rare cases, seizures and coma.

Author: Kathy Sentena, PharmD

Case reports suggest that an average of 7% of deaths in patients with T1DM are due to hypoglycemia.[4] Hypoglycemia symptoms can appear at glucose levels of 65 mg/dL or lower; however, some individuals are less sensitive to glucose changes and are asymptomatic at low blood glucose levels.[3]

Hypoglycemia can be defined as severe hypoglycemia (requires assistance from another person to administer carbohydrate or glucagon), symptomatic hypoglycemia (symptoms with blood glucose less than 70 mg/dL), asymptomatic hypoglycemia (no symptoms but blood glucose less than 70 mg/dL), and pseudohypoglycemia (typical symptoms are present but glucose values are 70 mg/mL or greater).[3,4]

It is recommended to treat hypoglycemia by administering 15-20 grams of fast-acting carbohydrate, such as glucose tablets, hard candy, or sweetened fruit juice.[5,6] Fifteen grams of glucose is required to increase blood glucose levels approximately 37 mg/dL within 20 minutes.[7] Administration of glucagon is required in patients with severe hypoglycemia who are not being treated in a medical setting.[3,5] Glucagon stimulates endogenous glucose production to increase blood glucose levels. Glucagon given subcutaneously (SQ) or IM increases blood glucose 54 mg/dL to 216 mg/dL in 60 minutes.[7] It is recommended that patients with T1DM always carry a form of glucagon (subcutaneous, intramuscular or nasal) that can be administered by a caregiver if needed.[1]

The 4 glucagon formulations available in the U.S. are outlined in **Table 1**. [8–11] Reconstituted glucagon products can be given SQ, IM or IV and products that are ready to use are administered SQ only. Nasal glucagon is administered intranasally via a device which dispenses a glucagon powder that is readily absorbed by the mucous membrane.[3] Administration of IV, IM or SC glucagon is usually associated with glucose recovery in about 15 minutes, while it is slightly longer (about 18 minutes) for intranasally administered glucagon.

Table 1. Glucagon Products

Brand	Formulation	Reconstitution	Route
Baqsimi™	spray	No	Nasal
Glucagen®	vial	Yes	SQ, IM or IV
Glucagon Emergency Kit	vial	Yes	SQ, IM or IV
Gvoke Hypopen™	auto injection	No	SQ
Gvoke Syringe™	syringe	No	SQ
Abbreviations: IM – intramuscular; IV – intravenous; SQ – subcutaneously			

Endpoints frequently used to determine the efficacy of glucagon products are normalization of glucose levels to 70 mg/dL or above, increase in glucose levels of at least 20 mg/dL and resolution of hypoglycemia symptoms (Appendix 3).

In Quarter 3 of 2019 there were 50 claims for glucagon products for Oregon Health Plan (OHP) fee-for-service (FFS) patients. Most prescription claims were for glucagon kits; however, intranasal glucagon and pre-filled syringes/auto-injectors were also prescribed. Glucagon products do not currently have an assigned PDL status.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing for Glucagon Products.

Brand Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Baqsimi™[9] (Lilly)	Antihypoglycemic agent indicated for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and older	3 mg intranasal spray powder	1 spray into 1 nostril Dose may repeat once after 15 minutes if no response
GlucaGen®[10] (Novo Nordisk)	Antihypoglycemic agent and a gastrointestinal motility inhibitor for the treatment of hypoglycemia and use as a diagnostic aid	1 mg/ 1mL SQ, IM, IV	Adults and children ≥ 55 lbs. (25 kg) 1 mL Children < 55 lbs (25 kg): 0.5 mL If weight unknown: Children < 6 years: 0.5 mL Children 6 years and older: 1 mL (must be reconstituted) Dose may be repeated if no response*
Glucagon Emergency kit[8] (Lilly)	Treatment for severe hypoglycemia in patients with diabetes mellitus and as a diagnostic aid	1 mg/ 1 mL SQ, IM, IV	Adults and children ≥44 lbs (20 kg): 1 mg Children <44 lbs (20 kg): 0.5 mg (or dose equivalent to 20-30 mcg/kg) (1 mg/mL reconstituted) Dose may be repeated if no response*
Gvoke™[11] (Xeris) Pre-filled syringe and auto-injector	Antihypoglycemic agent indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above	0.5 mg/0.1 mL or 1 mg/0.2 mL SQ	Adults and pediatric patients 12 years and older: 1 mg Pediatric patients 2 to under 12 years: < 45 kg: 0.5 mg ≥ 45 kg: 1 mg Dose may be repeated after 15 minutes if no response

Abbreviations: IM – intramuscular; IV -intravenous; SQ – subcutaneous
Key: * Dosing interval not specified

Table 2. Summary of Pivotal Studies Completed.

Study	Comparison	Population	Primary Outcome	Results
Rickels, et al[2] Phase 3, CO, MC, NI, RCT	Glucagon nasal powder 3 mg Vs. Intramuscular glucagon 1 mg	Adults with T1DM (n = 75)	Treatment success (increase in plasma glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from glucose nadir) within in 30 minutes of receiving glucagon	Nasal glucagon: 98.7% Intramuscular glucagon: 100% TD 1.3% (upper end of 97.5% CI, 4.0%) *Nasal glucagon was non-inferior to intramuscular glucagon*
Sherr, et al[12] Phase 1, CO, MC, RCT	Glucagon nasal powder† Vs. Intramuscular glucagon†	Youth (4 to < 17 years) patients with T1DM (n = 48)	Pharmacokinetic study achieving at least a 25 mg/dL increase in glucose above the nadir within 20 minutes of administration	Nasal glucagon: 100% Intramuscular glucagon: 100% *Nasal glucagon was equal to intramuscular glucagon in raising glucose levels*

Key: † Patients 4 years to < 8 years and 8 years to < 12 years were randomly assigned to 2 or 3 mg intranasal glucagon dose in two separate sessions or a single, weight-based dose of intramuscular glucagon.
Abbreviations: CO – cross-over; MC – multi-center; NI – non-inferiority; RCT – randomized clinical trial; T1DM – type 1 diabetes mellitus; TD – treatment difference

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

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

Systematic Reviews:
After review, one systematic review was excluded due to poor quality (e.g., low-quality of evidence).[13]

Guidelines:
High Quality Guidelines:

NICE – Type 1 Diabetes in Adults
The diagnosis and management of adult patients with T1DM was updated in a 2015 clinical guideline by NICE. For the purposes of this review, only the medical interventions for hypoglycemia will be presented. Evidence from two trials found a slower recovery in patients in a hypoglycemic coma given 1 mg glucagon, IM or IV, compared to 50 mL 50% IV dextrose (evidence based on data from quasi-experimental study [IIb]).

Recommendation:

- Adults with T1DM with a decreased level of consciousness as a result of hypoglycemia and therefore unable to take oral treatment should:
    - Be given IM glucagon by a caregiver or IV glucose by a healthcare professional that is able to obtain IV access.
    - Monitored for 10 minutes and given IV glucose if consciousness is not improving.
    - Oral carbohydrates should be given when it is safe to administer and the patient should continue to be monitored for relapse.

After review, 3 guidelines were excluded due to poor quality.[4,6,7]

References:

1. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. Guidance and guidelines NICE. https://www.nice.org.uk/guidance/ng17. Accessed June 28, 2017.
2. Rickels MR, Ruedy KJ, Foster NC, et al. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. *Diabetes Care*. 2016;39(2):264-270. doi:10.2337/dc15-1498.
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7. Yale J-F, Paty B, Senior PA. Hypoglycemia. *Canadian Journal of Diabetes*. 2018;42:S104-S108. doi:10.1016/j.jcjd.2017.10.010.
8. Glucagon [prescribing information]. Indianapolis, IN: Lilly, USA, LLC, April 2018.
9. Baqsimi (glucagon)[product information].Indianapolis, IN: Lilly USA, LLC, July 2019.
10. GlucaGen (glucagon) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk A/S, July 2018.
11. Gvoke (glucagon) [prescribing information]. Chilcago, IL: Xeris Pharmaceuticals, September 2019.
12. Sherr JL, Ruedy KJ, Foster NC, et al. Glucagon Nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care*. 2016;39(4):555-562. doi:10.2337/dc15-1606.
13. Boido A, Ceriani V, Pontiroli AE. Glucagon for hypoglycemic episodes in insulin-treated diabetic patients: a systematic review and meta-analysis with a comparison of glucagon with dextrose and of different glucagon formulations. *Acta Diabetologica*. 2015;52(2):405-412. doi:10.1007/s00592-014-0665-0.

Appendix 1: Specific Drug Information

Generic	Brand	Form	Route
glucagon	BAQSIMI	SPRAY	NS
glucagon,human recombinant	GLUCAGEN	VIAL	IJ
glucagon,human recombinant	GLUCAGON EMERGENCY KIT	VIAL	IJ
glucagon	GVOKE HYPOPEN	AUTO INJCT	SQ
glucagon	GVOKE SYRINGE	SYRINGE	SQ

Table 3. Clinical Pharmacology and Pharmacokinetics (T1DM adult patients).

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Glucagon (Baqsimi™)[9]	Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver.	Intranasal: 6130 pg/mL	Degraded by the liver, kidney and plasma.	• Half-life: 35 minutes • Cmax: NR • AUC: NR • Vd: 885 L
Glucagon (GlucaGen®)[10]	Same as above	NA	Same as above	• Half-life: 45 minutes • Cmax: 1686 pg/mL • AUC: NR • Vd: NR
Glucagon (Emergency kit)[8]	Same as above	NA	Same as above	• Half-life: 8-18 minutes • Cmax: 7.9 ng/mL • AUC: NR • Vd: 0.25 L/kg
Glucagon (Gvoke™)[11]	Same as above	NA	Same as above	• Half-life: 32 minutes • Cmax: 2481.3 pg/mL • AUC: 3454.6 pg/mL • Vd: NR
Abbreviation: AUC – are under the curve; Cmax – maximum concentration; NA – not applicable; NR – not reported; T1DM – type 1 diabetes mellitus; VD – volume of distribution				

Use in Specific Populations: Glucagon should not be used in patients with pheochromocytoma and is contraindicated in patients with insulinoma. Patients with decreased hepatic glycogen may not respond to glucagon.

Drug Safety:
Boxed Warnings: none

Risk Evaluation Mitigation Strategy Programs: none

Contraindications: Do not use glucagon in patients with pheochromocytoma, insulinoma, or hypersensitivity to glucagon.

Table 4. Summary of Warnings and Precautions.

Warning/Precaution	Glucagon (Baqsimi™)	Glucagon (GlucaGen®)	Glucagon (Emergency kit)	Glucagon (Gvoke)
Catecholamine release in patients with pheochromocytoma	X	X	X	X
Hypoglycemia in patients with insulinoma	X		X	X
Hypersensitivity and allergic reactions	X	X	X	X
Lack of efficacy in patients with decreased hepatic glycogen	X	X	X	X
Necrolytic migratory erythema		X		X
Hypoglycemia in patients with glucagonoma				X
Caution in patients with cardiac disease		X		

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 26, 2019

Search Strategy:

#	Searches	Results
1	Glucagon/ or glucagon.mp.	47022
2	glucagon injection.mp.	218
3	glucagon spray.mp.	0
4	1 or 2 or 3	47022
5	limit 4 to (english language and humans and yr="2000 -Current")	11641
6	limit 5 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	378

Appendix 3: Key Inclusion Criteria

Population	Patients with T1DM and T2DM
Intervention	Glucagon spray, vial, and auto-injector
Comparator	Glucagon formulations by differing routes
Outcomes	Normalization of glucose levels to 70 mg/dL or above, increase in glucose levels of at least 20 mg/dL and resolution of hypoglycemia symptoms
Timing	Onset of hypoglycemia
Setting	Outpatient

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New Drug Evaluation: lefamulin

Date of Review: February 2020
Generic Name: lefamulin

End Date of Literature Search: 12/2019
Brand Name (Manufacturer): Xenleta™ (Nabriva Therapeutics, Inc)
Dossier Received: Yes

Research Questions:

1. Is there comparative evidence that lefamulin is more effective or safer than current standard of care in the treatment of community-acquired pneumonia (CAP) caused by susceptible bacterial organisms?
2. Are there subpopulations of patients for which lefamulin may be more effective or associated with less harm in the treatment of CAP?

Conclusions:

- There is low quality evidence based on two phase 3 double-blind, noninferiority trials that lefamulin 150 mg intravenous (IV) every 12 hours and 600 mg oral every 12 hours is non-inferior in early clinical response to moxifloxacin IV and oral in the treatment of CAP caused by common bacterial pathogens, with a risk difference of -2.9% (95% confidence interval [CI] -8.5 to 2.8) with IV therapy and 0.1% (95% CI -4.4 to 4.5%) with oral therapy.[1,2]
- There is insufficient evidence to make conclusions about the efficacy and safety of lefamulin in patients at risk or with suspected resistant organisms , in patients with significant hepatic disease, in severe CAP, or compared to other standard of care (beta-lactam in combination with a macrolide).
- There is low quality evidence of no difference in discontinuations due to adverse events or treatment emergent serious adverse events between lefamulin and moxifloxacin. [1,2] The most common adverse events include injection site reactions with IV therapy and diarrhea with oral therapy. Additional safety concerns include hepatic enzyme elevation, QT interval prolongation and drug-drug interactions through CYP3A4.
- There is insufficient evidence that lefamulin is more effective or associated with less harm in any subpopulations based on disease severity or baseline comorbidities.

Recommendations:

- Make lefamulin non-preferred in the miscellaneous antibiotic PDL class.

Author: Megan Herink, PharmD

Background:
Pneumonia is among the leading causes of morbidity and mortality worldwide. Community acquired pneumonia (CAP) is a lower respiratory infection acquired outside of a hospital or other acute care facility.[3] The incidence of CAP is 24.8 per 10,000 adults and is higher with older age and in those with medical comorbidities. Common causes include both respiratory viruses (influenza, rhinovirus, respiratory syncytial virus, etc.) and bacterial pathogens. The most common bacterial pathogens include *Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae, Staphylococcus aureus,* and atypical pathogens (*Mycoplasma pneumoniae, Legionella,* and *Chlamydia pneumoniae).*[4] *S. pneumoniae* and respiratory viruses are the most frequently detected pathogens in CAP. Patients with recent hospitalization and intravenous (IV) antibiotics, those who are immunosuppressed, and those with a history of respiratory infection with multidrug resistant bacteria may be at an increased risk of infection caused by gram negative bacilli, methicillin resistant *staphylococcus aureus* (MRSA), and/or *Pseudomonas aeruginosa*.[4]

Antibiotics approved by the FDA and recommened in clinical practice guidelines for the treatment of CAP include macrolides (azithromycin), fluoroquinolones, cephalosporins and other beta-lactam drugs.[3] The choice of the antibacterial drug depends on the severity of illness, underlying comorbidities, the likely pathogen, treatment setting (community vs. hospital) and the adverse event profile of the drug. First-line regimens typically include a macrolide or doxycycline in combination with a beta-lactam or a respiratory fluoroquinolone. High rates of macrolide resistant *S. pneumoniae* have limited the use of macrolide monotherapy. Other broad spectrum agents (beta-lactam/beta-lactamase inhibitor combinations) are reserved for patients with suspected resistant organisms or who are at risk for *Pseudomonas.* Overall, there are many current antibiotics that are options for the treatment of CAP. Lefamulin is a pleuromutilin antibiotic that inhibits bacterial protein synthesis and is available in both oral and intravenous (IV) formulations.[5] Lefamulin is bactericidal against *S. pneumoniae, H. influenzae and M. pneumoniae* (including macrolide-resistant strains), and bacteriostatic against *S. aureus (*methicillin-susceptible isolates) and *S. pyogenes* at clinically relevant concentrations.[6] In vitro activity has also been demonstrated against MRSA. It is not active against Enterobacteriaceae and *Pseudomonas aeruginosa.* Resistance induction is unknown but appears unaffected by several common mechanisms seen in other major antibiotic classes.

Severity of infection and a decision to treat in the hospital or outpatient is assessed using the pneumonia severity index or pneumonia outcomes research team (PORT) score which uses 20 variables and assigned patients to 1 of 5 categories which estimates the risk of mortality (**Table 1**).[5] The PORT trial uses data from demographics, comorbidities, physical exam, laboratory and radiographic results.

Table 1: Pneumonia Outcomes Research Team Scoring and Classification[5]

PORT Score	Risk Class	Predicted Mortality (%)	Recommended Treatment Setting
≤ 70	II	0.6	Outpatient
71-90	III	0.9	Outpatient vs. Observation Admission
91-130	IV	9.3	Hospital
130	V	27	Hospital
No risk factor is Risk Class I (low risk of mortality)			

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:
FDA approval of lefamulin was based upon two, phase 3, multicenter, multinational, double-blind, active-control, double-dummy, non-inferiority trials.[1,2] These trials demonstrated noninferiority of lefamulin to moxifloxacin in the treatment of CAP due to common bacterial pathogens (*S. pneumoniae, S. aureus, H. influenzae, etc.).* The primary efficacy endpoint in both trials was early clinical response (ECR) responder rate in the intent-to-treat (ITT) population. Early clinical response was defined as an improvement in at least 2 CAP signs/symptoms, no worsening of any signs/symptoms, and no concomitant antibiotic for CAP administered at 96 hours (within a 24-hour window) after receipt of first dose of study drug.[5]

The Lefamulin Evaluation Against Pneumonia 1 (LEAP 1) trial included subjects with Pneumoniae Outcome Research Team (PORT) scores of ≥3 and compared IV lefamulin 150 mg every 12 hours to IV moxifloxacin 400 mg every 24 hours.[2] Patients were able to switch to oral therapy after 3 days. Moxifloxacin patients who met criteria for suspected methicillin-resistant *S. aureus* (MRSA) also received linezolid 600 mg IV every 12 hours, which was discontinued upon confirmation of a negative MRSA baseline culture and lefamulin treated patients received a linezolid placebo.[2] Patients in the lefamulin group initially received 5 days of treatment for CAP (but received 7 days after a protocol amendment), while moxifloxacin patients were given 7 days. Prior to protocol amendment, patients with MRSA, *L. pneumophila*, or bacteremia secondary to *S. pneumoniae* received 10 days of antibiotics in either group; post-amendment, only patients with MRSA were extended to 10 days. Approximately 25% of the study population was enrolled prior to protocol amendment.[2] The LEAP 2 trial included those with PORT scores of 2-4 who were candidates for oral therapy and compared oral lefamulin 600 mg twice daily for 5 days to oral moxifloxacin 400 mg daily for 7 days.[1] Confirmed or suspected MRSA was an exclusion criteria in LEAP 2.

The ECR rates for lefamulin were noninferior to moxifloxacin in both studies, and the difference between the treatment groups met the predefined noninferiority margin (**Table 5**). In LEAP 1, non-inferiority was achieved with a -2.9% (95% CI, -8.5 to 2.8%) difference in ECR responder rate between lefamulin and moxifloxacin.[2] In LEAP 2, the difference was 0.1% (95% CI, -4.4 to 4.5%).[1] Lefamulin had similar ECR rates compared to moxifloxacin in various demographic and baseline health status subgroups (history of heart and lung disease, moderate renal impairment, and severe CAP) in both trials. Additionally, clinical response rates in the population with confirmed pathogens did not reveal any meaningful differences between the treatment arms for any particular baseline pathogen, noting that some pathogens were isolated from relatively small numbers of subjects. The most common bacterial pathogens isolated were consistent with current practice and included *S. pneumoniae, H. influenzae,* and atypical organisms. In addition, investigator-assessed clinical response at the test-of-cure visit, 5-10 days after completing therapy and up to 30 days after starting therapy did not show meaningful differences between the treatment groups.[1,2]

Despite the high responder rates in LEAP 1, rescue antibacterial medication (due to insufficient therapeutic effect of study drug or due to treatment-limiting adverse events resulting in discontinuation of study drug) was administered to 36 subjects in the lefamulin arm (13.0%) and 34 subjects in the moxifloxacin arm (12.4%).[5] In LEAP 2, there was in imbalance in rescue antibiotic use (10.5% of subjects in the lefamulin arm and 7.1% in the moxifloxacin arm). The primary reason was due to insufficient therapeutic effect of study drug.[5]

Applicability to several important subgroups is limited, including elderly and patients with severe CAP (PORT class V). Overall, the study populations were much healthier with fewer comorbidities than what is seen in clinical practice. Excluded populations included those with any degree of immunosuppression, hepatic disease, severe renal disease (CrCl < 30 mL/min) and those at risk for prolonged QT interval. There were not enough patients with MRSA to draw any conclusions about efficacy, and lefamulin should not be used when MRSA is suspected until additional data are provided. It is unclear if body mass index (BMI) affects drug efficacy and oral bioavailability is poor. A beta-lactam and/or macrolide comparator arm with predetermined superiority criteria would have improved robustness of the evidence since fluoroquinolone use is declining due to safety concerns and alternative options.[4]

The methods are unclear as to the study setting (inpatient vs. outpatient) or if the setting differed for patients relative to the severity of initial PORT risk class, making it difficult to assess study care in relation to normal clinical practice. Additionally, there was risk for high selection bias in both trials trial due to unclear randomization and allocation concealment procedures and differences in baseline characteristics (details in Table 5). The majority of study sites were in Eastern Europe. In LEAP 1, less than 1% of subjects were in the United States; in LEAP 2, approximately 3% of subjects were in the United States.

Clinical Safety:
In the two Phase 3 studies, there were 36 subjects in the lefamulin group (5.6%) and 31 subjects in the moxifloxacin group (4.8%) who experienced at least one treatment-emergent serious adverse event.[5] Patients were followed up for 30 days. Side effects of concern included diarrhea (oral therapy), injection site reactions (IV therapy) and hepatic enzyme elevations. No *C. difficile* cases were reported in either group within the 30-day follow-up period. There were 6 deaths in the lefamulin arm and 5 in the moxifloxacin arm. None were considered by investigators to be related to the study drug.[5] Discontinuations due to adverse events were low and similar between lefamulin and moxifloxacin in clinical trials. The most common adverse events are included below.

Table 2: Adverse reactions in ≥ 2% of patients in LEAP 1 (IV dosing)[6]

Adverse Reaction	Lefamulin (n=273)	Moxifloxacin (n=273)
Administration site reactions	7%	3%
Hepatic enzyme elevation	3%	3%
Nausea	3%	2%
Hypokalemia	3%	2%
Insomnia	3%	2%
Headache	2%	2%

Table 3: Adverse reactions in ≥ 2% of patients in LEAP 2(oral dosing)[6]

Adverse Reaction	Lefamulin (n=368)	Moxifloxacin (n=368)
Diarrhea	12%	1%
Nausea	5%	2%
Vomiting	3%	1%
Hepatic enzyme elevation	2%	2%

In Phase 3 trials, lefamulin was associated with prolonged QT interval to a similar extent as moxifloxacin, and adverse effect was added by the FDA in the Warnings and Precautions section of the lefamulin labeling. The average increase in the corrected post-dose QTc interval on day 3 was 19.8 msec for lefamulin and 21.4 msec for moxifloxacin. Treatment was discontinued in one lefamulin-treated patient and 3 moxifloxacin-treated patients secondary to prolonged QTc intervals. However, patients at risk for or known to have QTc prolongation were excluded.

Lefamulin is metabolized by CYP3A4. Concomitant administration of lefamulin with CYP3A4 or p-glycoprotein (P-gp) inducers or inhibitors could affect serum concentrations.[6]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Clinical Cure
2) Symptom Relief
3) Mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Early clinical response rate at 96 hours

Table 4. Pharmacology and Pharmacokinetic Properties[6]

Parameter	
Mechanism of Action	Lefamulin is a systemic pleuromutilin antibacterial. It inhibits bacterial protein synthesis through interactions (hydrogen bonds, hydrophobic interactions, and Van der Waals forces) with the A- and P-sites of the peptidyl transferase center (PTC) in domain V of the 23s rRNA of the 50S subunit. The binding pocket of the bacterial ribosome closes around the mutilin core for an induced fit that prevents correct positioning of tRNA
Oral Bioavailability	25%
Distribution and Protein Binding	Protein binding 94.8% to 97.1%, volume of distribution of 86.1 L
Elimination	IV: 77.3% in feces and 15.5% in urine. Oral: 88.5% in feces and 5.3% in urine
Half-Life	8 hours
Metabolism	CYP3A4

Abbreviations: IV: intravenous; L: liter; CYP: cytochrome P450 enzyme

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. LEAP 1 Phase 3, MC, DB, AC, noninferiority RCT	1. Lefamulin 150 mg IV Q12H 2. Moxifloxacin 400 mg IV Q24H +/- Linezolid 600 mg IV Q12h Duration 5-10 days *Patients could be switched from IV to oral at the discretion of the investigator*	Demographics: -Mean age 60 y -~60% male -86% white -72% PORT risk class 2 -60% *S. pneumoniae* Key Inclusion Criteria: - Age ≥ 18 y - LRTI with ≥3 of the following: dyspnea, cough, purulent sputum chest pain, and ≥2 vital sign abnormalities - radiographically documented pneumonia - PORT class ≥3 and requires IV therapy Key Exclusion Criteria: - Concomitant antibiotics - hospitalized for ≥2 days within past 90 or resides in a nursing home or LTCF - suspected resistant pathogens - prolonged QT interval or risk factors for TdP (hypokalemia, cardiac disease), strong P-gp or CYP3A4 inhibitor or inducer - CNS disorders - CrCl < 30mL/min - hepatic disease	ITT: 1. 276 2. 275 PP: 1. 247 2. 248 Attrition: 1. 29 (10.5%) 2. 27 (9.8%)	ECR (responder rate at 96H): 1. 241 (87.3%) 2. 248 (90.2%) RD -2.9%; (95% CI -8.5 to 2.8%)* Investigator-assessed clinical response (5-10 days after last dose): 1. 223 (81.7%) 2. 230 (84.2%) RD -2.6%; (95% CI -8.9 to 3.9&)* *met noninferiority margins	NA NA	Discontinuations due to adverse event(s): 1. 8 (3.9%) 2. 11 (4%) Infusion site pain or phlebitis: 1. 14 (5.1%) 2. 3 (1.1%)	NS NA	**Risk of Bias (low/high/unclear)**: Selection Bias: high: unclear randomization procedures; baseline differences noted in age, mean procalcitonin, and rates of bacteremia Performance Bias: low: double-dummy design Detection Bias: unclear: unclear blinding of outcome assessors Attrition Bias: unclear: attrition similar between groups but slightly high (>10%) for a short-term study. Several treatment discontinuations not adequately explained. Reporting Bias: high: low rate of IV to oral transition in lefamulin group (38%) and moxifloxacin (44%) not explained. The FDA primary endpoint was only analyzed in the ITT group, rather than both ITT and per protocol for a non-inferiority trial. Other Bias: high: All manuscript authors are Nabriva employees or consultants; trial funded by Nabriva. The protocol amendment complicates interpretation of results. Over 50% of subjects had a documented protocol deviation. **Applicability**: Patient: Significant exclusion criteria limits generalizability of patient population. Less than 1% of patients were from North America Intervention: FDA-approved dose/frequency Comparator: Beta-lactam +/- macrolide recommended first-line therapy Outcomes: ECR is an appropriate outcome, though these short-term surrogate indicators use subjective criteria. Information regarding results of late follow-up visit were not reported or listed as an endpoint. Setting: 66 study sites in 18 countries. 79% Eastern Europe, few sites in North America (<1%)

2.LEAP 2 Phase 3, MC, DB, AC, noninferiority RCT	1. Lefamulin 600 mg oral Q12H for 5 days 2. Moxifloxacin 400 mg oral Q24H for 7 days	Demographics: -Mean age 57 y -~52% male -86% white -50% PORT risk class 2 -37% PORT class 3 -63.7% *S. pneumoniae* Key Inclusion Criteria: - Age ≥ 18 y - LRTI with ≥3 of the following: dyspnea, cough, purulent sputum chest pain, and ≥2 vital sign abnormalities, - radiographically documented pneumonia - PORT class of 2-4 and a candidate for oral therapy Key Exclusion Criteria: See LEAP 1	ITT: 1. 370 2. 368 PP: 1. 345 2. 340 Attrition: 1. 23 (6.2%) 2. 28 (7.6%)	ECR (responder rate at 96H): 1. 336 (90.8%) 2. 334 (90.8%) RD 0.1%; (95% CI -4.4 to 4.5%)* Investigator-assessed clinical response (5-10 days after last study dose): 1. 322 (87.5%) 2. 328 (89.1%) RD -1.6%; (95% CI -6.3 to 3.3%)* *met noninferiority margin	 NA NA	Discontinuations due to adverse event(s): 1. 11 (3%) 2. 8 (2.2%) NS 28-day mortality 1. 3 (0.8%) 2. 3 (0.8%) NS	 NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: high: unclear randomization/allocation concealment procedures; baseline differences noted in sex, and enrollment region. Race/ethnicity designation may have been misclassified, given methods to collect these data may not have been consistent across sites Performance Bias: low: double-dummy design Detection Bias: unclear: unknown blinding of outcome assessors Attrition Bias: low: attrition similar between groups and overall low Reporting Bias: high: The FDA primary endpoint was only analyzed in the ITT group, rather than both ITT and per protocol for a non-inferiority trial. Other Bias: unclear: All manuscript authors are Nabriva employees or consultants and the trial was funded by Nabriva, presenting potential for conflicts of interest. **Applicability**: Patient: Significant exclusion criteria limits generalizability of patient population to those with common comorbidities and only 3% of patients from United States. Patients with suspected MRSA excluded Intervention: See LEAP 1 Comparator: See LEAP 1 Outcomes: See LEAP 1 Setting: 66 study sites in 18 countries. 60% Eastern Europe, limited sites in United States (3%)

Abbreviations [alphabetical order]: AC = active control; ARR = absolute risk reduction; CI = confidence interval; CNS = central nervous system; CrCl = creatinine clearance; DB = double blind; ECR = early clinical response; H = hours; ITT = intention to treat; IV = intravenous; LRTI = lower respiratory tract infection; LTCF = long-term care facility; mITT = modified intention to treat; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; PORT = pneumonia outcomes research team; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; TdP = Torsades de pointes; y = years.

References:

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2. File TM, Goldberg L, Das A, et al. Efficacy and Safety of Intravenous-to-oral Lefamulin, a Pleuromutilin Antibiotic, for the Treatment of Community-acquired Bacterial Pneumonia: The Phase III Lefamulin Evaluation Against Pneumonia (LEAP 1) Trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;69(11):1856-1867.
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5. FDA Center for Drug Evaluation and Research. Lefamulin: Multi-Discipline Review. Application Number 211672Orig1s000. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211673.
6. XENLETA (lefamulin) Precribing Information. Nabriva Therapeutics. Ireland DAC. 8/2019.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XENLETA (lefamulin) injection, for intravenous use
XENLETA (lefamulin) tablets, for oral use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

XENLETA is a pleuromutilin antibacterial indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms. (1.1)

To reduce the development of drug resistant bacteria and maintain the effectiveness of XENLETA and other antibacterial drugs, XENLETA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)

DOSAGE AND ADMINISTRATION

- For treatment of adults with CABP, the recommended dosage of XENLETA is as follows:

Dosage	Treatment Duration
150 mg every 12 hours by intravenous infusion over 60 minutes* (2.1)	5 to 7 days
600 mg orally every 12 hours. (2.1)	5 days

*With the option to switch to XENLETA Tablets 600 mg every 12 hours to complete the treatment course.

- Patients with Hepatic Impairment: Reduce the dosage of XENLETA Injection to 150 mg infused over 60 minutes every 24 hours in patients with severe hepatic impairment (Child-Pugh Class C). XENLETA Tablets have not been studied in and are not recommended for patients with moderate (Child-Pugh Class B) or severe hepatic impairment (2.2).
- Administration Instruction for XENLETA Tablets: Take at least 1 hour before a meal or 2 hours after a meal. Swallow XENLETA Tablets whole with water (6 to 8 ounces). (2.3)
- Administration Instruction for XENLETA Injection: Infuse over 60 minutes. (2.3)
- See Full Prescribing Information for additional information on the administration and preparation of XENLETA Tablets and Injection. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection
- A single-dose clear glass vial containing 150 mg of lefamulin in 15 mL of 0.9% sodium chloride for further dilution prior to intravenous infusion. (3)

Tablets
- 600 mg of lefamulin. (3)

CONTRAINDICATIONS

- XENLETA is contraindicated in patients with known hypersensitivity to lefamulin, pleuromutilin class drugs, or any of the components of XENLETA. (4.1)
- Concomitant use of XENLETA tablets with CYP3A substrates that prolong the QT interval is contraindicated. (4.2)

WARNINGS AND PRECAUTIONS

- QT Prolongation: Avoid use in patients with known QT prolongation, ventricular arrhythmias including torsades de pointes, and patients receiving drugs that prolong the QT interval such as antiarrhythmic agents. (5.1)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.2, 8.1, 8.3)
- *Clostridium difficile*-associated Diarrhea (CDAD): Evaluate patients who develop diarrhea. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) are:
- XENLETA Injection: administration site reactions, hepatic enzyme elevation, nausea, hypokalemia, insomnia, headache. (6.1)
- XENLETA Tablets: diarrhea, nausea, vomiting, hepatic enzyme elevation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Nabriva Therapeutics US, Inc. at 1-855-5NABRIVA or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

XENLETA Injection	
Strong or moderate CYP3A inducers or P-gp inducers	Avoid XENLETA unless the benefit outweighs the risk. Monitor for reduced efficacy. (7.1)
XENLETA Tablets	
Strong or moderate CYP3A inducers or P-gp inducers	Avoid XENLETA unless the benefit outweighs the risk. Monitor for reduced efficacy. (7.1)
Strong CYP3A inhibitors or P-gp inhibitors	Avoid XENLETA. (7.1)
Moderate CYP3A inhibitors or P-gp inhibitors	Monitor for adverse reactions. (7.1)
CYP3A substrates that prolong the QT interval	Concomitant use is contraindicated. (4.2, 7.2)
Midazolam and other sensitive CYP3A substrates	Monitor for adverse reactions. (7.2)

USE IN SPECIFIC POPULATIONS

Lactation: A lactating woman should pump and discard human milk for the duration of treatment with XENLETA and for 2 days after the final dose. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2019

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluations: Biologics for Autoimmune Conditions

Date of Review: February 2020

Generic Names: upadacitinib
risankizumab-rzaa

Date of Last Review: January 2019
Dates of Literature Search: 09/01/2018 – 10/23/2019
Brand Name (Manufacturer): Rinvoq™ (AbbVie, Inc.)
Skyrizi™ (AbbVie, Inc.)
Dossiers Received: yes

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

Purpose for Class Update: New comparative evidence for existing biologics for autoimmune conditions will be reviewed. In addition, safety and efficacy for two new biologic response modifiers recently approved by the United States (U.S.) Food and Drug Administration (FDA) will be evaluated. Oral upadacitinib is approved for treatment of adult patients with moderate-to-severe rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX). Risankizumab-rzaa is approved for subcutaneous administration in the treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy.

Research Questions:
1. Is there new comparative evidence that biologic response modifiers differ in effectiveness for alleviating symptoms and stabilizing disease in patients with RA, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), or PsO?
2. Is there new comparative evidence that biologic response modifiers differ in harms?
3. Are there specific subpopulations for which one agent is better tolerated or more effective than other available agents?
4. Is upadacitinib safer or more effective then currently available agents for the treatment of adult patients with moderate-to-severe RA?
5. Is risankizumab-rzaa safer or more effective than currently available agents for the treatment of moderate-to-severe PsO?

Conclusions:
CLASS UPDATE
- The Health Evidence Review Commission (HERC) restructured the Prioritized List of Health Services in 2019. Consequently, moderate-to-severe Hidradenitis Suppurativa (HS) is now funded on line 419, effective January 2020.[1] Per Guideline Note 198, initial treatment of moderate-to-severe HS with adalimumab is limited to adults whose disease has not responded to at least a 90-day trial of conventional therapy (e.g., oral antibiotics), unless such a trial is not tolerated or contraindicated.[2]

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- Three new high quality systematic reviews evaluating safety and efficacy of specific biologic agents in CD and RA have been published since the last class update.[3-5]
- A Cochrane review evaluated the efficacy and safety of certolizumab pegol for the induction of remission in CD.[3] Moderate quality evidence showed certolizumab pegol was superior to placebo for achieving clinical remission [Relative Risk (RR) 1.36, 95% Confidence Interval (CI) 1.11 to 1.66] and clinical response at week 8 (RR 1.29, 95% CI 1.09 to 1.53).[3] Serious adverse events included worsening Crohn's disease, infections, and malignancy. Moderate quality evidence revealed serious adverse events occurred in 8.7% and 6.2% of participants in the certolizumab pegol and the placebo groups, respectively, but the difference was not statistically significant (RR 1.35, 95% CI 0.93 to 1.97).[3]
- A high quality systematic review and meta-analysis evaluated infection risk associated with Janus kinase (JAK) inhibitors administered in RA patients.[4] Estimated risk ratios of serious infections compared with placebo were not statistically significant: 1.22 (95% CI 0.60 to 2.45) for tofacitinib, 0.80 (95% CI 0.46 to 1.38) for baricitinib, and 1.14 (95% CI 0.24 to 5.43) for upadacitinib.[4] The estimated risk ratios of herpes zoster compared with placebo were 1.38 (95% CI 0.66 to 2.88) for tofacitinib, 2.86 (95% CI 1.26 to 6.50) for baricitinib and 0.78 (95% CI 0.19 to 3.22) for upadacitinib.[4] These data indicate a statistically significant difference in the risk of herpes zoster with baricitinib compared with placebo that is not seen with tofacitinib or upadacitinib.[4] Absolute values were not reported.
- A high quality systematic review and meta-analysis evaluated the impact of JAK inhibitors on risk of cardiovascular events (CVEs) in patients with RA.[5] No significant difference was observed regarding all CVE risks following JAK inhibitor administration ranging from 12 to 24 weeks [Odds Ratio (OR) 1.04, (95% CI 0.61 to 1.76), P=0.89].[5] There was no significant difference in incidence of major adverse cardiovascular events (MACEs); [OR 0.80 (95 % CI 0.36 to 1.75), P=0.57] or venous thromboembolism events (VTEs); [OR 1.16, (95 % CI 0.48 to 2.81), p = 0.74] with JAK inhibitor treatment.[5] Dose-dependent impact of JAK inhibitors on the risks of all CVEs, MACEs and VTEs was not observed with tofacitinib (5 mg vs.. 10 mg) or upadacitinib (15 mg vs.. 30 mg), whereas baricitinib 2 mg was found to be safer than 4 mg in all CVE incidence [OR 0.19 (95% CI 0.04 to 0.88), p = 0.03].[5] In summary, the existing evidence from randomized clinical trials (RCTs) could not identify significant short-term cardiovascular risk for JAK inhibitor-treated RA patients.[5] However, post-marketing data are needed to ascertain the cardiovascular safety of JAK inhibitors because of increased risk of VTE found for baricitinib at the higher 4 mg dose.[5]
- New comparative studies for selected biologics are summarized in **Table 4**, and trial abstracts are presented in **Appendix 3**.
- In the past year, the National Institute for Health and Care Excellence (NICE) developed guidance documents for tildrakizumab certolizumab pegol and risankizumab.[6-8] Tildrakizumab, certolizumab pegol or risankizumab are recommended as options for treatment of PsO in adults if PsO is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10; and PsO has not responded to other systemic treatments, including cyclosporine, MTX and phototherapy, or these options are contraindicated or not tolerated.[6-8]
- The American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guidelines for the management and treatment of psoriasis with biologics were published April 2019.[9] High quality evidence supports the use of etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, or tildrakizumab at FDA-approved dosing, as monotherapy treatment options in adult patients with moderate-to-severe PsO.[9]
- Expanded indications were FDA-approved for the following medications:
    - ustekinumab for treatment of moderately to severely active ulcerative colitis
    - rituximab for treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children 2 years of age and older in combination with glucocorticoids
    - certolizumab pegol for treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation
    - apremilast for treatment of oral ulcers associated with Behcet's Disease
    - ixekizumab for treatment of adults with AS

- tildrakizumab for use in moderate-to-severe PsO for adults
- belimumab for use in patients aged 5 years and older with active, autoantibody-positive, Systemic Lupus Erythematosus (SLE) who are receiving standard therapy.

UPADACITINIB

- Four phase 3 studies were submitted to the FDA for approval of upadacitinib.[10] Upadacitinib was compared to placebo, MTX, and adalimumab administered over 12 to 14 weeks.
- The SELECT-NEXT trial evaluated the efficacy and safety of upadacitinib compared to placebo over 12 weeks in 661 RA patients who had inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).[11] Moderate quality evidence showed more patients in the upadacitinib 15 mg (64%) and 30 mg (66%) treatment groups met the co-primary endpoint of 20% response on the American College of Rheumatology assessment (ACR20) at week 12 compared with 36% in the placebo group [15 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, Number Needed to Treat (NNT)=4; 30 mg vs. placebo difference=31%, (95% CI 22 to 30), P<0.0001, NNT=4].[11] Moderate quality evidence showed similar results with the co-primary endpoint of Disease Activity Score/C-Reactive Protein (DAS28-CRP) less than or equal to 3.2 at week 12 in the patients receiving upadacitinib 15 mg (48%) and 30 mg (48%) compared with 17% of patients in the placebo group [15 mg vs. placebo difference=29%, (95% CI 19 to 38), P<0.0001, NNT=4; 30mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4].[11]
- The SELECT-BEYOND trial used a similar study design to evaluate upadacitinib in 499 RA patients who had inadequate response to at least one biologic disease modifying antirheumatic drugs (bDMARD).[12] Moderate quality evidence showed more patients in the upadacitinib 15 mg (65%) and 30 mg (56%) treatment groups met the co-primary endpoint of ACR20 at week 12 compared with 28% in the placebo group [15 mg vs. placebo difference=37%, (95% CI 26 to 46), P<0.0001, NNT=3; 30 mg vs. placebo difference=28%, (95% CI 18 to 38), P<0.0001, NNT=4].[12] Significantly more patients met the co-primary endpoint of DAS28-CRP less than or equal to 3.2 at week 12 in the upadacitinib 15 mg (43%) and 30 mg (42%) groups compared with 14% in the placebo group [15 mg vs. placebo difference=29%, (95% CI 20 to 30), P<0.0001, NNT=4; 30 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4, moderate quality evidence).[12]
- The SELECT-COMPARE trial evaluated the efficacy and safety of upadacitinib compared to placebo and adalimumab in 1,629 patients with active RA on stable doses of MTX but with inadequate response to MTX.[13] Moderate quality evidence showed more patients in the upadacitinib 15 mg (71%) treatment group met the co-primary endpoint of ACR20 at week 12 compared with 36% in the placebo group [15 mg vs. placebo difference=34%, (95% CI 29 to 39), P≤0.001, NNT=3).[13] More patients met the co-primary endpoint of DAS28-CRP less than 2.6 at week 12 in the upadacitinib 15 mg group (29%) compared with 6% in the placebo group [15 mg vs. placebo difference=23%, (95% CI 19 to 27), P≤0.001, NNT =5; moderate quality evidence].[13] A DAS score of 2.6 is considered to correspond to remission. Moderate quality evidence demonstrated more patients receiving upadacitinib achieved ACR20 (79%) and DAS28-CRP less than 2.6 (29%) compared with 63% of patients who achieved ACR 20 with adalimumab and 11% who achieved DAS28-CRP less than 2.6 with adalimumab [ACR 20 upadacitinib vs. adalimumab difference=8%, (95% CI 1.2 to 13.8), P≤0.05, NNT=13 and DAS28-CRP upadacitinib vs. adalimumab difference=11%, (95% CI 5 to 16), P≤0.001, NNT=10).[13]
- The SELECT-MONOTHERAPY trial evaluated the efficacy and safety of switching to upadacitinib monotherapy compared with continuing MTX in 648 patients with an inadequate response to MTX.[14] Eligible patients must have shown active disease despite treatment with MTX, defined as at least six swollen joints out of 66, at least six tender joints out of 68, and more than 3 mg/L C-reactive protein (upper limit of normal 2.87 mg/L).[14] Patients were randomly assigned in a 1:1:1 ratio to receive upadacitinib 15 mg, upadacitinib 30 mg, or stabilized dose of MTX for 14 weeks. Based on moderate quality evidence, both upadacitinib groups had more responders at week 14 for the ACR20 response [15 mg (68%) and 30 mg (71%)] compared with the MTX group [15 mg vs. MTX difference=27%, (95% CI 18 to 36), P<0.0001, NNT=4; 30 mg vs. MTX difference=30% (95% CI 21 to 30), p<0.0001, NNT=4].[14] For the co-primary endpoint of DAS28-CRP less than or equal to 3.2, similar results were observed [15 mg (45%) and 30 mg (53%)] compared to the MTX

cohort (19%) [15 mg vs. MTX difference=26%, (95% CI 16 to 33); P<0.001, NNT=4; 30mg vs. MTX difference=33%, (95% CI 25 to 42), P<0.001, NNT=3 moderate quality evidence).[14]

- Reported safety data from these Phase 3 trials demonstrated that patients treated with upadacitinib 15 mg experienced a 1% or greater frequency of adverse events compared to placebo, including upper respiratory infection, nausea, cough, and pyrexia [15] Patients treated with upadacitinib 30 mg experienced a higher percentage of adverse effects that led to study drug discontinuation compared to either the upadacitinib 15 mg or placebo groups.[10] The most common adverse effect leading to discontinuation of upadacitinib was pneumonia (15 mg: 0.5 events/100 patient years, 30 mg 0.9 event/100 patient years).[10] Upadacitinib prescribing information contains FDA Black Boxed warnings for serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections.[15] Other FDA Black Boxed warnings include risk of lymphoma and thrombosis associated with JAK inhibitor administration.[15]
- There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with upadacitinib compared to other treatments for moderate to severe RA.

RISANKIZUMAB

- The efficacy and safety of risankizumab in patients with moderate-to-severe plaque PsO was evaluated in 2 similar double-blind, randomized, placebo-controlled and ustekinumab-controlled phase 3 trials (UltIMMa-1 and UltIMMa-2).[16] The primary objective of the 2 studies was to demonstrate superiority of risankizumab over placebo and ustekinumab. In a third phase 3 study, the IMMVent trial, risankizumab was compared with adalimumab in patients with moderate-to-severe PsO.[17]
- In both the UltIMMa-1 and UltIMMa-2 trials, more risankizumab-treated patients, compared with those receiving placebo or ustekinumab, achieved the co-primary endpoints of 90% improvement in the PASI-90 and achievement of 0 or 1 (clear or almost clear) on the static Physician's Global Assessment (sPGA scale) at week 16. Moderate quality evidence showed at week 16 in the UltIMMa-1 trial, PASI-90 was achieved by 75.3% risankizumab-treated patients compared with 4.9% placebo-treated patients and 42% ustekinumab-treated patients [risankizumab vs. placebo difference=70%, (95% CI 64 to 76), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=33%, (95% CI 22 to 44), p<0.0001, NNT=3].[16] In UltIMMa-2, 74.8% risankizumab-treated patients, compared with 2% placebo-treated patients and 47.5% ustekinumab-treated patients, achieved PASI-90 [risankizumab vs. placebo difference=72%, (95% CI 66 to 78), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=27%, (95% CI 16 to 38), p<0.0001, NNT=4, moderate quality evidence].[16] In UltIMMA-1, moderate quality evidence showed sPGA 0 or 1 was achieved by 87.5% of patients receiving risankizumab versus 7.8% receiving placebo and 63% receiving ustekinumab [risankizumab vs. placebo difference=79%, (95% CI 73 to 86), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=25%, (95% CI 15 to 35), p<0.0001, NNT=4].[16] Similar results were observed in UltIMMA-2, as sPGA 0 or 1 at week 16 was observed in 83.7% of patients receiving risankizumab versus 5.1% receiving placebo and 61.6% receiving ustekinumab [risankizumab vs. placebo difference=78%%, (95% CI 72 to 84), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=22%, (95% CI 12 to 32), p<0.0001, NNT=5, moderate quality evidence].[16]
- In the IMMVent trial at week 16, PASI 90 was achieved in 72% patients given risankizumab and 47% of patients given adalimumab (adjusted absolute difference 24.9% [95% CI 17.5 to 32.4%; p<0.0001]), and sPGA scores of 0 or 1 were achieved in 84% of patients given risankizumab and 60% patients given adalimumab (adjusted absolute difference 23.3% [95% CI 16.6–30.1; p<0.0001, moderate quality evidence]).[17]
- Analyses of the reported safety data from Phase 3 trials demonstrates that risankizumab-treated subjects experienced a 1% or greater frequency of adverse events compared to placebo, including upper respiratory infections, headache, fatigue, injection site reactions and tinea infections.[18]
- There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with risankizumab compared to other treatments for moderate to severe PsO.

Recommendations:

- Modify prior authorization (PA) criteria to reflect revisions to the Oregon Health Authority (OHA) Prioritized List of Health Services. Effective January 2020, adalimumab is funded for treatment of moderate-to-severe Hidradenitis suppurativa (HS) per Guideline Note 198.
- Modify PA criteria to reflect updated indications and age ranges for specific biologic response modifiers as follows:
    - Ustekinumab for treatment of moderately to severely active ulcerative colitis
    - Rituximab for treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children 2 years of age and older in combination with glucocorticoids
    - Upadacitinib for use in moderate-to-severe RA for adults
    - Certolizumab pegol for treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation
    - Apremilast for treatment of oral ulcers associated with Behcet's Disease
    - Ixekizumab for treatment of adults with AS
    - Tildrakizumab for use in moderate-to-severe PsO for adults
    - Belimumab for use in patients aged 5 years and older with active, autoantibody-positive, Systemic Lupus Erythematosus (SLE) who are receiving standard therapy
- No PDL changes recommended based on the clinical evidence. Maintain upadacitinib and risankizumab-rzaa as non-preferred drugs on the Oregon Health Plan Preferred Drug List (PDL).
- Evaluate comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

The last comparative review of biologic drugs for autoimmune conditions was presented to the Pharmacy and Therapeutics (P and T) Committee at the January 2019 meeting. Two biologic response modifiers, tildrakizumab and baricitinib, were added to the PA criteria for biologic agents. The preferred biologic agents on the PDL, adalimumab and etanercept, have broad indications for use including AS, JIA, PsO, PsA, and RA. Adalimumab is also approved for management of inflammatory bowel diseases including CD and UC. All the other drugs in the biologic class are non-preferred based on evidence presented at previous P and T meetings and require PA as outlined in **Appendix 4**.

OHP FFS Utilization:

In the third quarter of 2019, there were approximately 157 pharmacy claims for biologic agents in the fee-for-service (FFS) population. Seventy-seven percent of the claims were for the preferred agents etanercept and adalimumab. For the non-preferred agents, 1-3% of all claims were for ixekizumab, anakinra, tocilizumab, and ustekinumab, and 4-6% of claims were for tofacitinib, certolizumab, secukinumab, and apremilast. There were no pharmacy claims for brodalumab, canakinumab, guselkumab, or baricitinib.

Background:

<u>Rheumatoid Arthritis</u>

Rheumatoid arthritis is characterized by chronic inflammation of synovial tissues and progressive erosion of bone leading to joint destruction and disability. Approximately 1% of the general population is affected worldwide, and although RA may occur at any age, the peak incidence of onset is usually between the 4th and 6th decades, with females being 2- to 3-times more likely affected than males.[19] The 2015 American College of Rheumatology [20] and 2016 European League against Rheumatism (EULAR) [21] recommendations suggest that treatment begin with csDMARDs such as MTX as soon as diagnosis of RA is established.

The optimal dose of MTX is 25 mg once a week.[22] Patients who cannot tolerate this MTX dose because of adverse effects may improve with a lower dose.[23] Other csDMARDs include sulfasalazine, hydroxychloroquine, and leflunomide.

Biologic DMARDs or targeted synthetic DMARDs (tsDMARDs) are recommended for patients with a suboptimal response or intolerance to csDMARDs. Biologic DMARDs are proteins that must be administered parentally. Targeted synthetic DMARDs are small chemical molecules that can be given orally. The Janus kinase (JAK) inhibitors (tofacitinib, baricitinib, and upadacitinib) are classified as tsDMARDs. Monotherapy with bDMARDs or tsDMARDs or combination therapy that includes MTX can be initiated as second-line therapy, depending on the patient's response to previous therapy and any pertinent comorbidities. Over the past decade, management of RA has shifted from controlling symptoms to preventing and controlling joint damage.[24] Additionally, with the availability of bDMARDs and tsDMARDs, a "treat-to-target" approach is now recommended, where the goals of treatment include remission or low disease activity and maintenance of remission.[20] These goals have been shown to lead to better outcomes such as prevention of progression of joint damage and improved quality of life.[24]

Janus kinase inhibitors are among the newest class of treatments for RA. The JAK family plays important roles in the signalling pathways of various cytokines, growth factors, and hormones involved in immunity and hematopoiesis.[25] JAK proteins (JAK1, JAK2, and JAK3 and tyrosine kinase 2 [TYK2]) are signal-transduction factors involved in the downstream signaling of cytokines to their receptors on the cell surface and are implicated in the pathogenesis of RA.[25] Three JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have been approved by the FDA and each has a different inhibitory profile for the JAK proteins (see **Table 1**). Upadacitinib is a selective JAK1 inhibitor, which in theory should have less side effects than tofacitinib and baricitinib. JAK1 plays a major role in signaling of inflammatory mediators, such as IL-6 and interferon. JAK inhibitors are potent immunosuppressants, and there are a number of well-known safety issues associated with use of this class of medications, including serious infections, malignancy, lymphoproliferative disorders, gastrointestinal perforations, lymphopenia, neutropenia, anemia, and lipid elevations.[10] Based upon accumulating data regarding the risk of thrombosis with JAK inhibitors, thrombosis is now also considered a class safety issue with JAK inhibitors.[10] **Table 1** summarizes the different DMARDs FDA-approved for management of RA.

Table 1. FDA-Approved Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis Treatment[23]

Drug and Maintenance Dosing Recommendations	Molecular Target	Structure	Adverse Events
Conventional Synthetic DMARDs			
Methotrexate (10-25 mg once a week)	Dihydrofolate reductase	Small chemical molecule	Nausea, stomatitis, elevated LFTs, bone marrow suppression, teratogenicity
Sulfasalazine (Azulfidine®) (2-4 g once a day)	Folate		Cutaneous hypersensitivity, nausea, diarrhea, agranulocytosis, drug-induced lupus, azoospermia
Leflunomide (Arava®) (20mg once a day)	Pyrimidine		Diarrhea, hypertension, hypersensitivity, elevated LFTs, leukocytopenia, teratogenicity
Biologic DMARDs			
Etanercept (Enbrel®) (50 mg SC once a week)	TNF	Receptor antagonist	Infections, reactivation of TB, psoriasiform skin changes, exacerbation of demyelinating diseases, drug-induced lupus, non-melanoma skin cancer, injection site or infusion reactions
Infliximab (Remicade®) (3-10mg/kg IV every 6-8 weeks)		Chimeric monoclonal antibody	
Adalimumab (Humira®) (40 mg SC every 2 weeks)		Human monoclonal antibody	
Golimumab (Simponi®) (50 mg SC once a month or 2 mg/kg IV every 8 weeks)		Human monoclonal antibody	
Certolizumab pegol (Cimzia®) (200 mg SC every 2 weeks or 400mg every 4 weeks)		Humanized monoclonal antibody	
Tocilizumab (Actemra®) (162 mg SC every 1-2 weeks or 4-8 mg/kg IV every 4 weeks)	IL-6	Humanized monoclonal antibody	Infections, reactivation of TB, bowel perforation, hypersensitivity reactions, neutropenia, injection site reactions, hyperlipidemia
Sarilumab (Kevzara®) (150 mg-200 mg every 2 weeks)		Human monoclonal antibody	
Rituximab (Rituxan®) (1000 mg IV every 6 months)	B cell	Chimeric monoclonal antibody	Hypersensitivity reactions, reactivation of hepatitis B, leukocytopenia, progressive multifocal leukoencephalopathy, tumor lysis syndrome
Abatacept (Orencia®) (125 mg SC once a week or 750-1000 mg IV every 4 weeks)	T-lymphocyte	Receptor antagonist	Infections, reactivation of TB, leukocytopenia, injection site reactions
Anakinra (Kineret®) (100 mg SC once a day)	IL-1	Receptor antagonist	Infections, injection site pain
Targeted Synthetic DMARDs			
Tofacitinib (Xeljanz®) (10 mg once a day)	JAK 1,2,3	Small chemical molecule	Infections, reactivation of TB, herpes zoster, cytopenia, hyperlipidemia, CPK level increase
Baricitinib (Olumiant®) (2-4mg once a day)	JAK 1,2		
Upadacitinib (Rinvoq™) (15 mg once a day)	JAK 1		
Abbreviations: CPK = creatine phosphokinase; DMARD = Disease-Modifying Antirheumatic Drug; FDA = Food and Drug Administration; g = grams; IL = interleukin; IV = intravenous; JAK = Janus kinase; LFT = liver function tests; mg = milligrams; SC = subcutaneous; TB = tuberculosis; tumor necrosis factor = TNF			

Primary endpoints used in RA clinical trials include the ACR response, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Disease Activity Score 28 (DAS-28). The ACR response score is a composite endpoint with 7 domains used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is a considered a measure of efficacy and overall disease activity.[26] Patients are said to meet ACR 20 criteria when they have at least 20% reductions in tender joint counts, 20% reduction swollen joint counts and 20% improvement in at least 3 of the 5 remaining domains.[26] The additional 5 domains include patient global assessment of arthritis on a visual analog scale, physician global assessment of arthritis on a visual analog scale, patient assessment of pain on a visual analog scale, patient assessment of physical functioning (e.g., health assessment questionnaire), and acute phase reactant (ESR or CRP). ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in ACR criteria.[26] ACR 50 and 70 are considered more clinically significant than ACR 20.[26] The HAQ-DI is a widely used self-reported measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[27] The minimal clinically important difference (MCID) of an improvement on the HAQ-DI is a change of at least 0.22 from baseline.[12] The DAS-28 is another index of disease activity (similar to the ACR response). The DAS is a continuous composite outcome that consists of: 1) the number of painful joints (Ritchie Articular Index, 0-78 joints), 44-joint count for swollen joints, erythrocyte sedimentation rate (ESR) and patient global assessment of disease activity or general health using a visual analogue scale.[11] A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 of low disease activity. A DAS score of 2.6 is considered to correspond to remission.[28]

Plaque Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory disorder of the skin and/or joints that affects about 2 to 3% of the population.[29] Two peaks in age of onset have been reported: one at 20 to 30 years of age and a second peak at 50 to 60 years.[29] Plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis.[30] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of the body surface area and has little to no impact on quality of life or function. Mild PsO is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[31] Per NICE guidance, first-line agents for PsO include: topical medications including corticosteroids, vitamin D analogs (e.g., calcipotriene) , retinoids (e.g., tazarotene) or calcineurin inhibitors (e.g., tacrolimus or pimecrolimus).[32] Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy. Systemic non-biologic treatments are recommended for patients with moderate-to-severe PsO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin. Biologics may be added for patients with moderate-to-severe PsO not controlled by other therapies. Injectable biologic agents used to treat PsO include adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab. An oral phosphodiesterase 4 (PD4) inhibitor, apremilast, is also approved for treatment of moderate-to-severe PSO. All the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression.[29] The various DMARDs FDA-approved to treat PsO are compared in **Table 2.**

Table 2. FDA approved Disease-Modifying Antirheumatic Drugs for Plaque Psoriasis[29]

Drug	Molecular Target	Approved Age Range for PsO	Maintenance Dosing	Warnings
Adalimumab (Humira®)	TNF	Adults	40 mg SC every other week	Serious Infections*, Malignancies including Lymphoma
Etanercept (Enbrel®)		Patients ≥ 4 years of age	50 mg SC once weekly (<63 kg, 0.8 mg/kg SC once weekly)	Serious Infections*, Malignancies including Lymphoma
Infliximab (Remicade®)		Adults	5 mg/kg IV every 8 weeks	Serious Infections*, Malignancies including Lymphoma
Certolizumab Pegol (Cimzia®)		Adults	400 mg SC every other week	Serious Infections*, Malignancies including Lymphoma
Ustekinumab (Stelara®)	IL-12 and IL-23	Patients ≥ 12 years of age	≤100 kg, 45 mg SC every 12 weeks >100 kg, 90 mg SC every 12 weeks	Serious Infections*, Malignancies including Lymphoma
Secukinumab (Cosentyx®)	IL-17	Adults	300 mg SC every 4 weeks	Crohn's Disease
Ixekizumab (Taltz®)			80 mg SC every 4 weeks	Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)
Brodalumab (Siliq™)			210 mg SC every 2 weeks	Suicide Ideation, REMS Program, Serious Infections*, Crohn's Disease
Guselkumab (Tremfya®)	IL-23	Adults	100 mg SC every 8 weeks	Upper respiratory infections, tinea infections, and herpes simplex infections
Tildrakizumab (Ilumya™)			100 mg SC every 12 weeks	
Risankizumab-rzaa (Skyrizi™)			150 mg SC every 12 weeks	
Apremilast (Otezla®)	PDE-4	Adults	30 mg orally twice daily	Worsening depression

Abbreviations: IL=interleukin; IV=intravenous; PASI=Psoriasis Area and Severity Index; PDE=phosphodiesterase; SC = subcutaneous; TNF= tumor necrosis factor
*Serious Infections include: bacterial sepsis, tuberculosis, invasive fungal and opportunistic infections

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the Psoriasis Area and Severity Index (PASI), the static Physician's Global Assessment scale (sPGA), or the Psoriasis Symptom Inventory (PSI). There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[33] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head, arms and legs, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[33,34] It does not take into account symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[33] In addition, though the PASI evaluates symptoms on a range of 0 to 72 points, in clinical practice, patients often do not have scores greater than 40.[34] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the

PASI score. However, an improvement of 100%, indicating complete disease clearance, is considered more clinically significant.[35] The sPGA is another physician-reported symptom severity scale which evaluates symptom severity at a single point in time with higher scores indicating more severe disease (range 0 to 5).Responders to therapy are typically defined as patients with a sPGA score of 0 or 1, corresponding to clear or almost clear skin or patients with an improvement of at least 2 points. In clinical trials of patients with moderate to severe disease, the proportion of patients with a sPGA score of 0 or 1 has a strong correlation with a 75% improvement in PASI.[35] Finally, the PSI evaluates patient-reported rather than physician-assessed symptoms. Eight individual symptoms in the prior 24 hours are assessed including itching, redness, scaling, burning, stinging, cracking, flaking and pain.[35] Individual symptoms are rated from 0 to 4 with total scores ranging from 0 to 32 points.[35] Patients with total scores of 8 or less with no single item rated greater than 1 are generally considered responders to therapy.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic inflammatory skin disease which has a prevalence of 1-4% worldwide and is 3 times more common in women than men.[36,37] The mean age of onset is 22 years. It is characterized by inflamed nodules which occur most frequently in the axillary, inguinal, and anogenital regions of the body.[36,37] These nodules are painful, recurrent, and can result in abscesses, chronic draining sinus tracts, scarring, disfigurement, and disability. Genetic predisposition, hormonal factors, immune factors, medications such as lithium and medroxyprogesterone acetate, obesity, and smoking all are potential contributors to the etiology.[37]

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.[38] About 69% of patients have stage 1 disease, while approximately 28% and 4% of patients have more severe stage 2 and 3 disease.[38] The minimum clinically significant change in Hurley staging is unclear.[39]

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.[37] Surgical treatment may also be an option for Hurley stage 2 and 3 patients.[37] Pharmacological treatments for HS include antibiotics, retinoids, corticosteroids, and immunosuppressive agents such as tumor necrosis factor (TNF)-alpha inhibitors.[37,38] However, the most commonly used treatments are topical and oral antibiotics.[40] Antibiotics can be used both for the acute treatment of an infected area as well as for maintenance treatment.[36,37,41] The most commonly used oral antibiotic treatments are tetracyclines.[40]

TNF-alpha inhibitors are often reserved for patients with moderate to severe HS (e.g. Hurley Stage II or Hurley Stage III).[37,38] 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.[40] 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.[40] Adalimumab was approved for moderate to severe HS in September 2015 and is the only medication FDA-approved for this condition.[42] In October 2018, the indication was expanded to include patients age 12 years and older, with varied dosing based on weight.[42]

A review of the safety and efficacy of adalimumab in treating HS was presented to the P and T committee at the November 2018 meeting. At that time, medical therapy for HS was not funded by the OHA. However, in 2019 the HERC restructured the Prioritized List of Health Services. Moderate-to-severe HS is now funded on line 419, effective January 2020.[1] Mild HS is included on Line 514 and remains unfunded.[2] Per Guideline Note 198, initial treatment of moderate-to-severe HS with adalimumab is limited to adults whose disease has not responded to at least a 90-day trial of conventional therapy (e.g., oral antibiotics), unless such a trial

is not tolerated or contraindicated.[2] Treatment with adalimumab after 12 weeks is only included on Line 419 for patients with a clear evidence of response, defined as: a) a reduction of 25% or more in the total abscess and inflammatory nodule count, AND b) no increase in abscesses and draining fistulas.[2]

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

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

Systematic Reviews:
After review, 6 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). [43-49]

Certolizumab pegol for induction of remission in Crohn's disease
A high quality Cochrane review published in August 2019 evaluated the efficacy and safety of certolizumab pegol for the induction of remission in CD.[3] The literature search was conducted through January 28, 2019. The main outcomes selected for analysis were clinical remission at week 8 (Crohn's Disease Activity Index [CDAI] P150), clinical response at week 8 (CDAI reduction Q 100 or clinical remission), and serious adverse events.[3] Four studies involving 1,485 participants with moderate- to-severe CD met the inclusion criteria and were used in the meta-analyses.[3] All 4 studies were randomized, double-blind, placebo-controlled multicenter trials sponsored by UCB Inc., the manufacturer of certolizumab pegol. One study was identified as high risk of bias due to a non-identical placebo while the other studies were judged to be at low risk of bias.[3]

Clinical remission at week 8 was achieved in 26.9% (225/835) of patients prescribed certolizumab pegol 100-400 mg every 2 to 4 weeks compared to 19.8% (129/650) in the placebo group, (RR 1.36, 95% CI 1.11 to 1.66; moderate certainty evidence).[3] Clinical response at week 8 was achieved in 40.2% (336/835) and 30.9% (201/650) of participants in the certolizumab pegol and the placebo groups, respectively (RR 1.29, 95% CI 1.09 to 1.53; moderate certainty evidence).[3] Serious adverse events were observed in 8.7% (73/835) and 6.2% (40/650) of participants in the certolizumab pegol and the placebo groups, respectively (RR 1.35, 95% CI 0.93 to 1.97; moderate certainty evidence).[3] Serious adverse events included worsening CD, infections, and malignancy.

In summary, moderate certainty of evidence suggests that certolizumab pegol is effective for induction of clinical remission and clinical response in people with moderate-to-severe CD. It is uncertain whether the risk of serious adverse events differs between certolizumab pegol and placebo as the 95% CI includes the possibility of a small decrease or doubling of events.[3]

Infection risk with JAK inhibitors

A high quality systematic review and meta-analysis of infection risk associated with JAK inhibitors in RA patients was published in April 2019.[4] Data from 21 trials were included in a meta-analysis of the risk for serious infection and herpes zoster associated with JAK inhibitor therapy. Eleven trials assessed tofacitinib (5,888 patients), 6 trials assessed baricitinib (3,520 patients), and 4 trials included upadacitinib (1,736 patients).[4] Assessment of study validity revealed few sources of bias.[4] All studies reported randomization and blinding of participants and clinical assessors.[4] Half of the trials did not describe methods of allocation concealment, and 3 studies did not account for incomplete outcome data.[4] The majority of the studies included patients with an inadequate response to DMARDs.[4] Six of the eleven tofacitinib trials and all of the baricitinib and upadacitinib trials recruited patients on background stable doses of MTX.[4] Patients were distributed globally.[4] Sixteen studies recruited patient from Asia, including three Japanese bridging studies.[4]

Estimates of serious infection incidence rates per 100 patient-years were 1.97 (95% CI 1.41 to 2.68) for tofacitinib, 3.16 (95% CI 2.07 to 4.63) for baricitinib, and 3.02 (95% CI 0.98 to 7.04) for upadacitinib.[4] In the pooled placebo group, estimates of incidence rates were 2.50 (95% CI 1.74 to 3.48) per 100 person-years, derived from 1.19 (95% CI 0.51 to 2.34) from the tofacitinib placebo group, 4.09 (95% CI 2.65 to 6.04) from baricitinib, and 1.75 (95% CI: 0.21 to 6.32) from upadacitinib.[4] The estimated incident risk ratios of serious infections compared with placebo in per protocol analyses were not statistically significant: 1.22 (95% CI 0.60 to 2.45) for tofacitinib, 0.80 (95% CI 0.46 to 1.38) for baricitinib and 1.14 (95% CI 0.24 to 5.43) for upadacitinib.[4]

The estimated incidence rates per 100 patient-years of herpes zoster were 2.51 (95% CI 1.87 to 3.30) for tofacitinib, 3.16 (95% CI 2.07 to 4.63) for baricitinib, and 2.41 (95% CI 0.66 to 6.18) for upadacitinib.[4] In the pooled placebo group, the incidence rate was 1.22 (95% CI 0.71 to 1.95) per 100 patient-years.[4] There were 8 serious or disseminated cases (4 with tofacitinib and 4 with baricitinib) versus 3 in the pooled placebo group.[4] Overall, these data indicate a statistically significant difference in the risk of herpes zoster with baricitinib compared with placebo (RR 2.86; 95% CI 1.26 to 6.50) that is not seen with tofacitinib (RR 1.38; 95% CI 0.66 to 2.88) or upadacitinib (RR 0.78; 95% CI 0.19 to 3.22).[4] While a statistically significant increase was not apparent with tofacitinib or upadacitinib, due to levels of uncertainty in the estimates, a true effect cannot be ruled out.[4] There are several considerations when interpreting these results. The increasing incidence of herpes zoster with age is well recognized.[4] It is a critical confounder and subtle differences in age distribution from these clinical trials could cause significant differences in herpes zoster events.[4] A geographic variation in rates of herpes zoster with JAK inhibitors exists, with highest rates seen in Japan and Korea.[4] This is relevant when examining data extrapolated from studies across different geographical regions.[4] A quarter of the studies in this meta-analysis did not recruit from countries in Asia, which may contribute to a lower overall incidence of herpes zoster.[4]

Cardiovascular event risk with JAK inhibitors

In August 2019, a high quality systematic review and meta-analysis evaluated the impact of JAK inhibitors on risk of cardiovascular events in patients with RA.[5] The literature search was conducted through October 2018. The primary outcome was the relationship between JAK inhibitors and all cardiovascular events.[5] The duration of therapy with JAK inhibitors ranged from 12 to 24 weeks. The secondary outcomes evaluated MACEs and VTEs, including pulmonary embolism (PE) and deep vein thrombosis (DVT).[5] Twenty-six RCTs (11,799 subjects) met inclusion criteria for the systematic review. No significant difference was observed regarding all CVEs risk following JAK inhibitor usage in general [OR 1.04 (95% CI 0.61 to 1.76), p = 0.89], tofacitinib [OR 0.63 (95% CI 0.26 to 1.54); p = 0.31], baricitinib [OR 1.21 (95% CI 0.51 to 2.83); p = 0.66], or upadacitinib [OR 3.29 (95% CI 0.59 to 18.44); p = 0.18].[5] Likewise, there was no significant difference for JAK inhibitor treatment overall regarding occurrence of MACEs [OR 0.80 (95 % CI 0.36 to 1.75); p = 0.57] or VTEs [OR 1.16 (95 % CI 0.48 to 2.81); p = 0.74].[5] Dose-dependent impact of JAK inhibitors on the risks of all CVEs, MACEs and VTEs were not observed with tofacitinib (5 mg vs. 10 mg) and upadacitinib (15 mg vs. 30 mg), whereas baricitinib 2 mg was found to be safer than 4 mg in all CVEs incidence [OR 0.19 (95% CI 0.04 to 0.88); p = 0.03].[5] In summary, evidence from RCTs indicate no significant short-term cardiovascular risk for JAK inhibitor-treated patients, but post-marketing data are needed to ascertain their long-term cardiovascular safety, especially at the higher doses, due to increased risk of VTE events for baricitinib at higher dosages.[5]

New Guidelines

NATIONAL INSTITUTE OF HEALTH AND CARE EXCELLENCE

The National Institute for Health and Care Excellence (NICE) has developed several guidance documents in the past year for recently marketed biologic agents approved to treat PsO. These guidelines are rated as high quality using the AGREE II Global Rating Scale. A systematic review process for new literature was performed and there was complete information to inform decision making. The recommendations are summarized below.

TILDRAKIZUMAB, CERTOLIZUMAB PEGOL, and RISANKIZUMAB

Guidance for treating moderate to severe PsO with tildrakizumab and certolizumab pegol was published in April 2019.[6,7] Guidance for treating moderate to severe PsO with risankizumab was published in August 2019.[8] Tildrakizumab, certolizumab pegol or risankizumab are recommended as options for treatment of PsO in adults if:

- PsO is severe, as defined by a total PASI of 10 or more and a DLQI of more than 10; and
- PsO has not responded to other systemic treatments, including cyclosporine, MTX and phototherapy, or these options are contraindicated or not tolerated.[6]
- Consider stopping tildrakizumab between 12 weeks and 28 weeks if there has not been at least a 50% reduction in the PASI score from when treatment started.[6]
- Stop tildrakizumab at 28 weeks if the PsO has not responded adequately. An adequate response is defined as:
  - 75% reduction in the PASI score from when treatment started; or
  - 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started.[6]
- Lowest maintenance dosage of certolizumab pegol should be used (200 mg every 2 weeks) after the loading dose.[7]
- Stop certolizumab pegol at 16 weeks if PsO has not responded adequately. An adequate response is defined as:
  - 75% reduction in the PASI score from when treatment started or
  - 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started.[7]
- Stop risankizumab treatment at 16 weeks if the PsO has not responded adequately. An adequate response is defined as:
  - 75% reduction in the PASI score from when treatment started or 50% reduction in the PASI score (PASI 50) and
  - 5-point reduction in DLQI from when treatment started.[8]
- If patients and their clinicians consider risankizumab to be one of a range of suitable treatments, including guselkumab, secukinumab and ixekizumab, the least expensive should be chosen (taking into account administration costs, dose, price per dose and commercial arrangements).[8]

AMERICAN ACADEMY OF DERMATOLOGY-NATIONAL PSORIASIS FOUNDATION

American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guidelines for the management and treatment of psoriasis with biologics were published in April 2019.[9] A multidisciplinary work group of psoriasis experts consisting of dermatologists, a rheumatologist, a cardiologist, and representatives from a patient advocacy organization was convened to update the previously published 2008 AAD psoriasis guidelines.[9] The focus of the recommendations are for the use of biologic agents in the treatment of psoriasis in adults. In accordance with American Academy of Dermatology (AAD) policy, a minimum 51% of work group members did not have any relevant conflicts of interest.[9] If a potential conflict was noted, the work group members recused themselves from discussion and drafting of recommendations pertinent to the topic area of interest.[9] The efficacy and safety of etanercept, infliximab, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab brodalumab, guselkumab, tildrakizumab, and risankizumab were evaluated as monotherapy or in combination with

other psoriasis therapies to treat moderate-to-severe psoriasis in adults.[9] A literature search was completed from January 1, 2008 through December 31, 2017 to guide development of the recommendations.

The Grade A recommendations, which are based on consistent and good-quality patient-oriented evidence, recommend etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, or tildrakizumab at FDA-approved dosing, as monotherapy treatment options in adult patients with moderate-to-severe PsO.[9]

Other recommendations to guide PsO treatment with biologics included:

- Certolizumab is likely to have class characteristics similar to those of other TNF-inhibitors (i.e., adalimumab, etanercept, and infliximab) regarding treatment combination, efficacy in difficult-to-treat areas, and possibly immunogenicity. However, there is no evidence available on these topics, and these statements are based on extrapolation of data from other TNF-inhibitors.[9]
- Recommendations to combine TNF inhibitors or ustekinumab with acitretin, MTX, apremilast, or cyclosporine to augment efficacy for the treatment of moderate-to-severe PsO is based on Grade B to C evidence (B=inconsistent or limited quality evidence; C = consensus or opinion based evidence). There is no evidence for systemic combination therapy with secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, or risankizumab.[9]
- Patients with a history of concomitant inflammatory bowel disease (IBD) might benefit from TNF-inhibitor therapy.[9] Adalimumab, infliximab, and certolizumab are approved for the treatment of IBD.[9]
- Patients with a history of concomitant multiple sclerosis or IBD might benefit from ustekinumab therapy.[9] Ustekinumab is FDA-approved for the treatment of Crohn's disease.
- Patients with a personal history of or active IBD might experience reactivation or worsening of their disease with administration of Il-17 inhibitors (i.e., secukinumab, ixekizumab, and brodalumab).[9] Although the number of patients presenting with this adverse effect in clinical trials was relatively small, it is recommended that the use of IL-17 inhibitors be avoided in patients with a personal history of or active IBD.[9]
- Rare cases of suicidal ideation and completed suicides have occurred with brodalumab treatment, resulting in a FDA Black Boxed warning.[9] Brodalumab should not be considered as a treatment option in patients with suicidal ideation, recent suicidal behavior, or history of suicidal ideation.[9]

New Formulations:

1. Ixifi™ (infliximab-qbtx) is biosimilar to Remicade® (infliximab) and received FDA approval December 2017. Ixifi™ is FDA-approved for all indications of Remicade® including: RA in combination with MTX, PsA, AS, CD, pediatric CD, UC, and PsO. As with infliximab, the biosimilar carries a Black Boxed warning for serious infection and malignancy risk. A second Remicade® biosimilar manufactured by Amgen, Avsola™ (infliximab-axxq) also received FDA approval December 2017.

2. Eticovo™ (etanercept-ykro) is biosimilar to Enbrel® (etanercept). The biosimilar received FDA approval April 2019 for treatment of RA, JIA in patients aged 2 years and older, PsA, AS, and PsO in patients 4 years and older. As with etanercept, the biosimilar carries a Black Boxed warning for serious infection and malignancy risk. In a 52-week phase 3 clinical study which randomized 596 patients with RA across 70 sites in 10 countries, etanercept-ykro demonstrated comparable safety and efficacy to etanercept as evidenced in ACR 20 response rate of 80.8% in the etanercept-ykro arm versus 81.5% in the etanercept arm.[50]

3. Hadlima™ (adalimumab-bwwd) is biosimilar to Humira® (adalimumab) and received FDA approval July 2019. The FDA-approved indications for Hadlima™ include: RA, JIA, PsA, AS, CD, UC, and PsO. As with adalimumab, the biosimilar carries a Black Boxed warning for serious infection and

malignancy risk. FDA approval was based on data derived from a randomized, double-blind 52-week phase 3 study in which 544 patients with moderate to severe RA despite MTX therapy were randomized to receive either adalimumab-bwwd or adalimumab. At Week 24, the ACR 20 response rate was 72.4% in the adalimumab-bwwd group versus 72.2% in the adalimumab group.[51] The safety profile of adalimumab-bwwd was comparable to adalimumab up to Week 24. The product is expected to launch in the United States in 2023.

4. Abrilada™ (adalimumab-afzb) is biosimilar to Humira® (adalimumab) and received FDA approval November 2019. Abrilada™ is FDA-approved to treat RA, JIA, PsO, PsA, AS, CD, and UC. As with adalimumab, the biosimilar carries a Black Boxed warning for serious infection and malignancy risk. Results from the REFLECTIONS B538-02 clinical comparative study found no clinically meaningful differences in efficacy, safety or immunogenicity compared to the reference product, each taken in combination with MTX, in patients with moderate to severe RA.[52]

5. Ruxience™ (rituximab-pvvr) is biosimilar to Rituxan® (rituximab). Ruxience™ received FDA approval July 2019 and is indicated for treatment of adults with Non-Hodgkins Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), and Granulomatosis with Polyangiitis (GPA) or Microscopic Polyangiitis (MPA) in combination with glucocorticoids. As with rituximab, the biosimilar carries a Black Boxed warning for infusion-related reactions, severe mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy. Results from the REFLECTIONS B3281006 clinical comparative study evaluated the efficacy, safety, immunogenicity, pharmacokinetics, and pharmacodynamics of rituximab-pvvr, and found no clinically meaningful differences in safety or efficacy compared to the reference product in patients with CD20-positive, low tumor burden follicular lymphoma.[53]

6. Truxima® (rituximab-abbs) is biosimilar to Rituxan® (rituximab). FDA-approval was granted November 2018. Truxima® is indicated for treatment of adults with NHL. Currently, Truxima® does not have FDA-approval for inflammatory conditions such as RA. Like rituximab, Truxima® has a label that carries a Black Boxed warning alerting providers and patients to the risk of fatal infusion reactions, skin and mouth reactions, and hepatitis B reactivation.

New Indications:

1. Stelara® (ustekinumab) received an expanded indication for treatment of moderately to severely active UC in adults in November 2019. Approval was based primarily on results from the UNIFI trial, in which subcutaneous injections of ustekinumab led to clinical remission rates of 38%-44% after 12 months, depending on the dosing interval (12 and 8 weeks, respectively), versus 24% in a placebo group.[54]

2. Rituxan® (rituximab) received FDA approval to treat GPA and MPA in patients 2 years of age and older in combination with glucocorticoids in September 2019. Previously approved indications include NHL, CLL, RA, and Pemphigus Vulgaris (PV) in adult patients.

3. Cimzia® (certolizumab pegol) received an expanded indication for treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation in March 2019.

4. Benlysta® (belimumab) received FDA approval for use in patients aged 5 years and older with active, autoantibody-positive SLE who are receiving standard therapy in April 2019.

5. Inflectra® (infliximab-dyyb) and Renflexis (infliximab-abda) received expanded indications to treat pediatric UC in patients 6 years and older in June 2019.

6. Erelzi™ (etanercept-szzs) received FDA approval for the expanded indications of PsA and PsO in October 2019.

7. Otezla® (apremilast) received an expanded indication to treat adult patients with oral ulcers associated with Behcet's Disease in July 2019.

8. Taltz® (ixekizumab) received FDA approval in August 2019 to treat adults with AS.

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Labeling Addition or Change	Description and Mitigation Principles (if applicable)
Infliximab-abda[55]	Renflexis®	3/2019	Warnings and Precautions	**Malignancies** Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents.[55] **Cardiovascular and Cerebrovascular Reactions** Serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of infliximab product infusion. Cases of transient visual loss have been reported during or within 2 hours of infusion of infliximab product. Monitor patients during infusion and if serious reaction occurs, discontinue infusion. Further management of reactions should be dictated by signs and symptoms.[55]
Guselkumab[56]	Tremfya®	4/2019 4/2019	Contraindications Warning and Precautions	Tremfya is contraindicated in patients with a history of serious hypersensitivity reaction to guselkumab or to any of the excipient.[56] Serious hypersensitivity reactions have been reported with postmarket use of Tremfya. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, discontinue Tremfya® and initiate appropriate therapy.[56]
Belimumab[57]	Benlysta®	9/19	Warnings and Precautions	In controlled clinical studies, psychiatric disorders (depression, suicidal ideation and behavior) have been reported more frequently in patients receiving Benlysta®. Physicians should assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with Benlysta® and continue to monitor patients during treatment. Patients receiving Benlysta® (and caregivers if applicable) should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or behavior, or other mood changes.[57]
Ustekinumab	Stelara®	11/19	Warnings and Precautions	Stelara® may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving Stelara®.[58]

Randomized Controlled Trials

A total of 396 citations were manually reviewed from the initial literature search. After further review, 392 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 4. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Paul C, et al.[59] IXORA-S DB, AC, RCT Duration: 52 weeks	1. Ixekizumab 160 mg SC at week 0, followed by 80 mg every 2 weeks to week 12, then 80 mg every 4 weeks (n=131) Vs. 2. Ustekinumab 45 or 90 mg SC at weeks 0, 4, 16, 28 and 40 (n=158)	Adults with moderate to severe PsO N=302	Co-primary outcomes: Proportion of patients who achieved PASI 90 and sPGA 0/1 at week 52	PASI 90: 1. 104 (77.4%) 2. 98 (59.2%) RR 1.308 (95% CI 1.102 to 1.513; P=0.003) sPGA 0/1: 1. 110 (83.6%) 2. 108 (65.8%) RR 1.271 (95% CI 1.100 to 1.442; P=0.002)
Reich K, et al.[60] ECLIPSE DB, AC, MC, RCT Duration: 48 weeks	1. Guselkumab 100 mg SC at weeks 0 and 4, then every 8 weeks (n=534) Vs. 2. Secukinumab 300 mg SC at weeks 0, 1, 2, 3 and 4, then every 4 weeks (n=514)	Adults with moderate to severe PsO N=1048	Proportion of patients who achieved PASI 90 response at week 48	PASI 90 (ITT) 1.451 (84%) 2.360 (70%) Treatment Difference: 14% (95% CI: 9.2 to 19.2%; P<0.0001)
Sands BE, et al.[61] DB, AC, MC, RCT Duration: 50 weeks	1. Vedolizumab 300 mg IV infusion on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (n=383) Vs. 2. Adalimumab 160 mg at week 1, 80 mg at week 2 and 40 mg every 2 weeks until week 50 (n=386)	Adults with moderate to severe UC N= 769	Proportion of patients with clinical remission (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12], with higher scores indicating more severe disease) at week 52	Clinical Remission: 1. 120 (31.3%) 2. 87 (22.5%) Treatment Difference: 8.8% (95% CI: 2.5 to 15.0%; P=0.006)

Mease PJ, et al[62] DB, RCT Duration: 24 weeks	1. MTX 20 mg PO plus PBO SC once a week (n=284) 2. Etanercept 50 mg SC plus PBO PO once a week (n=284) 3. Etanercept 50 mg SC plus MTX 20 mg PO once a week (n=283)	Adults with PsA N=851	Proportion of patients with ACR 20 response at week 24	ACR 20: 1. MTX: 50.7% 2. Etanercept: 60.9% 3. Etanercept + MTX: 65% 1 vs. 2: p = 0.029 1 vs... 3: p=0.005 95% CI not reported
Abbreviations: AC = Active Comparator; ACR = American College of Rheumatology; CI = confidence interval; DB = double blind; ITT = intention to treat; IV = intravenous; MC=multi-center; MTX = methotrexate; N = number; PASI = Psoriasis Area and Severity Index; PBO = placebo; PO= oral; PsA = psoriatic arthritis; PsO= plaque psoriasis; sPGA = static Physician's Global Assessment; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneous				

NEW DRUG EVALUATION: Upadacitinib (Rinvoq™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including FDA Black Boxed warnings, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Upadacitinib (Rinvoq™) is an oral JAK inhibitor indicated for the treatment of adults with moderate to severe RA who have had an inadequate response or intolerance to MTX.[15] Use of upadacitinib in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.[15] The recommended dose of upadacitinib is 15 mg orally once a day via an extended-release tablet, either as monotherapy or in combination with MTX or other non-biologic DMARDs.

Four published phase 3 studies and 1 unpublished trial were submitted to the FDA for upadacitinib approval.[10] These trials, collectively named the SELECT RA program, evaluated the efficacy and safety of upadacitinib in treating patients with moderately to severely active RA. The trials were conducted in Australia, New Zealand, Israel, South Africa, Asia, North/Central/South America, and Europe. Two doses of upadacitinib (15 mg and 30 mg once daily) were studied in clinical trials. There were numerical differences in treatment response between the two doses of upadacitinib generally favoring the 30 mg dose; however, the clinical benefit of the 30 mg dose over the 15 mg dose is small.[10] Given the increased safety concerns with the higher dose (e.g. anemia, neutropenia), the incremental benefit of the 30 mg dose does not outweigh the increased risk.[10] Therefore, the manufacturer is only marketing the 15 mg strength of upadacitinib.

Comparators to upadacitinib in the phase 3 trials included placebo, MTX, and adalimumab administered over 12 to 14 weeks. In all 5 trials, patients were switched from placebo or MTX to upadacitinib after the initial 3-month assessment with an option to participate in ongoing extension trials planned for up to 5 years. The co-primary efficacy endpoints assessed were the proportion of subjects who achieved an ACR20 response and reduced disease activity, as measured by DAS28-CRP. Secondary endpoints included ACR50 and ACR70 response rates and patient function, as assessed by improvements in the HAQ-DI score from baseline. The SELECT RA trials included patient populations known to exhibit different degrees of response based on past treatment history, with or without concurrent csDMARDs, in subjects who had an inadequate response to csDMARDs and/or bDMARDs. Results for the 4 published trial are summarized below. Additional trial details are presented in **Table 7.**

The SELECT-NEXT trial evaluated the efficacy and safety of upadacitinib in 661 RA patients who had inadequate response to csDMARDs (MTX, sulfasalazine, or leflunomide) compared to placebo over 12 weeks.[11] Patients in this trial had little or no exposure bDMARDs. Moderate quality evidence showed more patients in the upadacitinib 15 mg (64%) and 30 mg (66%) treatment groups met the co-primary endpoint of ACR20 at week 12 compared with 36% in the placebo group [15 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT = 4; 30 mg vs. placebo difference=31%, (95% CI 22 to 30), p<0.0001, NNT=4].[11] Similarly, more patients met the co-primary endpoint of DAS28-CRP less than or equal to 3.2 at week 12 in the upadacitinib 15 mg (48%) and 30 mg (48%) groups compared with 17% of patients in the placebo group [15 mg vs. placebo difference=29%, (95% CI 19 to 38), P<0.0001, NNT=4; 30 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4, moderate quality evidence].[11] The short duration of the placebo-controlled phase in this trial limits the efficacy assessment to 12 weeks of therapy. Data from the 5-year extension trial has not yet been published.

The SELECT-BEYOND trial used a similar study design as the SELECT-NEXT trial. The efficacy and safety of upadacitinib were evaluated in 499 RA patients who had inadequate response to at least one bDMARD.[12] The placebo-controlled period of 12 weeks was followed by an ongoing double-blind extension study of up to 5 years. More patients in the upadacitinib 15 mg (65%) and 30 mg (56%) treatment groups met the primary endpoint of ACR20 at week 12 compared with 28% in the placebo group [15 mg vs. placebo difference=37%, (95% CI 26 to 46), P<0.0001, NNT=3; 30 mg vs. placebo difference=28%, (95% CI 18 to 38), P<0.0001, NNT=4].[12] More patients met the co-primary endpoint of DAS28-CRP less than or equal to 3.2 at week 12 in the upadacitinib 15 mg (43%) and 30 mg (42%) groups compared with 14% in the placebo group [15 mg vs. placebo difference=29%, (95% CI 20 to 30), P<0.0001, NNT=4; 30 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4].[12] Study limitations included the short study duration, relatively small number of patients, lack of geographic diversity in the patient population, and inadequate assessment of the effect of upadacitinib on progressive structural joint damage.[12]

The SELECT-COMPARE trial evaluated the efficacy and safety of upadacitinib compared to placebo and adalimumab in 1,629 patients with active RA and an inadequate response to MTX.[13] Patients were randomized (2:2:1) to receive upadacitinib (15 mg once daily), placebo, or adalimumab (40 mg every other week) while continuing to take a stable dose of MTX. The primary end points were achievement of ACR20 and a DAS28-CRP less than 2.6 at week 12. Inhibition of radiographic progression was evaluated at week 26. At weeks 14, 18, and 22, if patients did not achieve 20% or greater improvement in the tender joint count (TJC) and swollen joint count (SJC) from baseline, treatment was changed as follows: adalimumab was switched to upadacitinib, upadacitinib was switched to adalimumab, and placebo was switched to upadacitinib.[13] At week 26, all placebo patients were switched to upadacitinib regardless of their response to placebo therapy. Patients remained on treatment through week 48. The study was also designed to test for the noninferiority and superiority of upadacitinib compared to adalimumab over 48 weeks.

Moderate quality evidence showed more patients in the upadacitinib group (71%) met the co-primary endpoint of ACR20 at week 12 compared with 36% in the placebo group [difference= 34%, (95% CI 29 to 39), P≤0.001, NNT=3].[13] More patients also met the co-primary endpoint of DAS28-CRP less than 2.6 at week 12 in the upadacitinib group (29%) compared with 6% in the placebo group [difference=23%, (95% CI 19 to 27), P≤0.001, NNT=5, moderate quality evidence].[13] Moderate quality evidence demonstrated more patients receiving upadacitinib achieved ACR20 (79%) and DAS28-CRP less than 2.6 (29%) compared with 63% of patients who achieved ACR 20 with adalimumab and 11% who achieved DAS28-CRP less than 2.6 with adalimumab [ACR 20 upadacitinib vs. adalimumab difference=8%, (95% CI 1 to 14), P≤0.05, NNT=13 and DAS28-CRP upadacitinib vs. adalimumab difference=11%, (95% CI 5 to 16), P≤0.001, NNT=10).[13] At 48 weeks, patients in the upadacitinib group had a greater response rate for both ACR20 (65%) and DAS28-CRP less than 2.6 (38%) compared with adalimumab (64%, P<0.01 and 28%, P<0.01, respectively).[13] The percentage of patients with no radiographic progression at week 26 was higher with upadacitinib (87%) compared to placebo (74%); P≤0.001). Lack of radiographic progression with adalimumab was noted in 88% of patients, but was not statistically significant compared to upadacitinib (P=0.448).[13] Study limitations include the shortened placebo-controlled period, which was permitted only until week 26 for ethical reasons). In addition, the rescue arms were not powered or designed to enable a valid statistical comparison for efficacy between patients who switched

treatment groups. Furthermore, only adalimumab was used as a comparator so it is unknown how upadacitinib compares with other bDMARDs or JAK inhibitors used for this indication.

The SELECT-MONOTHERAPY trial evaluated the efficacy and safety of switching to upadacitinib monotherapy compared with continuing MTX in 648 patients with an inadequate response to MTX.[14] Eligible patients must have shown active disease despite treatment with MTX, defined as at least six swollen joints out of 66, at least six tender joints out of 68, and more than 3 mg/L C-reactive protein (upper limit of normal 2.87 mg/L).[14] Patients were randomly assigned in a 1:1:1 ratio to receive upadacitinib 15 mg, upadacitinib 30 mg or MTX for 14 weeks. Patients randomized to MTX at week 0 were switched to receive either upadacitinib 15 mg or upadacitinib 30 mg at week 14 for up to 5 years, whereas patients randomized to upadacitinib at week 0 continued to receive their assigned dose from week 14 for up to 5 years.[14] Moderate quality evidence showed both upadacitinib treatment groups resulted in higher proportion of ACR20 responders at week 14 [15 mg (68%) and 30 mg (71%)] compared with the MTX group (41%) [15 mg vs. MTX difference=27%, (95% CI 18 to 36), P<0.0001, NNT=4; 30 mg vs. MTX difference=30% (95% CI 21 to 30), p<0.0001, NNT=4].[14] For the co-primary endpoint of DAS28-CRP less than or equal to 3.2, similar results were observed [15 mg (45%) and 30 mg (53%)] compared to the MTX cohort (19%) [15 mg vs. MTX difference=26%, (95% CI 16 to 33); P<0.001, NNT=4; 30mg vs. MTX difference=33%, (95% CI 25 to 42), P<0.001, NNT=3 moderate quality evidence).[14] Results of the 5-year extension trial have not yet been published. One of the limitations of the study was a relatively short MTX-controlled period (14 weeks); however, this was done to avoid undertreating patients in the continued MTX arm for an extended period (average previous duration of 3.6 years).[14] The trial design did not include radiographic assessments, and the trial was not designed to assess combination therapy with upadacitinib and MTX compared with monotherapy with upadacitinib.[14]

Current ongoing phase 3 trials are investigating the efficacy of upadacitinib in patients with moderate to-severe atopic dermatitis, CD, UC, PsA, and giant cell arteritis.

Clinical Safety:
Reported safety data from these Phase 3 trials showed upadacitinib 15 mg-treated subjects experienced a greater frequency of adverse events compared to placebo, including upper respiratory infection, nausea, cough pyrexia, pneumonia, herpes zoster, herpes simplex, and oral candidiasis.[15] Based on findings in animal studies, upadacitinib may cause fetal harm when administered to a pregnant woman.[15] **Table 5** describes the most prevalent adverse reactions reported with upadacitinib 15 mg compared to placebo during clinical trials.

Table 5. Adverse reactions reported with upadacitinib compared to placebo in clinical trials[15]

Adverse Reaction	Upadacitinib 15 mg N = 1035	Placebo N = 1042
Upper respiratory tract infection	13.5%	9.5%
Nausea	3.5%	2.2%
Cough	2.2%	1.0%
Pyrexia	1.2%	0%

In clinical trials, patients treated with upadacitinib 30 mg had a higher exposure adjusted event rates of adverse effects leading to discontinuation than patients treated with upadacitinib 15 mg. The most common adverse effect leading to discontinuation of upadacitinib was pneumonia (15 mg: 0.5 events/100 patient years, 30 mg 0.9 event/100 patient years).[10] There was a dose-dependent effect observed with higher rates of herpes zoster infections in patients treated with

upadacitinib 30 mg compared to upadacitinib 15 mg patients in the controlled and long- term periods.[10] In the placebo controlled trials, upadacitinib 15 mg and 30 mg event rates of herpes zoster infections were 2.3 events/100 patient years and 8.2 events/100 patient years, respectively.[10]

Upadacitinib prescribing information contains black box warnings for serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections.[15] In addition, lymphoma and other malignancies have been observed in patients treated with upadacitinib.[15] Finally, thrombosis, including DVT, PE, and arterial thrombosis, have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions.[15] Data have been presented for upadacitinib only up to 24 weeks, and show a numeric increase in malignancies and cardiovascular events versus placebo.[15]

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

Table 6. Pharmacology and Pharmacokinetic Properties.[15]

Parameter	
Mechanism of Action	Janus kinase inhibitor
Oral Bioavailability	Maximum absorption occurs within 2-3 hours after a single dose.
Distribution and Protein Binding	Upadacitinib is 52% bound to plasma proteins. Volume of distribution is estimated as 224 liters.
Elimination	53% of drug is excreted unchanged in urine (24%) and in feces (38%) - 34% of upadacitinib excreted as inactive metabolites.
Half-Life	8 to 14 hours
Metabolism	Metabolism is mediated primarily by CYP3A4 and to a minor extent by CYP2D6 hepatic enzymes.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Symptomatic improvement (ACR 50, ACR 70)
2) Clinical remission
3) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:
1) Proportion of patients achieving ACR20 at 12 to 14 weeks
2) Proportion of patients with DAS28-CRP score of 3.2 or less at 12 to 14 weeks

Table 7. Comparative Evidence Table: Upadacitinib

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Burmester GR, et al.[11] SELECT-NEXT DB, PC, MC, Phase 3 RCT 150 sites in 35 countries N=661 12 weeks	1. UPA 15 mg po QDay 2. UPA 30 mg po QDay 3. Placebo po QDay All administered in combination with csDMARDs (MTX, chloroquine, sulfasalazine, hydroxychloroquine and/or leflunomide). Trial followed by ongoing DB extension study up to 5 yrs. Patients on placebo were randomized to UPA 15 mg or 30 mg.	Demographics: -Mean age: 56 yrs -Female: 79% -Mean time since RA diagnosis: 7.3 yrs -Previous bDMARD exposure: 13% -MTX monotherapy at baseline: 60% -Mean DAS28-CRP score: 5.6 Key Inclusion Criteria: -Adults ≥18 yrs -Active RA ≥ 3 mos -2 concomitant csDMARDs ≥ 3 mos -Stable csDMARD dose for ≥ 4 weeks at baseline -Inadequate response to MTX, sulfasalazine, or leflunomide Key Exclusion Criteria: -Inadequate response to bDMARDs -Previous exposure to a JAK inhibitor -History of inflammatory joint disease other than RA -Hepatic or renal impairment	ITT: 1. 221 2. 219 3. 221 PP: 1. 210 2. 201 3. 207 Attrition: 1. 11 (5%) 2. 18 (8%) 3. 14 (6%)	Co-Primary Endpoints: 1. ACR20 at week 12: 1. 141 (64%) 2. 145 (66%) 3. 79 (36%) 1 vs. 3 Difference: 28% (95% CI 19 to 37); p<0.0001 2 vs.3 Difference: 31% (95% CI 22 to 39); p<0.0001 2. DAS28-CRP score ≤ 3.2 at week 12: 1. 107 (48%) 2. 105 (48%) 3. 38 (17%) 1 vs. 3 Difference: 29% (95% CI 19 to 38) p<0.0001 2 vs. 3 Difference: 28% (95% CI 19 to 37) P<0.0001 Secondary Endpoints: 1. ACR50 at week 12: 1. 83 (38%) 2. 95 (43%) 3. 33 (15%) 1 vs. 2 Difference: 23% 95% CI NR; p<0.0001 2 vs. 3 Difference: 28% 95% CI NR; p<0.0001 2. Mean change in HAQ-DI at week 12: 1. -0.61 2. -0.55 3. -0.26 1 vs. 3 Difference: -0.35 (95% CI -0.4 to -0.3) p<0.0001 2 vs. 3 Difference: -0.28 (95% CI -0.4 to -0.2) p<0.0001	28/4 31/4 29/4 28/4 23/5 28/4 NA NA	AEs: 1. 125 (57%) 2. 118 (54%) 3. 108 (49%) SAEs: 1. 9 (4%) 2. 6 (3%) 3. 5 (2%) AEs leading to discontinuation of drug: 1. 7 (3%) 2. 13 (6%) 3. 7 (3%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IRT and stratified by bDMARD exposure and geographic region. Baseline demographics and disease activity balanced between 3 groups. Performance Bias: Low. Patients, investigators, and AbbVie personnel were blinded to allocation. Placebo and study drug were identical in appearance Detection Bias: Low. Investigators blinded to interventions. Attrition Bias: Low. More subjects receiving UPA 30 mg withdrew due to AE while more subjects receiving placebo withdrew due to lack of efficacy. Did not impact overall rates of attrition. Reporting Bias: Low. Protocol available online. Authors reported endpoints clearly and as outlined in methods Reasons for protocol deviations and percent of patients with deviations included in supplementary appendix. Other Bias: Unclear. Funded by AbbVie. AbbVie had a role in study design, data collection, data analysis, data interpretation and writing of report. Authors had received grants from manufacturers. **Applicability**: Patient: Adults with moderate to severe RA and inadequate response to csDMARDs. Intervention: 15 mg dose is FDA-approved but 30 mg dose is not. All subjects continued csDMARD therapy. Comparator: Placebo is appropriate to evaluate safety and efficacy. Would be helpful to compare to another JAK-I (tofacitinib or baricitinib) Outcomes: ACR 50 and 70 considered more clinically significant than ACR 20. Short duration of treatment (12 weeks).

								Setting: 150 sites in 35 countries: North America (40%); Eastern Europe (34%); Western Europe (10%); Asia (7%); Latin and South America (4%); Australia, New Zealand, & South Africa (4%)
2. Fleischmann R, et al.[13] SELECT-COMPARE MC, DB, PC, AC, Phase 3 RCT N=1629 12 weeks	1. UPA 15 mg po QDay 2. Placebo po QDay 3. Adalimumab 40 mg SC every other week All subjects continued stable background dose of MTX 12 week efficacy assessment. At 26 weeks all placebo patients switched to UPA for an additional 22 week study period. Total study period: 48 weeks	Demographics: -Mean age: 54 yrs -Female: 79% -Mean time since RA diagnosis: 8 yrs -Mean DAS28-CRP score: 5.8 -Average MTX dose: 17 mg/week -Prior bDMARD exposure: 9% Key Inclusion Criteria: -Adults ≥18 yrs -Moderate to severe RA ≥3 mos -Stable MTX therapy ≥3 mos with stable dose of 15 to 25 mg per week ≥4 wks., but w/ inadequate response to therapy - < 3-mos exposure to bDMARDs Key Exclusion Criteria: -Prior exposure to JAK inhibitor -Intolerance or inadequate response to bDMARD (except for adalimumab) -Hepatic or renal impairment -History of inflammatory joint disease other than RA	ITT: 1. 651 2. 651 3. 327 PP: 1. 620 2. 620 3. 300 Attrition: 1. 31 (5%) 2. 31 (5%) 3. 27 (8%)	Co-Primary Endpoints: 1. ACR20 response at week 12: 1. 456 (71%) 2. 237 (36%) 3. 206 (63%) 1 vs. 2: Difference: 34% (95% CI, 29 to 39); p≤0.001 1 vs. 3: Difference: 8% (95% CI, 1 to 14); p≤0.05 2. DAS28-CRP < 2.6 at week 12: 1. 189 (29%) 2. 20 (6%) 3. 118 (18%) 1 vs. 2: Difference: 23% (95% CI, 19 to 27); p≤0.001 1 vs. 3: Difference: 11% (95% CI, 5 to 16); p<0.001 Secondary Endpoints: 1. ACR50 response at week 12: 1. 292 (45%) 2. 98 (15%) 3. 95 (29%) 1 vs. 2 Difference: 30% (95% CI 25.6 to 35.0); P<0.001 2 vs. 3 Difference: 16% (95% CI 9.0 to 22.3); P<0.001 2.Mean change in HAQ-DI at week 12: 1. -0.60 2. -0.28 3. -0.49 1 vs. 2 Difference: -0.32 (95% CI NR); p<0.001 1 vs. 3 Difference: -0.11	34/3 8/13 23/5 11/10 30/4 16/7 NA NA	AEs: 1. 417 (64%) 2. 347 (53%) 3. 197 (60%) SAEs: 1. 24 (4%) 2. 19 (3%) 3. 14 (4%) AEs leading to discontinuation of drug: 1. 23 (3.5%) 2. 15 (2%) 3. 20 (6%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:2:1 using IRT and stratified by bDMARD exposure and geographic region. Baseline demographics and disease activity balanced between 3 groups. Performance Bias: Low. Patients, investigators, caregivers, and funding personnel all blinded to treatment arm through week 48. Detection Bias: Unclear. Not clear how blinding was maintained for therapy re-assignment during rescue period after 12 weeks. Attrition Bias: Low. More subjects in the adalimumab arm withdrew due to adverse effects, but not concerning enough to increase risk of attrition bias. Withdrawal rates even between UPA and placebo. Reporting Bias: Low. Protocol available online. Authors reported endpoints clearly and as outlined in methods. Other Bias: Unclear. AbbVie funded the trial, contributed to the design of the study, and was involved in data collection and analysis, interpretation of the results, and preparation, review, and approval of the final version. **Applicability**: Patient: Patients with an inadequate response to MTX. Intervention: UPA 15 mg po once daily is an FDA approved dose with background MTX therapy. Comparators: Placebo and adalimumab (non-inferiority and superiority). Would be informative to compare UPA to another JAK inhibitor (baricitinib or tofacitinib). Outcomes: ACR 20 response and DAS28-CRP used in previous UPA trials. ACR 50 and 70

				(95% CI NR); p<0.01				considered more clinically significant than ACR 20. Setting: 286 sites in 46 countries: Eastern Europe (40%); South/Central America (27%); North America (19%); Western Europe (6%); Asia (3%); Other regions (6%)
3. Smolen JS, et al.[14] SELECT-MONO-THERAPY MC, DB, AC RCT N=648 14 weeks	1. UPA 15 mg po QDay 2. UPA 30 mg po Qday 3. Maintenance MTX dose (15 to 25 mg per week).	Demographics: -Mean age: 54 yrs -Female: 79% -Mean time since RA diagnosis: 7 yrs -MTX monotherapy: 60% -Mean DAS28-CRP score: 5.6 Key Inclusion Criteria: -Adults ≥18 yrs -Moderate to severe RA -Stable MTX therapy ≥ 3 mos (15 to 25 mg/week ≥ 4 weeks) -Only using MTX as csDMARD therapy Key Exclusion Criteria: -Prior exposure to JAK inhibitor or bDMARD therapy -History of inflammatory joint disease other than RA -Hepatic or renal impairment	ITT: 1. 217 2. 215 3. 216 PP: 1. 199 2. 202 3. 197 Attrition: 1. 18 (8%) 2. 13 (6%) 3. 19 (9%)	Primary Endpoints: 1. ACR20 response at week 14: 1. 147 (68%) 2. 153 (71%) 3. 89 (41%) 1 vs. 3 Difference: 27% (95% CI 18 to 36); p≤0.0001 2 vs. 3 Difference: 30% (95% CI 21 to 39); p≤0.0001 2. DAS28-CRP ≤ 3.2 at week 14: 1. 97 (45%) 2. 114 (53%) 3. 42 (19%) 1 vs. 3 Difference: 26% (95% CI 16 to 33); p≤0.0001 2 vs. 3 Difference: 34% (95% CI 25 to 42); p≤0.0001 Secondary Endpoints: 1. ACR50 response at week 14: 1. 91 (42%) 2. 112 (52%) 3. 33 (15%) 1 vs. 3 Difference: 27% (95% CI 19 to 35) P<0.0001 2 vs. 3 Difference: 37% (95% CI 29 to 45) P<0.0001 1. Least square mean change in HAQ-DI at week 14: 1. -0.65 2. -0.73 3. -0.32 (95% CI NR) P<0.001	27/4 30/4 26/4 34/3 27/4 37/3 NA	AEs: 1. 103 (47%) 2. 105 (49%) 3. 102 (47%) SAEs: 1. 11 (5%) 2. 6 (3%) 3. 6 (3%) AEs leading to discontinuation of drug: 1. 8 (4%) 2. 6 (3%) 3. 6 (3%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IRT and stratified by geographical region. Patient demographics and disease activity were balanced across the treatment arms. Performance Bias: Low. Patients, investigators, and funding personnel all blinded to study drug allocation. Detection Bias: Unclear. Method of blinding study drug from placebo not described. Attrition Bias: Low. Similar proportions of patients withdrew from each arm. Reporting Bias: Low. Protocol available online. Authors reported endpoints clearly and as outlined in methods. Other Bias: Unclear. Funded by AbbVie. AbbVie was involved in data analysis, the interpretation of results and the preparation, review and approval of the final version of this report. **Applicability**: Patient: Patients with inadequate response to MTX. Intervention: UPA 15 or 30mg once daily. Comparator: UPA monotherapy compared to MTX monotherapy. Outcomes: ACR20 and DAS28-CRP<3.2 at 14 weeks. ACR 50 and 70 considered more clinically significant than ACR 20. Setting: 138 sites in 24 countries: Eastern Europe (37%); North America (30%); South/Central America (14%); Japan (10%); Western Europe (4%); South Africa/Tukey/Israel (6%).

4. Genovese MC, et al.[12] SELECT-BEYOND MC, DB, PC N=499 12 weeks	1. UPA 15 mg po QDay 2. UPA 30 mg po QDay 3. Placebo po QDay All continued background csDMARDs	Demographics: -Mean age: 57 yrs -Female: 84% -Mean time since RA diagnosis: 13 yrs -Failed ≥ 1 TNF-I: 91% -Mean DAS28-CRP score: 5.8 Key Inclusion Criteria: -Adults ≥18 yrs -Active RA ≥ 3 mos -bDMARD ≥ 3 mos or intolerance or toxicity to ≥1 bDMARD -csDMARD ≥3 mos and on stable dose for ≥4 weeks Key Exclusion Criteria: -H/o inflammatory joint diseases other than RA -Any previous exposure to a JAK inhibitor - Impaired renal or hepatic function	ITT: 1. 164 2. 165 3. 169 PP: 1. 148 2. 156 3. 147 Attrition: 1. 17 (10%) 2. 8 (5%) 3. 22 (13%)	Primary Endpoint: 1. ACR20 response at week 12: 1. 106 (65%) 2. 93 (56%) 3. 48 (28%) 1 vs. 3 Difference: 37% (95% CI 26 to 46); P<0.0001 2 vs. 3 Difference 28% (95% CI 18 to 38); P<0.0001 2. DAS28-CRP < 3.2 at week 12: 1. 71 (43%) 2. 70 (42%) 3. 24 (14%) 1 vs. 2 Difference: 29% (95% CI 20 to 38); p<0.0001 2 vs. 3 Difference: 28% (95% CI 19 to 37); p<0.0001 Secondary Endpoints: 1. ACR50 response at week 12: 1. 56 (34%) 2. 59 (36%) 3. 20 (12%) 1 vs. 2 Difference: 2% 2 vs. 3 Difference: 24% (95% CI NR); P<0.0001 for both doses 1. Least square mean change in HAQ-DI at week 12 1. -0.41 2. -0.44 3. -0.16 (95% CI NR); P<0.0001 for both doses	37/3 28/4 29/4 28/4 2/50 24/5 NA	AEs at week 12: 1. 91 (55%) 2. 111 (67%) 3. 95 (56%) SAEs at week 12 1. 8 (5%) 2. 12 (7%) 3. 0 AEs leading to discontinuation of drug at week 12 1. 4 (2%) 2. 15 (9%) 3. 9 (5%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IRT and stratified by the number of previous bDMARDs used and geographic region. At baseline, demographic and disease characteristics were balanced across the treatment groups. Performance Bias: Low. Patients, investigators, and funding personnel blinded to study drug allocation Placebo and study drug identical in appearance. Detection Bias: Low. Investigators blinded to interventions. Attrition Bias: Unclear. Proportion of patients who discontinued the study drug because of adverse events was higher in the UPA 30 mg group than in the UPA 15 mg and placebo groups. Proportion of patients who discontinued the study drug because of lack of efficacy was higher in the placebo group than in the UPA groups. Reporting Bias: Low. Protocol available as well as description of protocol deviations on line. Authors reported endpoints clearly and as outlined in methods. Other Bias: Unclear. Funded by AbbVie, which also had a role in study design, data collection, data analysis, data interpretation, and writing of the report. Authors report grants from several manufacturers including AbbVie. **Applicability**: Patient: More difficult to treat cohort given stipulation of failure to ≥ 1 bDMARD Intervention: Only UPA 15 mg dose is approved by FDA. Comparator: Placebo is appropriate to evaluate safety and efficacy. Would be helpful to compare to another JAK-I (tofacitinib or baricitinib) Outcomes: ACR20 and DAS28-CRP<3.2 at 12 weeks. ACR 50 and 70 considered more clinically significant than ACR 20. Setting: 153 sites in 26 countries. Most of the sites were located in North America (66%).

Abbreviations: AC=active comparator; ACR20=American College of Rheumatology 20% response rate; ACR50=American College of Rheumatology 50% response rate; AE=adverse events; ARR=absolute risk reduction; bDMARDs=biologic Disease-Modifying Antirheumatic Drugs; CI=confidence interval; csDMARDs=conventional synthetic Disease-Modifying Antirheumatic Drugs; DAS28-CRP=28-joint disease activity score based on C-reactive protein; DB=double blind; HAQ-DI=health assessment questionnaire-disability index; ITT=intention to treat; IRT=interactive response technology; JAK=Janus kinase; MTX=methotrexate; MC=multi-center; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NR=not reported; PC=placebo control; PO=oral; PP=per protocol; RA=rheumatoid arthritis; RCT=randomized clinical trial; SAE=serious adverse events; SC=subcutaneous; TNF-I=tumor necrosis factor inhibitor; UPA =upadacitinib; yrs=years

NEW DRUG EVALUATION: Risankizumab-rzaa (Skyrizi™)

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:

Risankizumab-rzaa is an IL-23 antagonist indicated for the treatment of moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy.[18] The FDA-approved dose is 150 mg administered via subcutaneous injection at week 0, week 4 and every 12 weeks thereafter.[18] The drug is supplied as a 75 mg/0.83 mL single-dose prefilled syringe. For each dose, the 2 injections should be administered at different anatomic locations such as thighs or abdomen.[18]

The efficacy and safety of risankizumab in patients with moderate-to-severe PsO was evaluated in 2 similar double-blind, randomized, placebo-controlled and ustekinumab-controlled phase 3 trials (UltIMMa-1 and UltIMMa-2).[16] The primary objective of the studies was to demonstrate superiority of risankizumab over placebo and ustekinumab. The ustekinumab used in these trials was the European Union (EU)-approved product, which is distinct from the product that is FDA-approved. One hundred thirty-nine sites in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Mexico, Japan, Poland, Portugal, Republic of Korea, Spain, and United States participated in the 2 trials.[16] The sites included hospitals, academic medical centers, clinical research units, and private practices.[16] Five hundred six patients were enrolled in UltIMMa-1 and 491 patients were enrolled in UltIMMa-2.[16]

The UltIMMa studies consisted of two parts: Part A and Part B. In Part A, during the 16 week double blind phase, patients received either 150 mg risankizumab, ustekinumab based on weight per label (45 mg for patients with body weight less than or equal to 100 kg or 90 mg for patients with body weight greater than 100 kg), or placebo at week 0 and 4.[16] In Part B (double-blind, weeks 16 through 52), patients initially randomized to placebo switched to 150 mg risankizumab at week 16; other patients continued their originally randomized treatment.[16] During Part B, patients received study drug at weeks 16, 28, and 40. Co-primary endpoints were proportions of patients who achieved 90% improvement in the PASI (PASI-90) and a sPGA score of 0 or 1 at week 16. Secondary endpoints included proportion of patients who achieved 100% improvement in the PASI (PASI-100) and a score of 0 or 1 on the DLQI at week 16.

In both studies, more patients who received risankizumab, compared with those who received placebo or ustekinumab, achieved the co-primary endpoints of PASI-90 and sPGA score of 0 or 1 at week 16. At week 16, moderate quality evidence showed PASI-90 was achieved by 75.3% risankizumab-treated patients compared with 4.9% placebo-treated patients and 42% ustekinumab-treated patients in UltIMMa-1 [risankizumab vs. placebo difference=70%, (95% CI 64 to 76), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=33%, (95% CI 22 to 44), p<0.0001, NNT=3].[16] In UltIMMa-2, 74.8% risankizumab-treated patients compared with 2% placebo-treated patients and 47.5% ustekinumab-treated patients achieved PASI-90 [risankizumab vs. placebo difference=72%, (95% CI 66 to 78), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=27%, (95% CI 16 to 38), p<0.0001, NNT=4, moderate quality evidence].[16] In UltIMMA-1,

moderate quality evidence showed sPGA score of 0 or 1 was achieved by 87.5% of patients who received risankizumab versus 7.8% who received placebo and 63% who received ustekinumab [risankizumab vs. placebo difference=79%, (95% CI 73 to 86), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=25%, (95% CI 15 to 35), p<0.0001, NNT=4].[16] Similar results were observed in UltIMMA-2 for sPGA 0 or 1 at week 16 [risankizumab vs. placebo difference=78%%, (95% CI 72 to 84), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=22%, (95% CI 12 to 32), p<0.0001, NNT=5, moderate quality evidence].[16] Additional details about these 2 trials are included in **Table 10**.

This trial had some limitations. Since psoriasis is a chronic disease, further studies are needed to evaluate longer-term outcomes. Additionally, as has been typical of studies in moderate-to-severe plaque PsO, patients in both trials were predominantly white and male. The applicant did not provide an adequate comparison between the US-licensed and the EU-approved ustekinumab.[18] Thus, the EU-approved ustekinumab may be considered distinct from the US-licensed ustekinumab.[18]

In the randomized, double-blind, phase 3 IMMVent trial, risankizumab was compared with adalimumab in patients with moderate-to-severe chronic PsO through week 16 (Part A).[17] In Part B, the efficacy and safety of switching to risankizumab through week 44, compared with continued adalimumab, was further evaluated in patients who achieved PASI-50 to less than PASI-90 (intermediate responders) with adalimumab at week 16.[17] Blinding for patients, investigators, and other study personnel was maintained in Phase B. The primary objective was to demonstrate superiority of risankizumab over adalimumab in both Parts A and B.[17] Sixty-six sites in Canada, Czech Republic, Finland, France, Germany, Mexico, Poland, Portugal, Sweden, Taiwan, and the United States participated in the study.

Patients were randomly assigned 1:1 to receive 150 mg risankizumab subcutaneously at weeks 0 and 4 or 80 mg adalimumab subcutaneously at randomization, then 40 mg at weeks 1, 3, 5, and every other week thereafter during Part A. For Part B, adalimumab intermediate responders were re-randomized 1:1 to continue 40 mg adalimumab or switch to 150 mg risankizumab. Co-primary endpoints in part A were proportion of patients who achieved PASI-90 and a sPGA score of 0 or 1 at week 16; for part B, the primary endpoint was PASI-90 at week 44. Moderate quality evidence showed at week 16, PASI-90 was achieved in 72% patients given risankizumab and 47% of patients given adalimumab [adjusted absolute difference 24.9% (95% CI 17.5 to 32.4); p<0.0001, NNT=5], and sPGA scores of 0 or 1 were achieved in 84% of patients given risankizumab and 60% patients given adalimumab [adjusted absolute difference 23.3% (95% CI 16.6 to 30.1); p<0.0001, NNT=5].[17] In part B, among adalimumab intermediate responders, PASI-90 was achieved by 66% of patients switched to risankizumab and 21% of patients continuing adalimumab (adjusted absolute difference 45.0%, (95% CI28.9 to 61.1%); p<0.0001 at week 44.[17]

There is no direct evidence comparing risankizumab with IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) or the IL-23 inhibitors (guselkumab or tildrakizumab), which are also FDA-approved to treat PsO. There is also uncertainty of the efficacy and safety benefit that long-term treatment with risankizumab may have over these other biologic treatments.

Clinical Safety:
Analyses of the reported safety data from Phase 3 trials demonstrates that risankizumab-treated subjects experienced a greater frequency of adverse events, compared to placebo including upper respiratory infections, headache, fatigue, injection site reactions and tinea infections.[18] **Table 8** describes the most prevalent adverse reactions reported with risankizumab compared to placebo during clinical trials. No reports of tuberculosis, opportunistic infections, adjudicated major adverse cardiac events (MACE) or serious hypersensitivity were reported during clinical trials.

Table 8. Adverse Reactions Occurring in > 1% of Subjects on risankizumab-rzaa through week 16[18]

Adverse Reactions	Risankizumab-rzaa 150 mg (n=1306) N (%)	Placebo (n=300) N (%)
Upper Respiratory Infections	170 (13)	29 (9.7)
Headache	46 (3.5)	6 (2)
Fatigue	33 (2.5)	3 (1)
Injection Site Reactions	19 (1.5)	3 (1)
Tinea Infections	14 (1.1)	1 (0.3)

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

Table 9. Pharmacology and Pharmacokinetic Properties[18]

Parameter	
Mechanism of Action	IL-23 antagonist
Bioavailability	After subcutaneous injection: 89%
Distribution and Protein Binding	Volume of distribution: 11.2 L
Elimination	Estimated clearance: 0.31 L/day
Half-Life	28 days
Metabolism	Not characterized. As a humanized IgG1 monoclonal antibody, risankizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Abbreviations: IgG=immune globulin G; IL=interleukin; L=liters

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptomatic improvement (e.g., PASI-100)
2) Functional status
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) PASI-90 at 16 weeks
2) sPGA 0/1 at 16 weeks

Table 10. Comparative Evidence Table: Risankizumab

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Gordon, et al[16] UltIMMa-1 DB, PC, AC, Phase 3 RCT N=506 16 weeks	1. Risankizumab 150 mg at week 0, 4, 16, 28 and 40 2. Ustekinumab 45 or 90 mg (weight-based) at week 0, 4, 16, 28, and 40 3. Placebo at weeks 0 and 4 followed by risankizumab 150 mg at week 16, 28 and 40 Part A: Weeks 0 to 16. Part B: Weeks 17 to 52. Patients assigned to placebo in Part A were switched to risankizumab 150 mg every 12 weeks x 3 doses. This phase was double blinded.	Demographics: -Male 70% -Mean Wt.: 88 kg -Mean BSA involvement: 26% -White 70% -Asian: 26% -Mean age: 48 yo -Prior TNF use: 21% Key Inclusion Criteria: -Adults ≥ 18 yo -Chronic PsO ≥6 mos -Stable moderate-to-severe chronic PsO with baseline metrics: a. ≥10% BSA involvement b. PASI ≥12 c. sPGA ≥3 -Candidate for systemic therapy or phototherapy -Candidate for treatment with ustekinumab Key Exclusion Criteria: -Non-plaque forms of PsO -Current drug-induced PsO -Active ongoing inflammatory diseases other than Ps and PsA -Prior exposure to	ITT: 1. 304 2. 100 3. 102 PP: 1. 299 2. 99 3. 98 Attrition at 16 weeks: 1. 5 (1.6%) 2. 1 (1.0%) 3. 4 (3.9%)	Co-Primary Endpoints: 1. PASI-90 at week 16: 1. 229 (75.3%) 2. 42 (42.0%) 3. 5 (4.9%) 1 vs. 2 AD = 33.5% (95% CI 22.7 to 44.3%) p<0.0001 1 vs. 3 AD = 70.3% (95% CI 64.0 to 76.7%) p<0.0001 2. sPGA 0/1 at week 16: 1. 267 (87.8%) 2. 63 (63.0%) 3. 8 (7.8%) 1 vs. 2 AD 25.1% (95% CI = 15.2 to 35.0%) P<0.0001 1 vs. 3 AD 79.9% (95% CI 73.5to 86.3%) P<0.0001 Secondary Endpoints: 1. PASI-100 at week 16: 1. 109 (35.9%) 2. 12 (12.0%) 3. 0 1 vs. 2 AD 23.8% (95% CI 15.5 to 32.1%) P<0.001 1 vs. 3 AD 35.5% (95% CI 30.0 to 41.0%) P<0.001 2. DLQI 0/1 at week 16:	33.5/3 70.3/2 25.1/4 79.9/2 23.8/5 35.5/3	1.AE 1. 151 (49.7%) 2. 50 (50.0%) 3. 52 (51.0%) 2.SAE 1. 7 (2.3%) 2. 8 (8.0%) 3. 3 (2.9%) AE leading to discontinuation of drug 1. 2 (0.7%) 2. 2 (2.0%) 3. 4 (3.9%) p-value and 95% CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Subjects randomized 3:1:1 to risankizumab, ustekinumab, or placebo via IRT and stratified by weight (≤ 100kg or > 100 kg) and previous TNFI exposure (yes or no). Baseline patient demographics generally balanced between treatment groups. Performance Bias: Low. Double blinding achieved through IRT. To maintain blinding, the studies utilized a double-dummy strategy wherein risankizumab and its matching placebo or ustekinumab and its matching placebo were identical in appearance. Detection Bias: Low. Patients, investigators, and study personnel involved in the trial conduct or analyses remained masked to treatment assignments until study completion. Attrition Bias: Low. Rates of discontinuation with similar patient loss across all 3 arms. Reporting Bias: Low. Protocol is available online. Other Bias: Unclear. Funded by AbbVie and Boehringer Ingelheim. Boehringer Ingelheim contributed to study design and participated in data collection. AbbVie did the data analysis, and participated in data interpretation. AbbVie and Boehringer Ingelheim participated in writing, review, and approval of the manuscript. All authors had full access to the data from both studies, reviewed and approved the final version, and were responsible for the decision to submit for publication. A medical writer, employed by AbbVie, assisted with manuscript preparation under the authors' direction. **Applicability**: Patient: Patient population primarily male, white participants with stable moderate-to-severe PsO. Intervention: Risankizumab dosing is the FDA approved dose. Comparator: Ustekinumab is an Il-12/23 antagonist, with similar mechanism of activity to study drug.

		ustekinumab or risankizumab -History of allergy or hypersensitivity biologic agent or its excipients		1. 200 (65.8%) 2. 43 (43.0%) 3. 8 (7.8%) <u>1 vs. 2</u> AD 23.0% (95% CI 11.9 to 34.0) P<0.001 <u>1 vs. 3</u> AD 57.9% (95% CI 50.4 to 65.3) P<0.001	23/5 57.9/2			<u>Outcomes</u>: PASI-90 and sPGA 0/1 are validated indicators of efficacy. <u>Setting</u>: 79 sites across 8 countries: Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, and the United States.
2. Gordon, et al[16] UltIMMa-2 DB, PC, AC, Phase 3 RCT N=491 16 weeks	1. Risankizumab 150 mg at week 0, 4, 16, 28 and 40 2. Ustekinumab 45 or 90 mg (weight-based) at week 0, 4, 16, 28, and 40 3. Placebo at weeks 0 and 4 followed by risankizumab 150 mg at week 16, 28 and 40 Part A: Weeks 0 to 16. Part B: Weeks 17 to 52. Patients assigned to placebo in Part A were switched to risankizumab 150 mg every 12 weeks x 3 doses. Double blinding maintained in this phase.	<u>Demographics:</u> -Male 68% -Mean Wt.: 92 kg -Mean BSA Involvement: 25% -White: 89% -Asian: 7% -Mean age: 47 yo -Prior TNF use: 25% <u>Inclusion Criteria:</u> See above <u>Exclusion Criteria:</u> See above	<u>ITT</u>: 1. 294 2. 99 3. 98 <u>PP</u>: 1. 292 2. 96 3. 94 <u>Attrition</u>: 1. 2 (0.6%) 2. 3 (3.0%) 3. 4 (4.3%)	<u>Co-Primary Endpoints</u>: 1. PASI-90 at week 16: 1. 220 (74.8%) 2. 47 (47.5%) 3. 2 (2.0%) <u>1 vs. 2</u> AD = 27.6% (95% CI 16.7 to 38.5%) p<0.0001 <u>1 vs. 3</u> AD = 72.5% (95% CI 66.8 to 78.2%) p<0.0001 2. sPGA 0/1 at week 16: 1. 246 (83.7%) 2. 61 (61.6%) 3. 5 (5.1%) <u>1 vs. 2</u> AD 22.3% (95% CI = 12.0 to 32.5%) P<0.0001 <u>1 vs. 3</u> AD 78.5% (95% CI 72.4 to 84.5%) P<0.0001 <u>Secondary Endpoints</u>: 1. PASI-100 at week 16: 1. 149 (50.7%) 2. 24 (24.2%) 3. 2 (2.0%) <u>1 vs. 2</u> AD 27% (95% CI 17.0 to 37.0%)	27.6/4 72.5/2 22.3/5 78.5/2	<u>1.AE</u> 1. 134 (45.6%) 2. 53 (53.5%) 3. 45 (45.9%) <u>2.SAE</u> 1. 6 (2.0%) 2. 3 (3.0%) 3. 1 (1.0%) <u>AE leading to discontinuation of drug:</u> 1. 1 (0.3%) 2. 0 3. 1 (1.0% p-value and 95% CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: See above <u>Performance Bias</u>: See above <u>Detection Bias</u>: See above <u>Attrition Bias</u>: Low. Rates of discontinuation with similar patient loss across all 3 arms. <u>Reporting Bias</u>: See above <u>Other Bias:</u> See above **Applicability**: <u>Patient</u>: See above <u>Intervention</u>: See above <u>Comparator</u>: See above <u>Outcomes</u>: See above <u>Setting</u>: 64 sites across 10 countries: Austria, Belgium, Canada, Germany, Mexico, Poland, Portugal, Spain, and the United States

				P<0.001 <u>1 vs. 3</u> AD 48.2% (95% CI 41.9 to 54.6%) P<0.001 2. DLQI 0/1 at week 16: 1. 196 (66.7%) 2. 46 (46.5%) 3. 4 (4.1%) <u>1 vs. 2</u> AD 20.2% (95% CI 9.1 to 31.4%) P<0.004 <u>1 vs. 3</u> AD 62.2% (95% CI 55.5 to 68.9%) P<0.001	27/4 48.2/3 20.2/5 62.2/2			
3. Reich, et al.[17] IMMVENT DB, AC, Phase 3 RCT N=605 16 weeks	1. Risankizumab 150 mg at week 0, 4, 16, 28 2. Adalimumab 80 mg at week 0, 40 mg at week 1 then every 2 weeks Part A: Weeks 0-16 Part B: Weeks 17-44. Adalimumab intermediate responders (PASI≥50 to <90) re-randomized 1:1 to continue adalimumab 40 mg or switch to risankizumab 150 mg	<u>Demographics</u>: -Male 70% -Mean Wt.: 90 kg -Mean BSA Involvement: 17% -White 80% -Mean Age: 48 yo -Prior TNF use: 30% <u>Key Inclusion Criteria</u>: -Age ≥18 yrs -Chronic mod-severe plaque PsO ≥6 mos with: ≥10% BSA involvement; PASI ≥12; and sPGA ≥3 <u>Key Exclusion Criteria</u>: -Non-plaque PsO -Drug-induced PsO -Active ongoing inflammatory diseases other than PsO and PsA	**Part A** <u>ITT</u>: 1. 301 2. 304 <u>PP</u>: 1. 294 2. 291 <u>Attrition</u>: 1. 7 (2.3%) 2. 13 (4.2%) **Part B** <u>ITT</u>: 1. 53 2. 56 <u>PP</u>: 1. 51 2. 51 <u>Attrition</u>: 1. 2 (3.7%) 2. 5 (8.9%)	<u>Co-Primary Endpoint</u>: 1. PASI 90 at week 16: 1. 218 (72.4%) 2. 144 (47.4%) AD 24.9% (95% CI 17.5 to 32.4%) P<0.001 2. SPGA 0/1 at week 16: 1. 252 (83.7%) 2. 183 (60.2%) AD 23.3% (95% CI 16.6 to 30.1%) P<0.001 <u>Secondary Endpoints</u>: 1. PASI 100 at week 16: 1. 120 (40%) 2. 70 (23%) AD 16.7% (95% CI 9.5 to 23.9%) P<0.0001 2. PASI 90 at week 44 1. 35 (66%) 2. 12 (21%) AD 45%	 24.9/5 23.3/5 16.7/6	<u>1.AE</u> 1. 168 (56%) 2. 173 (57%) <u>2.SAE</u> 1. 10 (3%) 2. 9 (3%) <u>AE leading to discontinuation of drug:</u> 1. 4 (1%) 2. 6 (2%)	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: See above <u>Performance Bias</u>: See above <u>Detection Bias</u>: See above <u>Attrition Bias</u>: See above <u>Reporting Bias</u>: See above <u>Other Bias</u>: See above **Applicability**: <u>Patient</u>: See above <u>Intervention</u>: See above <u>Comparator</u>: Adalimumab is a TNFI, with different mechanism of activity than an IL-23 antagonist. <u>Outcomes</u>: See above <u>Setting</u>: 66 sites in 11 countries: Canada, Czech Republic, Finland, France, Germany, Mexico, Poland, Portugal, Sweden, Taiwan, and the United States

		-Prior exposure to risankizumab or adalimumab -History of allergy or hypersensitivity to biologic agent or its excipients		(95% CI 28.9 to 61.1%) P<0.0001	45/3			

Abbreviations: AC=active comparator; AD=adjusted difference; AE=adverse effects; BSA body surface area; CI = confidence interval; DB = double blind; DLQI = Dermatology Life Quality Index; IL=interleukin; IRT=interactive response technology; ITT=intention to treat; kg=kilogram; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; PASI= Psoriasis Area Severity Index; PC=placebo controlled; PP=per protocol; PsA=psoriatic arthritis; P=psoriasis; PsO=plaque psoriasis; RCT=randomized clinical trial; SAE=serious adverse effects; sPGA=static Physician's Global Assessment; TEAE=treatment-emergent adverse event ; TNFI=tumor necrosis factor inhibitor; yo=years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
adalimumab	HUMIRA PEN	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA PEN CROHN'S-UC-HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA PEN PSOR-UVEITS-ADOL HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA(CF) PEN	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA(CF) PEN CROHN'S-UC-HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA(CF) PEN PSOR-UV-ADOL HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA	SYRINGEKIT	SQ	Y
adalimumab	HUMIRA PEDIATRIC CROHN'S	SYRINGEKIT	SQ	Y
adalimumab	HUMIRA(CF)	SYRINGEKIT	SQ	Y
adalimumab	HUMIRA(CF) PEDIATRIC CROHN'S	SYRINGEKIT	SQ	Y
etanercept	ENBREL MINI	CARTRIDGE	SQ	Y
etanercept	ENBREL SURECLICK	PEN INJCTR	SQ	Y
etanercept	ENBREL	SYRINGE	SQ	Y
etanercept	ENBREL	VIAL	SQ	Y
abatacept	ORENCIA CLICKJECT	AUTO INJCT	SQ	N
abatacept	ORENCIA	SYRINGE	SQ	N
abatacept/maltose	ORENCIA	VIAL	IV	N
anakinra	KINERET	SYRINGE	SQ	N
apremilast	OTEZLA	TAB DS PK	PO	N
apremilast	OTEZLA	TABLET	PO	N
baricitinib	OLUMIANT	TABLET	PO	N
belimumab	BENLYSTA	AUTO INJCT	SQ	N
belimumab	BENLYSTA	SYRINGE	SQ	N
belimumab	BENLYSTA	VIAL	IV	N
brodalumab	SILIQ	SYRINGE	SQ	N
canakinumab/PF	ILARIS	VIAL	SQ	N
certolizumab pegol	CIMZIA	KIT	SQ	N
certolizumab pegol	CIMZIA	SYRINGEKIT	SQ	N
golimumab	SIMPONI	PEN INJCTR	SQ	N
golimumab	SIMPONI	SYRINGE	SQ	N
golimumab	SIMPONI ARIA	VIAL	IV	N
guselkumab	TREMFYA	AUTO INJCT	SQ	N
guselkumab	TREMFYA	SYRINGE	SQ	N
infliximab	REMICADE	VIAL	IV	N
infliximab-abda	RENFLEXIS	VIAL	IV	N
infliximab-dyyb	INFLECTRA	VIAL	IV	N
ixekizumab	TALTZ AUTOINJECTOR	AUTO INJCT	SQ	N

ixekizumab	TALTZ AUTOINJECTOR (2 PACK)	AUTO INJCT	SQ	N
ixekizumab	TALTZ AUTOINJECTOR (3 PACK)	AUTO INJCT	SQ	N
ixekizumab	TALTZ SYRINGE	SYRINGE	SQ	N
natalizumab	TYSABRI	VIAL	IV	N
risankizumab-rzaa	SKYRIZI	SYRINGE	SQ	N
risankizumab-rzaa	SKYRIZI (2 SYRINGES) KIT	SYRINGEKIT	SQ	N
rituximab	RITUXAN	VIAL	IV	N
sarilumab	KEVZARA	PEN INJCTR	SQ	N
sarilumab	KEVZARA	SYRINGE	SQ	N
secukinumab	COSENTYX PEN	PEN INJCTR	SQ	N
secukinumab	COSENTYX PEN (2 PENS)	PEN INJCTR	SQ	N
secukinumab	COSENTYX (2 SYRINGES)	SYRINGE	SQ	N
secukinumab	COSENTYX SYRINGE	SYRINGE	SQ	N
tildrakizumab-asmn	ILUMYA	SYRINGE	SQ	N
tocilizumab	ACTEMRA ACTPEN	PEN INJCTR	SQ	N
tocilizumab	ACTEMRA	SYRINGE	SQ	N
tocilizumab	ACTEMRA	VIAL	IV	N
tofacitinib citrate	XELJANZ XR	TAB ER 24H	PO	N
tofacitinib citrate	XELJANZ	TABLET	PO	N
ustekinumab	STELARA	SYRINGE	SQ	N
ustekinumab	STELARA	VIAL	IV	N
vedolizumab	ENTYVIO	VIAL	IV	N

Appendix 2: Abstracts of Comparative Clinical Trials

Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study[59]

BACKGROUND: Biologics targeting interleukin 17A (IL-17A) allow for rapid clearance of psoriatic plaques, with a clinically favorable safety profile.
OBJECTIVES: To compare the safety and efficacy of ixekizumab, an IL-17A antagonist, with the safety and efficacy of the IL-12/23 inhibitor ustekinumab through 52 weeks of treatment in the head-to-head trial IXORA-S.
METHODS: Patients were randomized to ixekizumab (n = 136) or ustekinumab (n = 166) and dosed per the approved labels. After 1 year, efficacy was assessed via improvements in Psoriasis Area and Severity Index (PASI) score (with PASI 90 indicating a 90% or greater improvement from baseline PASI score) and a static Physician's Global Assessment (sPGA) response of either 0 or 0 or 1, with dropouts counted as non-responders. Safety analyses included treatment-emergent adverse events (AEs).
RESULTS: At week 52, significantly more ixekizumab-treated patients (P < .01) reported PASI 90 (104 [76.5%]), an sPGA response of 0 (72 [52.9%]), or an sPGA response of 0 or 1 (110 [82.1%]) responses than did ustekinumab-treated patients (PASI 90, 98 [59.0%]; sPGA response of 0, 60 [36.1%]; and sPGA response of 0 or 1, 108 [65.1%]). Treatment-emergent AEs, serious AEs, and discontinuation rates were not different between the treatment groups. Injection site reactions occurred more frequently in the ixekizumab-treated group (ixekizumab, 22 [16.3%]; ustekinumab, 2 [1.2%]) (P < .001).
LIMITATIONS: This study was not designed to compare safety end points related to rare events.
CONCLUSIONS: Compared with ustekinumab, ixekizumab showed superior efficacy and comparable safety outcomes through 52 weeks of treatment.

Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial.[60]

BACKGROUND: Antibodies targeting interleukin (IL)-23 and IL-17A effectively treat moderate-to-severe psoriasis. ECLIPSE is the first comparator study of an IL-23p19 inhibitor, guselkumab, versus an IL-17A inhibitor, secukinumab. The primary objective of this study was to show superiority of clinical response at week 48 for guselkumab versus secukinumab.
METHODS: In this phase 3, multicenter, double-blind, randomised, comparator-controlled trial at 142 outpatient clinical sites in nine countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Poland, Spain, and the USA), eligible patients were aged 18 years or older, had moderate-to-severe plaque-type psoriasis, and were candidates for phototherapy or systemic therapy. Eligible patients were randomly assigned with permuted block randomization using an interactive web response system to receive either guselkumab (100 mg at weeks 0 and 4 then every 8 weeks) or secukinumab (300 mg at weeks 0, 1, 2, 3, and 4, and then every 4 weeks). The primary endpoint, the proportion of patients in the intention-to-treat population who achieved 90% reduction or more from baseline of Psoriasis Area and Severity Index (PASI 90 response) at week 48, and major secondary endpoints (the proportions of patients in the guselkumab group and in the secukinumab group who achieved a PASI 75 response at both weeks 12 and 48, a PASI 90 response at week 12, a PASI 75 response at week 12, a PASI 100 response at week 48, an Investigator's Global Assessment [IGA] score of 0 [cleared] at week 48, and an IGA score of 0 or 1 [minimal] at week 48) were to be tested in a fixed sequence to control type I error rate. Safety was evaluated in patients who received one or more doses of study drug from week 0 to 56.
FINDINGS: This study was done between April 27, 2017, and Sept 20, 2018. 1048 eligible patients were enrolled and, of these, 534 were assigned to receive guselkumab and 514 to receive secukinumab. The proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group (451 [84%]) than in the secukinumab group (360 [70%]; p<0·0001). Although non-inferiority (margin of 10 percentage points) was established for the first major secondary endpoint (452 [85%] of patients in the guselkumab group vs. 412 [80%] of patients in the secukinumab group achieving a PASI 75 response at both weeks 12 and 48), superiority was not established (p=0·0616). Consequently, formal statistical testing was not done for subsequent major secondary endpoints. Proportions of patients with adverse events, infections, and serious adverse events were similar between the two treatments and, in general, safety findings were consistent with registrational trial observations.

INTERPRETATION: Guselkumab showed superior long-term efficacy based on PASI 90 at week 48 when compared with secukinumab for treating moderate-to-severe psoriasis. This finding could assist health-care providers in their decision making process when selecting a biologic for treating moderate-to-severe psoriasis.

Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis[61]

BACKGROUND: Biologic therapies are widely used in patients with ulcerative colitis. Head-to-head trials of these therapies in patients with inflammatory bowel disease are lacking.

METHODS: In a phase 3b, double-blind, double-dummy, randomized trial conducted at 245 centers in 34 countries, we compared vedolizumab with adalimumab in adults with moderately to severely active ulcerative colitis to determine whether vedolizumab was superior. Previous exposure to a tumor necrosis factor inhibitor other than adalimumab was allowed in up to 25% of patients. The patients were assigned to receive infusions of 300 mg of vedolizumab on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus injections of placebo) or subcutaneous injections of 40 mg of adalimumab, with a total dose of 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50 (plus infusions of placebo). Dose escalation was not permitted in either group. The primary outcome was clinical remission at week 52 (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no sub score >1 [range, 0 to 3] on any of the four Mayo scale components). To control for type I error, efficacy outcomes were analyzed with a hierarchical testing procedure, with the variables in the following order: clinical remission, endoscopic improvement (sub score of 0 to 1 on the Mayo endoscopic component), and corticosteroid-free remission at week 52.

RESULTS**:** A total of 769 patients underwent randomization and received at least one dose of vedolizumab (383 patients) or adalimumab (386 patients). At week 52, clinical remission was observed in a higher percentage of patients in the vedolizumab group than in the adalimumab group (31.3% vs.. 22.5%; difference, 8.8 percentage points; 95% confidence interval [CI], 2.5 to 15.0; P = 0.006), as was endoscopic improvement (39.7% vs.. 27.7%; difference, 11.9 percentage points; 95% CI, 5.3 to 18.5; P<0.001). Corticosteroid-free clinical remission occurred in 12.6% of the patients in the vedolizumab group and in 21.8% in the adalimumab group (difference, -9.3 percentage points; 95% CI, -18.9 to 0.4). Exposure-adjusted incidence rates of infection were 23.4 and 34.6 events per 100 patient-years with vedolizumab and adalimumab, respectively, and the corresponding rates for serious infection were 1.6 and 2.2 events per 100 patient-years.

CONCLUSIONS: In this trial involving patients with moderately to severely active ulcerative colitis, vedolizumab was superior to adalimumab with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.

Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial.[62]

OBJECTIVE: To examine the efficacy of methotrexate monotherapy relative to etanercept monotherapy and the value of combining methotrexate and etanercept for the treatment of patients with psoriatic arthritis (PsA).

METHODS: In this double-blind study, 851 patients with PsA were randomized to 1 of 3 treatment arms, as follows: oral methotrexate (20 mg) plus subcutaneous placebo given weekly (n = 284), subcutaneous etanercept (50 mg) plus oral placebo given weekly (n = 284), or subcutaneous etanercept (50 mg) plus oral methotrexate (20 mg) given weekly (combination therapy; n = 283). The American College of Rheumatology 20% improvement (ACR20) response and Minimal Disease Activity (MDA) response at week 24 were the primary end point and key secondary end point, respectively. Other measures of inflammatory arthritis, radiographic progression, and nonarticular disease manifestations were also assessed.

RESULTS: Patients with PsA had a mean ± SD age of 48.4 ± 13.1 years, and the mean ± SD duration of PsA was 3.2 ± 6.3 years (median 0.6 years). ACR20 and MDA response rates at week 24 were significantly greater in patients who received etanercept monotherapy compared with those who received methotrexate monotherapy (ACR20, 60.9% versus 50.7% of patients [P = 0.029]; MDA, 35.9% versus 22.9% of patients [P = 0.005]), and both were significantly greater in the combination therapy group compared with the methotrexate monotherapy group at week 24 (ACR20, 65.0% versus 50.7% of patients [P = 0.005]; MDA, 35.7% versus 22.9% of patients [P = 0.005]). Other secondary outcomes (ACR50 and ACR70 response rates, proportions of patients achieving a Very Low Disease

Activity score, and PsA disease activity scores) showed between-group differences that were consistent with the primary and key secondary end point results. Furthermore, patients in both etanercept treatment arms showed less radiographic progression at week 48 compared with patients who received methotrexate monotherapy. Outcomes were similar in the combination therapy and etanercept monotherapy groups, except for some skin end points. No new safety signals were seen.
CONCLUSION: Etanercept monotherapy and combination therapy with etanercept and methotrexate showed greater efficacy than methotrexate monotherapy in patients with PsA, according to the ACR and MDA response rates and extent of radiographic progression at follow-up. Overall, combining methotrexate and etanercept did not improve the efficacy of etanercept.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 3 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to October 23, 2019

1 Adalimumab/	4685
2 Etanercept/	5199
3 tocilizumab.mp.	2504
4 Abatacept/	1847
5 Infliximab/	8777
6 Rituximab/	11624
7 golimumab.mp.	1014
8 apremilast.mp.	456
9 tofacitinib.mp.	1010
10 certolizumab.mp.	1074
11 Certolizumab Pegol/	515
12 secukinumab.mp.	750
13 Abatacept/	1847
14 ixekizumab.mp.	357
15 Ustekinumab/	837
16 Natalizumab/	1378
17 vedolizumab.mp.	683
18 brodalumab.mp.	219
19 guselkumab.mp.	120
20 anakinra.mp.	1462
21 canakinumab.mp.	570
22 sarilumab.mp.	71
23 baricitinib.mp	188
24 guselkumab.mp	120
25 ixekizumab	357
26 risankizumab.mp	40
27 tildrakizumab.mp	64
23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	36181
24 Arthritis, Psoriatic/or Arthritis, Rheumatoid/or Arthritis/ or Arthritis, Juvenile	61751
25 PSORIASIS/	17093
27 Spondylitis, Ankylosing/	6564
28 Crohn Disease/	20265
29 Colitis, Ulcerative/	15589
30 Arthritis, Juvenile/	5065
31 24 or 25 or 26 or 27 or 28 or 29 or 30	111992
32 23 and 31	14302
33 limit 32 to (yr="2018-current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	396

Appendix 4: Prescribing Information Highlights

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

RINVOQ™ (upadacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2019

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving RINVOQ. (5.1)**
- **If a serious infection develops, interrupt RINVOQ until the infection is controlled. (5.1)**
- **Prior to starting RINVOQ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting RINVOQ. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Lymphoma and other malignancies have been observed in patients treated with RINVOQ. (5.2)**
- **Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. (5.3)**

INDICATIONS AND USAGE

RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. (1)
Limitation of Use: Use of RINVOQ in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of RINVOQ is 15 mg once daily. (2.1)
- RINVOQ may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. (2.1)
- Avoid initiation or interrupt RINVOQ if absolute lymphocyte count is less than 500 cells/mm^3, absolute neutrophil count is less than 1000 cells/mm^3, or hemoglobin level is less than 8 g/dL. (2.2, 2.3, 5.4)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 15 mg (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of RINVOQ in patients with active, serious infection, including localized infections. (5.1)
- Malignancy: Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known malignancy. (5.2)
- Thrombosis: Consider the risks and benefits prior to treating patients who may be at increased risk of thrombosis. Promptly evaluate patients with symptoms of thrombosis and treat appropriately. (5.3)
- Gastrointestinal Perforations: Use with caution in patients who may be at increased risk. (5.4)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.5)
- Embryo-Fetal Toxicity: RINVOQ may cause fetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)
- Vaccinations: Avoid use of RINVOQ with live vaccines. (5.7)

ADVERSE REACTIONS

Adverse reactions (greater than or equal to 1%) are: upper respiratory tract infections, nausea, cough, and pyrexia. (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

- RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors (e.g., ketoconazole). (7.1)
- Coadministration of RINVOQ with strong CYP3A4 inducers (e.g., rifampin) is not recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment: RINVOQ is not recommended in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2019

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

SKYRIZI™ (risankizumab-rzaa) injection, for subcutaneous use
Initial U.S. Approval: 2019

---------- **INDICATIONS AND USAGE** ----------
SKYRIZI is an interleukin-23 antagonist indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. (1)

---------- **DOSAGE AND ADMINISTRATION** ----------
- 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4 and every 12 weeks thereafter. (2.1)

---------- **DOSAGE FORMS AND STRENGTHS** ----------
- Injection: 75 mg/0.83 mL in each single-dose prefilled syringe. (3)

---------- **CONTRAINDICATIONS** ----------
- None (4)

---------- **WARNINGS AND PRECAUTIONS** ----------
- Infections: SKYRIZI may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If such an infection develops, do not administer SKYRIZI until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment with SKYRIZI. (5.1)

---------- **ADVERSE REACTIONS** ----------
Most common adverse reactions (≥ 1%) are upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections. (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** ----------
Avoid use of live vaccines in patients treated with SKYRIZI. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2019

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 y	≥6 yo(Humira) ≥18 yo(biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo		
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo

								TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo		Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥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	
Ixekizumab (TALTZ)	≥ 18 yo			≥18 yo	≥18 yo			
Risankizumab-rzaa (SKYRIZI)				≥18 yo				
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥~~218~~yo MPA ≥ 2 yo Pemphigus Vulgaris ≥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	
Upadacitinib (RINVOQ)						≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo		≥18 yo	
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: BD = Behcet's Disease; 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; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; MPA = microscopic polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; nr-axSpA = non-radiographic axial spondyloarthritis; 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 annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. May approve for up to 3 months to allow time for screening.

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 • Non-radiographic axial spondyloarthritis • Oral ulcers associated with Behcet's Disease 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 or had inadequate response 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 or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; and • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
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 #17
13. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® product or an Enbrel® product for at least 3 months? • AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
14. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to #16	**No:** Go to #15
~~15. Is the patient on concurrent DMARD therapy with plans to continue concomitant use OR does the patient have documented intolerance or contraindication to DMARDs?~~	~~**Yes:** Approve for up to 6 months.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.~~

Approval Criteria		
~~16.~~15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis
~~17.~~16. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 17	**No:** Go to # 18
17. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90 day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
18. 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 # 19	**No:** Go to # 20

Approval Criteria		
19. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? AND • 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.
20. Is the diagnosis for an FDA approved diagnosis and age as outlined in Table 1, and is the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis or rheumatoid arthritis?	**Yes:** Go to # 42	**No:** Go to # 23
2. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 3	**No:** Go to # 5

Renewal Criteria		
3. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: A) a reduction of 25% or more in the total abscess and inflammatory nodule count, AND B) no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
~~2.~~4. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #~~43~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~3.~~5. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

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

Belimumab (Benlysta®)

Goal(s):
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:
- 6 months

Requires PA:
- Benlysta® (belimumab)

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.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active lupus nephritis or severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient aged 5 years or older?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to # 7
7. Is the drug being prescribed by or in consultation with a rheumatologist or a provider with experience treating SLE?	**Yes:** Go to # 8	**No:** Pass to RPh. Deny; medical appropriateness
8.Does the patient have active autoantibody-positive SLE and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Go to # 9. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient currently receiving standard of care treatment for Systemic Lupus Erythematosus (SLE) e.g., hydroxychloroquine, systemic corticosteroids, non-steroidal anti-inflammatory drugs, azathioprine, mycophenolate, or methotrexate?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied as monotherapy in patients with SLE.

Renewal Criteria		
1. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to #2
2. Has the patient's SLE disease activity improved as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *2/20 DM, 5/18 (DM)*
Implementation: *TBD; 7/1/18*

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Narcolepsy Agents

Date of Review: February 2020

Generic Name: pitolisant

Date of Last Review: July 2019
Dates of Literature Search: 01/01/2015 – 10/04/2019
Brand Name (Manufacturer): Wakix® (Harmony Biosciences, LLC)
Dossier Received: No

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

Purpose for Class Update:
The purpose of this update is to evaluate new comparative evidence for pharmacological treatments for excessive daytime sleepiness due to chronic conditions (e.g., narcolepsy or obstructive sleep apnea [OSA]) and determine place in therapy for pitolisant, a new drug recently approved by the Food and Drug Administration (FDA) for the treatment of narcolepsy. Pitolisant is currently classified as a physical health, non-carveout drug.

Research Questions:
1. What is the efficacy or effectiveness of pharmacological treatments for excessive daytime sleepiness compared to placebo or other pharmacotherapy?
2. Is there evidence that pharmacological treatments for excessive daytime sleepiness differ in harms?
3. What is the evidence for efficacy and safety of pitolisant for the treatment of narcolepsy?
4. Are there subpopulations (based on diagnosis, age, or gender) for which pharmacological treatments for excessive daytime sleepiness are more effective or associated with more harms?

Conclusions:
Modafinil and armodafinil
- There is insufficient evidence to support use of modafinil or armodafinil for fatigue in patients with prior stroke, primary brain tumor, or on palliative care based on results from 3 systematic reviews.[1-3]
- In patients with OSA adherent to continuous positive airway pressure (CPAP), modafinil or armodafinil improved the proportion of patients with an Epworth Sleepiness Score (ESS) less than 10 (59% vs. 31%; RR 1.95; 95% CI 1.48 to 2.56; low quality evidence) and the maintenance of wakefulness test (MWT; 3.54 minutes; 95% CI 2.57 to 4.50; moderate quality evidence) compared to placebo.[4] ESS scores less than 10 correspond to normal symptoms, but average improvement in ESS was -2.08 points (95% CI -2.70 to -1.46; moderate quality evidence) indicating the difference from baseline may not be clinically significant for many patients.[4] The proportion of patients who discontinued treatment due to adverse events was increased with modafinil or armodafinil

compared to placebo (6.2% vs. 2.8%; RR 2.03; 95% CI 1.12 to 3.67; moderate quality evidence).[4] The most commonly reported adverse events included headache, vertigo and anxiety.[4]

- There was insufficient evidence to assess differences between modafinil, armodafinil, and placebo for outcomes of multiple sleep latency test (MSLT), memory improvement, function, or quality of life for patients with OSA adherent to CPAP.[4]

Pitolisant

- There was insufficient evidence that pitolisant improved ESS compared to placebo over 7 to 8 weeks in patients with narcolepsy. Evidence was downgraded based on unclear risk of bias, presence of publication bias, and indirectness. The average improvement in ESS ranged from 2.2 (95% CI -4.17 to -0.22) to -3.5 points (95% CI -5.03 to -1.92) in 3 clinical trials.[5-7] Though a minimum clinically significant response has not been established in the literature, some studies suggest ESS improvements of 20-33% from baseline may be clinically significant.[2,8] The FDA considered a change of 3 points on the ESS to represent a minimum clinically significant improvement as this would likely be associated with a change from severe to moderate or moderate to mild symptoms.[6]
- Evidence was insufficient for improvement of other secondary outcomes of CGI-C, MWT, and number of cataplexy attacks with pitolisant compared to placebo. Evidence was inconsistent across studies, and at least one study failed to rule out no effect for each outcome.[5-7] None of the trials demonstrated any improvement in quality of life based on the EuroQol-5D (EQ-5D) scale.
- There was insufficient evidence of no difference between modafinil 100 to 400 mg daily and pitolisant for any outcome based on results of 2 small trials.
- There is insufficient evidence to evaluate long-term efficacy or safety of pitolisant. The most common adverse events associated with treatment included insomnia (6%), nausea (6%), and anxiety (5%).[9] Psychiatric adverse events including hallucinations, irritability, and anxiety have been documented in post-marketing reports, and labeling for pitolisant includes warnings for prolonged QT syndrome.[9]

Recommendations:

- No preferred drug list (PDL) changes recommended based on clinical information.
- Update safety edits for narcolepsy drugs to incorporate modafinil, armodafinil, solriamfetol and pitolisant in a single criteria (**Appendix 6**).
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Previous reviews have not identified clinically significant comparative differences in efficacy or harms between agents for narcolepsy including modafinil, armodafinil, solriamfetol, or sodium oxybate. There is insufficient evidence on health outcomes (i.e., wakefulness, executive functioning, incidence of cataplexy attacks, adverse reactions) or off-label dosage consideration to delineate any changes to preferred or non-preferred status. Currently modafinil, armodafinil, and solriamfetol are carve-out medications, paid for by fee-for-service (FFS), and designated as voluntary non-preferred on the Oregon Health Plan (OHA) preferred drug list (PDL). Sodium oxybate is classified as a physical health drug and is non-preferred.
- In an analysis of Oregon Medicaid claims data in 2015, funded off-label diagnoses were associated with 26.5% of patients prescribed armodafinil or modafinil. This data prompted implementation of the current policy that limits modafinil and armodafinil use to FDA approved or evidence-based dosages and indications. Current safety edits for modafinil and armodafinil require a 90-day trial with evidence of efficacy for continued use. A similar safety edit for solriamfetol limits use to FDA-approved doses and indications, requires a cardiovascular risk assessment, and asks for documentation of benefit after 6 months. About 72% of patients have prescriptions written for modafinil with 28% of patients prescribed armodafinil.

Background:
Narcolepsy is a sleep disorder characterized by at least 3 months of poor nighttime sleep and excessive daytime sleepiness (EDS).[10] Other symptoms of narcolepsy may include hallucinations during sleep onset or awakening and sleep paralysis.[10] These symptoms can have a significant impact on quality of life and can lead to slower reaction times, difficulty performing prolonged tasks, and increased motor vehicle accidents. Diagnosis is most common in children or young adults, and estimated prevalence of narcolepsy ranges from between 25 and 50 per 100,000 individuals in the general population.[10] Narcolepsy is categorized into 2 distinct types. Type 1 is characterized by cataplexy, a sudden loss of muscle function triggered by strong emotions, or a proven absence of hypocretin-1 in the cerebrospinal fluid.[10] In type 2, there is no cataplexy and no proven hypocretin-1 deficiency.[10] The exact etiology of narcolepsy is unclear but type 1 disease is thought to be caused by loss of hypocretin-producing neurons in the hypothalamus.[10] Disease onset may involve a variety of genetic, environmental, and immunologic factors. Diagnosis is typically based on polysomnography and multiple sleep latency test (MSLT) with a mean sleep latency of less than 8 minutes and at least 2 sleep onset rapid eye movement periods during the MSLT or 1 sleep onset rapid eye movement period within 15 minutes of sleep onset on polysomnography.[10] According to the 2007 American Academy of Sleep Medicine, first-line pharmacological options for patients with narcolepsy include modafinil.[10,11] Second-line pharmacological options include stimulants such as methylphenidate, sodium oxybate, armodafinil, or combination treatment with 2 agents.[10,11] In patients with cataplexy, sodium oxybate may be a reasonable treatment choice though it has high potential for abuse and may be associated with serious side effects including psychosis, confusion, and sedation.[10,11] Other drugs used off-label for cataplexy include tricyclic antidepressants and fluoxetine, but the quality of published clinical evidence varies.[11] In early 2019, solriamfetol was also FDA-approved for treatment of narcolepsy and OSA providing another treatment option for patients with these conditions.

Obstructive sleep apnea is characterized by upper airway obstruction during sleep.[12] It is typically diagnosed by polysomnography with at least 5 obstructive events per hour.[12] OSA occurs most commonly in patients who are overweight, male, or elderly and often occurs in conjunction with comorbid conditions such as hypertension, heart failure, atrial fibrillation, coronary artery disease, stroke, and metabolic syndrome.[12] Untreated OSA is a known risk factor for major cardiovascular events, traffic accidents, and increased mortality.[12,13] Multiple guidelines from the American College of Physicians, American Thoracic Society, American Academy of Sleep Medicine address treatment of OSA. All guidelines consistently recommend CPAP for first-line treatment of adults with OSA.[14-16] Other non-pharmacological treatments include weight reduction in patients who are overweight and oral appliances in patients unresponsive or unable to tolerate CPAP.[12,14] Stimulant medications may be prescribed conjunction with first-line nonpharmacological treatment to improve excessive daytime sleepiness, but should not be used as monotherapy as they do not correct the underlying disease process.[12] According to the American College of Physicians, there is insufficient evidence to recommend pharmacotherapy as primary treatment of OSA.[14] The American Thoracic Society also recommends against use of stimulant medications for the sole purpose of reducing driving risk in high-risk drivers with OSA.[15]

Common outcomes used in clinical trials to evaluate symptom improvement include the MWT, ESS, and scales to assess overall patient improvement and disease severity. The MWT evaluates sleep latency (measured objectively in minutes via electroencephalogram) and is often used in conjunction with the MSLT to comprehensively evaluate the patient's ability to fall asleep (MSLT) and their ability to stay awake (MWT) in a quiet, non-stimulating setting. For both the MSLT and the MWT, there have been no large, multicenter, prospectively collected data to establish normative values, and data from smaller, more limited studies have been utilized to extrapolate thresholds for diagnostic and clinical significance.[17,18] In patients with narcolepsy, mean sleep latency on the 40-min MWT of less than 8.0 minutes has been considered abnormal, and values of 8 to 40 minutes are of uncertain significance.[17,18] When used to evaluate the response to a stimulant or CPAP treatment, there are no established thresholds for a change in mean sleep latency which are associated with clinical improvement in symptoms. The ESS measures the propensity of a patient to fall asleep in daily situations. Patients rate 8 theoretical scenarios on a 0 to 3 scale (total scores range from 0 to 24) with higher scores indicating greater daytime sleepiness. An ESS score of greater than or equal to 10 indicates excessive sleepiness which requires further assessment.[19] ESS has not been validated in conditions associated with chronic fatigue and there has been no established

minimum clinically important difference in the literature. Some studies suggest that changes of 20-25% on the ESS (corresponding to approximate differences of 4-6 points for patients with severe symptoms) may represent clinically meaningful differences in patients with narcolepsy.[8] Other studies suggest that a 33% improvement from baseline in fatigue scales may be associated with a clinical improvement in symptoms.[2] For approval of pitolisant the FDA considered a change of 3 points on the ESS to be clinically significant.[6] Other scales often used to assess symptom improvement include the clinical global impression of severity scale (CGI-S) and clinical global impression of change scale (CGI-C). These are clinician-rated scales which evaluate improvement on a 1 to 7 scale from 1 (very much improved) to 7 (very much worse) and severity on a 1 to 7 scale with higher scores indicating greater disease severity.[18]

Narcolepsy is a funded condition listed on line 203 of the prioritized list of health services, and in 2018 there were approximately 450 Oregon Health Plan patients with a diagnosis of narcolepsy without cataplexy and 240 patients with a diagnosis of narcolepsy with cataplexy based on medical claims.

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

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

Systematic Reviews:
Pharmacotherapy for excessive daytime sleepiness in patients with obstructive sleep apnea adherent to CPAP was evaluated in a high quality 2016 systematic review.[4] Eight clinical trials were included in the review which evaluated use of modafinil or armodafinil compared to placebo over 2 to 12 weeks.[4] Patients enrolled in the clinical trials were primarily white males with an average age of 48-54 years.[4] In 6 studies, random sequence generation was unclear, and all studies had unclear risk of detection bias.[4] Seven studies had high risk for selective outcome reporting and all were industry funded.[4] The primary outcome was improvement in daytime sleepiness as measured by the ESS, MSLT or MWT. Excessive daytime sleepiness as evaluated by ESS improvement to less than 10 points (a normal score) was improved with modafinil compared to placebo (59% vs. 31%; RR 1.95; 95% CI 1.48 to 2.56; low quality evidence due to imprecision and risk for publication bias).[4] On average, improvement from baseline in ESS scores with either modafinil or armodafinil was -2.08 points compared to placebo (95% CI -2.70 to -1.46; moderate quality evidence).[4] Average improvement from baseline in MWT was 3.54 minutes in patients treated with modafinil or armodafinil compared to placebo (95% CI 2.57 to 4.50; moderate quality evidence).[4] Similar improvements were documented with modafinil and armodafinil separately.[4] Clinical improvement was documented by the CGI-C with armodafinil or modafinil compared to placebo (71% vs. 41%; NNT 3; RR 1.79; 95% CI 1.54 to 2.08; moderate quality evidence).[4] There was low quality evidence that attention and alertness (as evaluated by the psychomotor vigilance test) were improved with modafinil compared to placebo (mean difference [MD] -0.8; 95% CI -1.13 to -0.29), but there was insufficient evidence to assess alertness in armodafinil.[4] There was insufficient evidence to assess differences in MSLT, memory improvement, function, or quality of life.[4] Safety analysis included discontinuations due to adverse events which was increased with modafinil or armodafinil compared to placebo (6.2% vs. 2.8%; RR 2.03; 95% CI 1.12 to 3.67; moderate quality evidence).[4] The most commonly reported adverse events included headache, vertigo and anxiety.[4]

A high quality systematic review evaluated modafinil use in post-stroke fatigue.[3] Two studies (n=77) included in the analysis demonstrated inconsistent results for the majority of outcomes over 6 to 12 weeks.[3] Outcomes evaluated included fatigue, disability, major adverse events, quality of life, cognition, work and productivity.[3] All outcomes were evaluated as very low quality based primarily on imprecision and risk of bias.[3] Neither study evaluated mortality. Overall, authors concluded that benefits and harms of modafinil for post-stroke fatigue are unclear, and evidence does not support routine use in clinical practice.[3]

A 2016 Cochrane review evaluated pharmacologic treatments for fatigue associated with palliative care.[2] The most common associated conditions included multiple sclerosis (n=13), cancer (n=18), and HIV/AIDS (n=7).[2] A wide variety of pharmacological treatments were evaluated in the review. This summary will focus primarily on results for modafinil (n=8) and armodafinil (n=1) compared to placebo or other treatments.[2] Overall analysis was limited by unclear risk of bias, small study sizes, and large placebo effects. The primary outcome, fatigue response rate, was defined as an improvement in fatigue intensity or score of at least 33%.[2] Use of armodafinil in patients with HIV (n=70) demonstrated improved fatigue response rates compared to placebo (75% vs. 26%) but no difference in depression rating scales.[2] Similar results were documented for improved fatigue response rate with use of modafinil compared to placebo in patients with HIV/AIDS (73% vs. 28%).[2] Improvement of fatigue with modafinil in cancer patients was evaluated in 2 studies with inconsistent results. The first demonstrated improvement with modafinil 200 mg compared to placebo only in patients with severe fatigue at baseline.[2] The second demonstrated no difference from placebo. For the treatment of fatigue associated with multiple sclerosis, there was no difference in modafinil treatment versus placebo in 2 studies (standardized mean difference [SMD] -0.14; 95% CI -0.48 to 0.21).[2] Authors conclude that further research is needed for use of modafinil or armodafinil in patients with advanced disease and fatigue as the available evidence does not currently support use.[2]

A 2016 Cochrane review evaluated pharmacological treatments for fatigue in patients with a primary brain tumor.[1] Only a single study (n=37) was identified which evaluated use of modafinil compared to placebo over 6 weeks.[1] Overall there was low quality evidence of no difference between modafinil and placebo for fatigue-related outcomes in patients with a primary brain tumor.[1] Risk for adverse events was increased with modafinil compared to placebo (30 events per 100 people; RR 2.79; 95% CI 0.59 to 13.16; low quality evidence).[1] Documented adverse events were primarily related to neurologic or psychiatric conditions and included tingling sensations, dizziness, headaches, vertigo, loss of appetite and seizures.[1]

After review, 8 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control), or outcome studied (e.g., non-clinical).[20-27]

New Guidelines:
No new or recently updated guidelines evaluating pharmacological treatment met quality inclusion criteria.

New Formulations or Indications:
No new formulations or expanded indications were identified.

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

Randomized Controlled Trials:
A total of 54 citations were manually reviewed from the initial literature search. After further review, 53 studies were excluded because of wrong study design (e.g., observational or post-hoc analyses), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Randomized controlled

trials related to pitolisant are evaluated in the evidence table, and the remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Roscoe, et al. 2015[28] PC, RCT Duration: 7 weeks	1. CBT-I + placebo 2. CBT-I + armodafinil 3. Armodafinil 4. Placebo N=88	Cancer survivors with chronic insomnia	Improvement in Insomnia Severity Index (range 0 to 28)	Mean change from baseline: 1. -4.93 (95% CI -8.63 to -1.22); p<0.01 2. -6.36 (95% CI -10.02 to -2.69); p=0.001 3. 1.04 (95% CI -2.74 to 4.82); p=0.584 4. -1.43 (95% CI -4.91 to 2.05); p=0.421 *CBT-I demonstrated improvement in insomnia, but armodafinil did not improve insomnia.*

Abbreviations: CBT-I = cognitive behavioral therapy for insomnia; CI = confidence interval; PC = placebo controlled; RCT = randomized controlled trial

NEW DRUG EVALUATION:

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

Clinical Efficacy:

Pitolisant was evaluated by the FDA using data from 3 double-blind, placebo-controlled clinical trials in adults with narcolepsy (HARMONY-1, HARMONY-CTP, and HARMONY I-BIS). One trial used for FDA approval was completed in 2012 but remains unpublished (HARMONY I-BIS). In 2 trials an active comparator of modafinil was also evaluated. The majority of patients included in the trials had narcolepsy with cataplexy (75-100%) and baseline rate of cataplexy attacks was 7-11 attacks per week.[5-7] The average ESS was 17-18 points at baseline with an average MSLT of 4-5 minutes indicating severe or pathological sleepiness.[5-7] The primary endpoints assessed in these trials were ESS and number of cataplexy attacks. Secondary endpoints included various scales to assess symptom improvement and quality of life including changes in the MWT, CGI-C, EQ-5D, and SART scales. Each trial was preceded by a 2-week wash-out period in which participants discontinued any concurrent stimulants, a 1-week baseline assessment period to assess baseline disease severity, and followed by a 1-week withdrawal period after study completion.[5-7] Applicability is limited as none of the trials included patients in the United States and patients with many common comorbid conditions were excluded from the studies. See **Table 4** for full baseline characteristics, inclusion criteria, and exclusion criteria.

Only 2 of the 3 trials evaluated for FDA approval are published and available for quality assessment (HARMONY-1 and HARMONY-CTP). Risk of selection bias was unclear in both trials as adequate randomization methods were used, but imbalances in baseline characteristics were still present for both trials. Imbalances may be a result of small population size, and the impact of these differences on study results was unclear. In HARMONY-CTP, patients randomized to treatment had higher rate of cataplexy attacks (11 vs. 9 attacks per week) indicating more severe baseline disease and use of concurrent and prior cataplexy treatment was more common with placebo.[7] Attrition was high for both groups with differential attrition rates in HARMONY-CTP (**Table 4**).[5,7] Primary analyses were conducted using last observation carried forward which may bias results in favor of treatment. Each trial also tested multiple secondary outcomes which were not pre-

specified or controlled for type 1 error increasing risk for a chance finding. There is high risk for publication bias as at least 2 phase 3 trials of pitolisant in narcolepsy remain unpublished though they have been completed for several years (HARMONY I-BIS [NCT01638403] and HARMONY IV [NCT01789398]).[29]

In HARMONY 1, treatment with pitolisant resulted in a mean ESS change of 5.8 points from baseline compared to 3.4 points with placebo (MD –3.0; 95% CI -5.6 to -0.4).[5] Similar results were observed in HARMONY-CTP and HARMONY I-BIS with mean improvement from baseline compared to placebo of 2.2 and 3.5 points.[6,7,9] These results indicate that pitolisant may be associated with a marginal clinical improvement compared to placebo in a patient's propensity to fall asleep. In all cases, measures of variance demonstrated significant variability in response, and in HARMONY I-BIS, statistical significance of results was dependent on the method of analysis used.[30]

The primary outcome was supported by changes in CGI-C scores for EDS, but statistical significance for other secondary outcomes was overall inconsistent across studies. Compared to placebo, the proportion of patients with an improved CGI-C score for EDS was statistically different with pitolisant in HARMONY-CTP (69% vs. 43%; NNT 4),[7] and according to FDA reviewers, achieved statistical significance in HARMONY I-BIS though specific results are not available.[6,30] Statistical differences were not calculated for HARMONY 1 but favored pitolisant treatment over placebo (61% vs. 46%).[5] MWT was improved with pitolisant compared to placebo in the 2 published studies with an average improvement of 1.47 to 0.89 minutes,[5,7] but did not achieve statistical significance the unpublished HARMONY I-BIS trial.[6,30] None of the trials demonstrated any improvement in quality of life based on the EQ-5D scale or improvement in symptoms based on the SART scale.[5-7,30] Improvement in cataplexy attacks based on proportion of patients with an improved CGI-C was documented with pitolisant in HARMONY-CTP compared to placebo (67% vs. 33%; NNT 3), but demonstrated no difference in other trials.[5-7,30]

Compared to modafinil, there was no difference in ESS scores. Pitolisant failed to achieve non-inferiority compared to modafinil in HARMONY 1 (MD 0.12; 95% CI -2.5 to 2.7; p=0.25) based on a prespecified non-inferiority margin of 2 points.[5] Similarly, there was no difference between modafinil and pitolisant for all other secondary efficacy outcomes.[5]

There is insufficient evidence in narcolepsy patients with comorbid conditions as patients were excluded if they had any significant comorbid psychiatric, substance use, cardiovascular, hepatic, renal, or sleep-related disorders. Evidence for treatment of excessive daytime sleepiness due to other conditions is insufficient. While pitolisant has been studied in phase 3 trials for Parkinson's disease (n=2) and OSA (n=2) before 2014, results of these studies remain unpublished.[29] One phase 3 trial in OSA remains ongoing with expected completion in 2020.[29]

Clinical Safety:
Safety analysis for pitolisant included 172 patients treated for up to 8 weeks and long-term extension studies have followed patients for up to 5 years. Discontinuation due to adverse events occurred in 3.9% of patients randomized to pitolisant compared to 3.5% of patients receiving placebo.[9] Common adverse events occurring in at least 5% of patients and twice as common compared to placebo included insomnia (6%), nausea (6%), and anxiety (5%). Other common adverse events which occurred in at least 2% of patients compared to placebo are listed in **Table 2**. Though there were no differences from placebo in psychiatric or depressive symptoms at baseline, pitolisant treatment was associated with a higher incidence of psychiatric adverse events including hallucinations, irritability and anxiety. Adverse events reported during post-marketing experience in Europe include primarily psychiatric events such as abnormal behavior or dreams, sleep disorders and nightmares, depression, bipolar disorder, suicidal ideation and suicide attempts.[9] Because these are voluntary post-marketing reports, the exact frequency of these adverse events is unknown. Heart rate was increased in 3% of patients compared to none treated with placebo, and pitolisant has a warning for prolonged QT syndrome.[9] Use in patients with known QT prolongation, cardiac arrhythmias, or in combination with other QT prolonging drugs is not

recommended. Risk of QT prolongation may be increased in patients with renal or hepatic impairment due to increased drug exposure, and use is not recommended in patients with end stage renal disease or severe hepatic impairment.[9]

Table 2. Common adverse events occurring in at least 2% of patients and 2% more frequently than placebo.[9]

	Pitolisant (n=152)	Placebo (n=114)
Headache	18%	15%
Insomnia	6%	2%
Nausea	6%	3%
Upper respiratory tract infection	5%	3%
Musculoskeletal pain	5%	3%
Anxiety	5%	1%
Increased heart rate	3%	0%
Hallucinations	3%	0%
Abdominal pain	3%	1%
Decreased appetite	3%	0%

Serious adverse events were infrequent in clinical trials, and while there is no long-term randomized controlled data available for pitolisant, it has been marketed in Europe since 2016. A single open-label extension study enrolled narcolepsy patients previously eligible for phase 3 trials and evaluated safety for up to 1 year (n=104).[31] The majority of patients (71%) enrolled in the extension study had been previously randomized to placebo.[31] Overall, 33% of the population discontinued the trial early.[31] Primary reasons for early treatment discontinuation were lack of efficacy (19%) and adverse events (11%).[31] The majority of adverse reactions leading to discontinuation were classified as psychiatric (38%) or nervous system disorders (21%). Interestingly, of the patients who discontinued treatment due to lack of efficacy, 25% had an improvement of at least 3 points in their ESS score indicating that ESS may not correlate to clinical improvement for some patients.[31] Data from post-marketing adverse event reporting databases in Europe are consistent with adverse events observed in clinical trials (including psychiatric and cardiovascular adverse events).[6] There is limited evidence of safety in patients treated with high dose pitolisant as only 62 patients were exposed to 35.6mg for at least 12 months in clinical trials.[6] Of note, pitolisant was associated with no risk for abuse, misuse, or withdrawal symptoms upon discontinuation. By comparison, all currently available treatments for narcolepsy are scheduled by the Drug Enforcement Agency (DEA) and have some potential for abuse or misuse.[6]

The safety of pitolisant has not been evaluated during pregnancy, lactation, or for pediatric populations. A registry study is available to evaluate pitolisant exposure during pregnancy. Evaluation in elderly patients (>65 years of age) has been limited to 12 subjects, but did not demonstrate any differences in pharmacokinetics compared to an adult population.[9] Additional monitoring is recommended as elderly patients have increased incidence of renal, hepatic, and cardiac abnormalities which may increase risk of adverse events. Because it is metabolized by CYP2D6 and CYP3A4 administration with strong CYP inducers or inhibitors may alter drug effects. Pitolisant may decrease efficacy of oral contraceptives and a non-hormonal method of birth control is recommended.[9] For patients with poor CYP2D6 metabolism, the maximum recommended dose of pitolisant is 17.8 mg daily.[9] The estimated prevalence of poor metabolizers is 2-10% of Caucasians and African Americans.[9]

Look-alike / Sound-alike Error Risk Potential: Pitolisant (Wakix®) may be confused with Pitocin® (brand name for oxytocin) or Lasix® (brand name for furosemide).

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement (sleep, fatigue, wakefulness, cataplexy attacks)
2) Quality of life
3) Functional impairment
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint(s):

1) Change in the Epworth Sleepiness Scale (ESS)
2) Change in cataplexy attacks

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Acts as an antagonist at histamine-3 receptors. The mechanism of action in EDS with narcolepsy is unclear.
Oral Bioavailability	90%
Distribution and Protein Binding	Vd: 700 L (5 to 10 L/kg) Protein binding 91-96%
Elimination	Clearance of 43.9 L/hour
Half-Life	20 hours
Metabolism	Metabolized primarily by CYP2D6. Some CYP3A4 metabolism.

Abbreviations: EDS = excessive daytime sleepiness; L = liters; Vd = volume of distribution

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Dauvillers, et. al. 2013.[5] HARMONY 1 DB, PC, double-dummy, PG, RCT	1. Pitolisant 10 to 40 mg once daily 2. Modafinil 100 to 400 mg once daily 3. Placebo once daily Duration: 8 weeks Flexible dosing allowed during first 3 weeks based on efficacy and tolerability followed by a 5 week stable dosing period and 1 week withdrawal period 3-week run-in period to discontinue stimulants and determine baseline characteristics prior to randomization	Demographics: - Cataplexy: 81% - Mean cataplexy attacks: 1 per day - Prior stimulant use: 45% - Concomitant therapy for cataplexy: 35% - Mean ESS: 18 - MSLT (minutes): 1. 3.7 2. 4.9 3. 5.4 - MWT: 12 minutes Key Inclusion Criteria: - Age ≥ 18 years - narcolepsy with or without cataplexy - EDS > 3 months - MSLT < 8 minutes or ≥2 sleep onset rapid eye movement periods - ESS ≥ 14 Key Exclusion Criteria: - Concurrent TCAs or stimulants - Comorbid sleep, psychiatric, substance use, cardiovascular, hepatic or renal disorders	ITT: 1. 32 2. 33 3. 30 mITT: 1. 31 2. 33 3. 30 PP 1. 26 2. 28 3. 25 Attrition: 1. 6 (19%) 2. 5 (15%) 3. 5 (17%)	Primary Endpoint: Change in ESS from baseline; range 0-24 1. -5.8 (SD 6.2) 2. -6.9 (SD 6.2) 3. -3.4 (SD 4.2) 1 vs. 3: MD –3.0 (95% CI -5.6 to -0.4); p=0.02 1 vs. 2: MD 0.12 (95% CI -2.5 to 2.7); p=0.25 Secondary Endpoints: MWT (minutes) 1. 1.32 2. 1.72 3. 0.88 1 vs. 3: MD 1.47 (95% CI 1.01 to 2.14); p=0.04 1 vs. 2: MD 0.77 (95% CI 0.52 to 1.13); p=0.17 SART (total) 1. 0.8 2. 0.89 3. 1.0 1 vs. 3: MD 0.80 (95% CI 0.64 to 1.00); p=0.05 1 vs. 2: MD 0.90 (95% CI 0.71 to 1.14) p=0.37 Improved CGI-C from baseline (EDS); range 1-7 1. 19 (61%) 2. 24 (72%) 3. 14 (46%) MD, 95% CI, and p-value NR Improved CGI-C from baseline (cataplexy); range 1-7 1. 9 (29%) 2. 8 (24%) 3. 6 (20%) MD, 95% CI, and p-value NR Mean change in EQ-5D from baseline (QOL) 1. 8.5 2. 13.9 3. 6.2 MD, 95% CI, and p-value NR	NA NA NS NA NA NA	SAE 1. 2 (6%) 2. 2 (6%) 3. 2 (7%) TAE 1. 1 (3%) 2. 5 (15%) 3. 0 (0%) Withdrawal symptoms 1. 0 (0%) 2. 3 (9%) 3. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Adequate randomization and allocation concealment via IWRS but differences in baseline characteristics were present for age, weight & disease duration. Performance Bias: LOW. Use of sealed capsules with similar appearance and taste. Detection Bias: LOW. Use of identical placebo. Attrition Bias: UNCLEAR. Attrition was high but equal between groups with missing data imputed using LOCF. Analyses using mixed model or WOCF had no difference in results. Use of mITT for primary endpoint, but it's unclear whether PP or ITT was used for secondary endpoints or to test non-inferiority compared to modafinil. Reporting Bias: HIGH. Protocol unavailable; Secondary endpoints were not prespecified and studies did not control for type-1 error. Several baseline and final scores were NR (CGI-C, EQ-5D) Other Bias: LOW. Sponsor (Bioprojet, France) involved in protocol development & writing article but had no role in collection, analysis or interpretation of data. During 3-week run-in period to assess baseline characteristics, 15% of patients screened were not randomized. **Applicability**: Patient: Extensive exclusion criteria limit applicability in patients with comorbidities. Patients allowed to maintain stable dose of other narcolepsy medications. Intervention: Mean dose was NR & dose studied differs from FDA max dose of 35.6 mg/day. Comparator: Comparator appropriate to establish efficacy and place in therapy. Mean dose was NR & modafinil dose could exceed FDA max dose. Outcomes: Frequent follow-up at 1, 2, 3, and 8 weeks may not reflect current practice. There was no difference in QOL measures and a significant placebo response for patient reported outcomes. Setting: May 2009 to June 2010 in France, Germany, Netherlands, Hungary, and Switzerland. Limited applicability to a US Medicaid population.

2. Szakacs, et al. 2017.[7] HARMONY CTP	1. Pitolisant 5 to 40 mg once daily 2. Placebo Duration: 7 weeks See HARMONY 1 for trial design Run-in period: 3 weeks Flexible dosing: 3 weeks Stable dosing: 4 weeks Withdrawal: 1 week	Demographics: - Mean cataplexy attacks: 9-11 per week - MSLT:4-5 minutes - Mean ESS: 17 - Prior therapy: 59% Key Inclusion Criteria: - Age ≥ 18 years - narcolepsy with cataplexy (EDS and cataplexy by PSG and MSLT with >2 sleep onset REM periods) - Cataplexy attacks /week ≥3 - ESS ≥ 12 Key Exclusion Criteria: - Concurrent stimulant or sedative drugs - Comorbid sleep, psychiatric, substance use, cardiovascular, hepatic or renal disorders.	ITT: 1. 54 2. 52 mITT: 1. 54 2. 51 PP: 1. 49 2. 42 Attrition: 1. 5 (9%) 2. 9 (17%)	Primary Endpoint: Change from baseline in weekly cataplexy attacks 1. 6.9 attacks/week; relative change of 75% 2. 2.8 attacks/week; relative change of 38% Rate ratio 0.51 (95% CI 0.44 to 0.60); p<0.0001 Secondary Endpoints: Change in ESS score; range 0-24 1. -5.4 2. -1.9 MD -3.48 (95% CI -5.03 to -1.92); p=0.0001 Proportion of patients with ESS ≤ 10 1. 39% 2. 18% MD 21%; p=0.035 MWT (minutes) 1. 1.95 2. 1.06 MD 0.89; RR 1.85 (95% CI 1.24 to 2.74); p=0.003 Improved CGI-C from baseline (cataplexy); range 1-7 1. 36 (67%) 2. 17 (33%) RR 4.0 (95% CI 1.54 to 10.38); p=0.004 Improved CGI-C from baseline (EDS); range 1-7 1. 37 (69%) 2. 22 (43%) RR 7.07 (95% CI 2.55 to 19.59); p=0.0002 EQ-5D 1. -0.4 2. -0.1 MD -0.33 (95% CI -0.70 to 0.03); p=0.075	NA NA 21%/5 NA 34%/3 26%/4 NS	SAE: 1. 0 (0%) 2. 0 (0%) TAE: 1. 15 (25%) 2. 6 (12%) P=0.048 Withdrawal symptoms 1. 0 (0%) 2. 1 (2%)	NA 13%/7 NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomized and allocation concealment via IWRS. Baseline cataplexy attacks were more frequent with pitolisant vs. placebo (11 vs. 9 per week). Prior history of cataplexy treatment (80% vs. 41%) and use of concurrent therapy (16% vs. 7%) was more common with placebo. Performance Bias: LOW. Use of sealed capsules with similar appearance and taste. Detection Bias: LOW. Patients and providers blinded with use of identical placebo. Attrition Bias: HIGH. Differential attrition between groups. Imputation based on mean of the 2 prior available values (may bias results toward therapy) Reporting Bias: UNCLEAR. Protocol unavailable. Secondary endpoints were not prespecified and studies did not control for type-1 error. Other Bias: LOW. Sponsor (Bioprojet, France) involved in protocol development, data collection, & writing article but had no role in analysis or interpretation of data. During 3-week run-in period to assess baseline characteristics, 9% of patients screened were not randomized. **Applicability**: Patient: Extensive exclusion criteria limit applicability in patients with comorbidities. Patients allowed to maintain stable dose of other narcolepsy medications. Narcolepsy with cataplexy diagnosis based on ICSD-2 definition (rather than ICSD-3) and trial did not include orexin concentrations to diagnose narcolepsy. Non-narcolepsy patients or patients with narcolepsy without cataplexy may have been included. Intervention: 67% of patients were given 40mg for the stable dosing period which is slightly higher than the FDA max dose of 35.6 mg/day. Comparator: Placebo suitable to establish efficacy. Outcomes: Frequent follow-up at 2, 3, 4, 6 and 7 weeks may not reflect current practice. No difference in QOL measures and significant placebo response for patient reported outcomes. Setting: From April 2013 to January 2015 in Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey, and Ukraine. Limited applicability to a US Medicaid population.

3. FDA Summary Review[6] FDA Clinical Review[30] HARMONY I-BIS DB, PC, double-dummy, PG, RCT	1. Pitolisant 4.45 to 17.8 mg once daily 2. Modafinil 100 to 400 mg once daily 3. Placebo Randomized 2:2:1 Duration: 8 weeks See HARMONY 1 for trial design	Demographics: - Median duration of disease (years): 1. 15 2. 10 3. 11 - Male: 46-48% - Mean Age: 41-44 years - White: 83-90% - Cataplexy: 75-81% - ESS: 18 - MSLT: 4.7-5.3 minutes - MWT: 7-8.3 minutes - EQ-5D: 65-71 Key Inclusion Criteria: See HARMONY 1 Key Exclusion Criteria: See HARMONY 1	ITT: 1. 67 2. 66 3. 33 Attrition: 1. 7 (10%) 2. 4 (6%) 3. 2 (6%)	Primary Endpoint: Change in ESS (range 0-24) from baseline to week 8 (mITT) 1. -5.0 2. NR 3. -2.7 1 vs. 3: MD -2.2 (95% CI -4.17 to -0.22); p=0.03 1 vs. 2: NR Secondary Endpoints: Pitolisant demonstrated no statistical difference compared to placebo in any of the following secondary outcomes when analyzed using the prespecified analysis plan. Specific results were unavailable. - Daily cataplexy rate - MWT - SART - CGI-C (cataplexy) - EQ-5D Improved CGI-C from baseline (EDS) 1. NR 2. NR 3. NR 1 vs. 3: MD NR; p<0.001 1 vs. 2: MD NR	NA for all	DC due to AE 1. 5 (7%) 2. 1 (1%) 3. 0 (0%) SAE: NR	NA for all	**Risk of Bias (low/high/unclear)**: Trial is unpublished and a full assessment for risk of bias could not be conducted. Selection Bias: UNCLEAR. Slightly lower rate of cataplexy and shorter duration of MSLT, MWT and lower ED-56 scores in pitolisant group though clinical significance of these differences is unclear Performance Bias: UNCLEAR. Blinding unspecified. Detection Bias: UNCLEAR. Blinding unspecified. Attrition Bias: HIGH. Differential attrition (4%) between treatment and comparators. Missing data imputed based on mean of the 2 prior available values (may bias results toward treatment) Reporting Bias: HIGH. Studies did not control for type-1 error for secondary endpoints. Analysis of secondary outcomes did not use pre-specified statistical analysis plan. When analyzed using the pre-specified analysis plan, results were not statistically significant. Statistical analysis method for primary endpoint was amended prior to unblinding of the study to artificially cluster small study centers. Without re-allocation of small study centers, there was no statistical difference in ESS from placebo. Other Bias: UNCLEAR. Role of study sponsor in trial design, data collection and analysis was unavailable. **Applicability**: Patient: See HARMONY 1 Intervention: Lower maximum dose than HARMONY 1 and FDA approved max dose which may impact efficacy results. Upon pooled analysis of all trials using LOCF for missing data, a dose response was documented. Comparator: See HARMONY 1. Results for modafinil comparisons were not available. Outcomes: See HARMONY 1. No statistical difference in the majority of secondary outcomes. Setting: From November 2010 to April 2012 in Argentina, Austria, Finland, France, Germany, Hungary, Italy, and Spain. Limited applicability to a US Medicaid population.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CGI-C = clinical global impression of change; CI = confidence interval; DB= double blind; DC = discontinuation; EDS = excessive daytime sleepiness; EQ-5D = European quality of life questionnaire; ESS = Epworth sleepiness score; FDA = Food and Drug Administration; ICSD-2 = international classification of sleep disorders (2nd edition); ITT = intention to treat; IWRS = interactive web response system; LOCF = last observation carried forward; MD = mean difference; mITT = modified intention to treat; MSLT = mean sleep latency test; MWT =

maintenance of wakefulness test; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; PC = placebo controlled; PG = parallel group; PP = per protocol; QOL = quality of life; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; START = sustained attention to response task; TAE = treatment-related AE; TCA = tricyclic antidepressants; WOCF = worst observation carried forward.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL	Carveout
armodafinil	ARMODAFINIL	TABLET	V	Y
armodafinil	NUVIGIL	TABLET	V	Y
modafinil	MODAFINIL	TABLET	V	Y
modafinil	PROVIGIL	TABLET	V	Y
solriamfetol HCl	SUNOSI	TABLET	V	Y
sodium oxybate	XYREM	SOLUTION	N	N
pitolisant	WAKIX	TABLET		

Appendix 2: Abstracts of Comparative Clinical Trials

Roscoe JA, Garland SN, Heckler CE, et al. Randomized placebo-controlled trial of cognitive behavioral therapy and armodafinil for insomnia after cancer treatment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33(2):165-171.

PURPOSE: Insomnia is a distressing and often persisting consequence of cancer. Although cognitive behavioral therapy for insomnia (CBT-I) is the treatment of choice in the general population, the use of CBT-I in patients with cancer is complicated, because it can result in transient but substantial increases in daytime sleepiness. In this study, we evaluated whether CBT-I, in combination with the wakefulness-promoting agent armodafinil (A), results in better insomnia treatment outcomes in cancer survivors than CBT-I alone.

PATIENTS AND METHODS: We report on a randomized trial of 96 cancer survivors (mean age, 56 years; female, 87.5%; breast cancer, 68%). The primary analyses examined whether ≥ one of the 7-week intervention conditions (ie, CBT-I, A, or both), when compared with a placebo capsule (P) group, produced significantly greater clinical gains. Insomnia was assessed by the Insomnia Severity Index and sleep quality by the Pittsburgh Sleep Quality Inventory. All patients received sleep hygiene instructions.

RESULTS: Analyses controlling for baseline differences showed that both the CBT-I plus A (P = .001) and CBT-I plus P (P = .010) groups had significantly greater reductions in insomnia severity post intervention than the P group, with effect sizes of 1.31 and 1.02, respectively. Similar improvements were seen for sleep quality. Gains on both measures persisted 3 months later. CBT-I plus A was not significantly different from CBT-I plus P (P = .421), and A alone was not significantly different from P alone (P = .584).

CONCLUSION: CBT-I results in significant and durable improvements in insomnia and sleep quality. A did not significantly improve the efficacy of CBT-I or independently affect insomnia or sleep quality.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1946 to September Week 4 2019

1	exp Modafinil/	1215
2	armodafinil.mp.	144
3	solriamfetol.mp.	3
4	exp Sodium Oxybate/	1717
5	pitolisant.mp.	64
6	1 or 2 or 3 or 4 or 5	2982
7	exp Fatigue Syndrome, Chronic/	5303
8	exp Multiple Sclerosis/	56383
9	exp Fatigue/	28763
10	exp "disorders of excessive somnolence"/ or exp sleep apnea syndromes/	39263
11	exp Depression/	111713
12	7 or 8 or 9 or 10 or 11	234733
13	6 and 12	658
14	limit 13 to yr="2015 -Current"	138
15	limit 14 to (english language and humans)	129
16	limit 15 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	54

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

WAKIX® (pitolisant) tablets, for oral use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

WAKIX is a histamine-3 (H3) receptor antagonist/inverse agonist indicated for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy (1)

DOSAGE AND ADMINISTRATION

- Administer once daily in the morning upon wakening.
- The recommended dosage range is 17.8 mg to 35.6 mg daily. Titrate dosage as follows:
  - Week 1: Initiate with 8.9 mg once daily
  - Week 2: Increase dosage to 17.8 mg once daily
  - Week 3: May increase to the maximum recommended dosage of 35.6 mg once daily (2.1)
- Hepatic impairment (2.2, 8.6, 12.3):
  - Moderate hepatic impairment: Initial dosage is 8.9 mg once daily. Titrate to a maximum dosage of 17.8 mg once daily after 14 days
- Renal impairment (2.3, 8.7, 12.3):
  - Moderate and severe impairment: Initial dosage is 8.9 mg once daily. Titrate to maximum dosage of 17.8 mg once daily after 7 days
  - End stage renal disease (ESRD): Not recommended
- Poor Metabolizers of CYP2D6: Maximum recommended dosage is 17.8 mg once daily (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 4.45 mg and 17.8 mg (3)

CONTRAINDICATIONS

WAKIX is contraindicated in patients with severe hepatic impairment (4)

WARNINGS AND PRECAUTIONS

QT Interval Prolongation: Increases in QT interval. Avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. Monitor patients with hepatic or renal impairment for increased QTc (5.1)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and twice placebo) for WAKIX were insomnia, nausea, and anxiety (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Harmony Biosciences at 1-800-833-7460 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong CYP2D6 Inhibitors: Maximum recommended dosage is 17.8 mg once daily (2.4, 7.1)
- Strong CYP3A4 Inducers: Decreased exposure of WAKIX; consider dosage adjustment (2.4, 7.1)
- Sensitive CYP3A4 Substrates (including hormonal contraceptives): WAKIX may reduce effectiveness of sensitive CYP3A4 substrates. Use an alternative non-hormonal contraceptive method during treatment with WAKIX and for at least 21 days after discontinuation of treatment (7.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2019

Appendix 5: Key Inclusion Criteria

Population	Patients with excessive daytime sleepiness, narcolepsy, or obstructive sleep apnea
Intervention	Drugs listed in **Appendix 1**
Comparator	Drugs listed in **Appendix 1**
Outcomes	Improved daytime sleepiness Improved quality of life or functional status
Setting	Outpatient

Appendix 6: Proposed Prior Authorization Criteria

~~Modafinil / Armodafinil (~~Sleep-Wake Medications~~)~~

Goal(s):

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

Length of Authorization:

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

Requires PA:

- Payment for drug claims for modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea
- Solriamfetol
- Pitolisant

Covered Alternatives:

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

Table 1. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Solriamfetol	Pitolisant
• Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older

• Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	Not FDA approved; insufficient evidence
• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome) • ADHD • Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

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

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

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

Approval Criteria		
2. Is the patient 18 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA- approved for narcolepsy in this age group.
3. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by OHP
4. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #5
~~4.~~5. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #6~~5~~	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~6. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #7~~6~~
~~Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?~~	~~**Yes:** Go to Renewal Criteria~~	~~**No:** Go to #7~~

Approval Criteria		
~~6.~~7. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Go to #8~~Pass to RPh. Deny; medical appropriateness.~~	**No:** Go to #9~~8~~
8. Is the request for pitolisant in a patient with documentation of all the following: • CYP2D6 testing which indicates the patient is not a poor metabolizer • Chart notes or provider attestation indicating lack of hepatic or renal impairment	**Yes:** Go to #9 Max dose for pitolisant is 35.6 mg daily.	**No:** Pass to RPh. Deny; medical appropriateness.
~~7.~~9. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #10 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for solriamfetol or pitolisant?	**Yes:** Go to #11	**No:** Go to #15
11. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is the request for solriamfetol?	**Yes:** Go to #13	**No:** Go to #15
13. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14

Approval Criteria		
14. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #15 Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
~~8.~~15. Is the request for treatment of narcolepsy for a drug FDA-approved for the condition (Table 1)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #16~~9~~
~~9.~~16. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) for a drug FDA-approved for the condition (see Table 1)?	**Yes:** Go to #17	**No:** Go to #18~~0~~
~~10.~~17. Is the patient compliant with recommended first-line treatments (e.g., CPAP or other primary therapy)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Pass to RPh; Deny; medical appropriateness
~~11.~~18. Is the request for off-label use of armodafinil, solriamfetol, or pitolisant (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. There is insufficient evidence for off-label use.	**No:** Go to #19~~1~~

Approval Criteria		
~~12.~~19. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.	**No:** Go to #20~~12~~
20~~12~~. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for "medical appropriateness". • Evidence to support cognition enhancement is insufficient and should be denied for "medical appropriateness". If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

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

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

P&T Review: *7/19; 03/16; 09/15*
Implementation: *8/19/19; 8/16, 1/1/16*

Retire this criteria:

Solriamfetol Safety Edit

Goal(s):
- Promote safe use of solriamfetol in patients with narcolepsy and obstructive sleep apnea.

Length of Authorization:
6 to 12 months

Requires PA:
- Solriamfetol

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

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

Approval Criteria		
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for continuation of therapy at the maintenance dose previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #6
6. Is the patient 18 years of age or older?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness; Recommend preferred alternative methylphenidate. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA- approved for narcolepsy in this age group.
7. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the request for less than or equal to 150 mg daily?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #11 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
11. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #12 Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
12. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Is the request for treatment of narcolepsy?	**Yes:** Approve for up to 6 months	**No:** Go to #14
14. Is the request for treatment of obstructive sleep apnea and has the patient been stable and adherent to primary OSA treatment (such as CPAP or other primary therapy) for at least one month?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #2	**No:** Go to #3

Renewal Criteria		
2. Is the patient adherent to primary OSA treatment (e.g., CPAP) based on chart notes?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness or fatigue is recommended to document clinical benefit.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 7/19 (SS)
Implementation: 8/19/19