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, March 22, 2018 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302
MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

	I. CALL TO ORDER	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Department Update	T. Douglass (OHA)
	D. Legislative Updates	T. Douglass (OHA)
	E. P&T Operating Procedures	S. Servid (OSU)
	II. CONSENT AGENDA TOPICS	T. Klein (Chair)
1:15 PM	A. Approval of Agenda and Minutes	
	B. Antiepileptics Literature Scan	
	1. Public Comment	
	III. DUR ACTIVITIES	
1:20 PM	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (DXC)
	C. RetroDUR Report	D. Engen (OSU)
	D. Oregon State Drug Reviews	K. Sentena (OSU)
	1. Recently Published Reviews	
	a. Marketing Claims of Newer Drugs and the Evidence	
	b. Current Landscape of the Antidepressant Class	
	2. Future Topic Recommendations	
	IV. PDL NEW BUSINESS	
1:45 PM	A. Bone Metabolism Drugs Class Update	D. Moretz (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Tymlos™ (abaloparatide) New Drug Evaluation	
	3. Public Comment	

	4. Discussion of Clinical Recommendations to OHA	
2:05 PM	B. Oral First and Second Generation Antipsychotics Class Update 1. Class Update/Safety Edits 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:20 PM	C. Luxturna™ (voretigene neparvovec) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:40 PM	D. Atopic Dermatitis DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Dupixent® (dupilumab) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:00 PM	BREAK	
3:10 PM	E. Keveyis® (dichlorphenamide) Drug Evaluation 1. Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	E. Hull (OSU)
3:30 PM	F. Anti-Parkinson's Agents Class Update 1. Class Update/Prior Authorization Criteria 2. Xadago® (safinamide) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	J. Page (OSU)
3:45 PM	G. Benlysta® (belimumab) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
4:05 PM	H. Fluoroquinolone Class Update 1. Class Update 2. Baxdela™ (delafloxacin) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
4:20 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

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

OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: March 2018

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. 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 90 days before the scheduled Committee meeting to ensure adequate time for the appointment process.

3. 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. 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.

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 Standard Methods for Quality Assessment of Evidence.

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 may be submitted and considered during the draft comment period prior to posting of final documents. 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.

HIGH COST MARGINAL BENEFIT THERAPIES POLICY

1. The goal of this policy is to collaborate with and assist the HERC to evaluate available evidence with a transparent process to encourage safe and financially sustainable policies that maximize access to high value medications for patients served by the OHP.

2. The P&T Committee evaluates drugs for evidence of clinical effectiveness and safety as defined by the P&T Committee Operating Procedures for PDL decision-making.

3. After the clinical review, cost is considered in the executive session. After the executive session, recommendations to be made to the OHA are made with a public vote.

4. The P&T Committee may elect to recommend the HERC consider adding drugs that exhibit one or more of the following characteristics to the Prioritized List of Health Services:

    a. Marginal clinical benefit
    b. No clinically important benefit
    c. Harms that outweigh benefits
    d. Very high cost in which the benefit does not justify the cost
    e. Significantly greater cost compared to alternate therapies when both have similar benefit
    f. Significant budget impact that could affect the overall Prioritized List funding level

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 25, 2018, 1:00-5:00 PM
Human Services Building
Salem, OR 97301

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

Members Present: Tracy Klein, PhD, FNP; Phil Levin, PhD; William Origer, MD; Rich Clark, MD, MPH; Walter Hardin, DO, MBA

Members Present by Phone: Caryn Mickelson, PharmD; Kelley Burnett, DO; Dave Pass, MD; Jim Slater, PharmD

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Trevor Douglass, DC, MPH; Sarah Servid, PharmD; Lindsay Newton; Kim Wentz, MD; Julia Verhulst, PharmD; Jonnaliz Corbett; Megan Herink, PharmD

Staff Present by Phone: Dean Haxby, PharmD; Kathy Sentena, PharmD

**Audience: ***Maria Agapova, Teva Pharmaceuticals; *Donna Thurston, Celgene, Inc.; Leslie Mann, Celgene, Inc.; Cheryl Fletcher, AbbVie; *Margaret Olman, AbbVie; Deron Grothe, Teva; Leo Yasinksi, Merck; Anthony Hager, BMS; *Barbara Perry, Pfizer; Michael Estoos, Pfizer; Nina Hartman, Neurocrin; Raulo Frear, Merck; Peirce Enjerson, OHSU; Sean Pascoe, Novartis; *Lisa Stroup, Neurocrine; *Sylvia Churchill, Amgen; Camille Kerr, Amgen; Lisa Boyle, WVP Health; Bruce Smith, Glaxo Smith Kline; Andrew Seaman, Central City Concern; Martyna Witkowska, Central City Concern; Jennifer Svec, MedImpact; Sher Adams, Sunovion; Jeana Colabianchi, Sunovion; *Bethany Jones, Sunovion; Lyle Laird, Sunovion; Venus Holder, Lilly

(*) Provided verbal testimony

Written testimony provided:

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:02 pm. Introductions were made by Committee members and staff.
B. Mr. Douglass discussed the roles and responsibilities of the P&T Committee.
C. Mr. Douglass discussed the new conflict of interest form and the requirements that each committee member fill it out and declare any new conflicts by contacting him.
D. The committee elected Tracy Klein as the chair and Caryn Mickelson as the vice chair.
E. Mr. Douglass provided a department update and legislative update.
F. Approval of agenda and November minutes presented by Mr. Citron. (pages 4-8)

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

II. CONSENT AGENDA TOPICS

A. Noctiva (desmopressin) abbreviated drug review (page 9)
    1. Restrict use for OHP-funded conditions through Prior Authorization.

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

B. Drugs for Asthma and COPD Literature Scan (pages 10-42)
    1. Update the LAMA/LABA PA criteria to accommodate Trelegy Ellipta based on evidence.
    2. Remove the coverage of uncomplicated chronic bronchitis from the ICS, LABA, LABA/ICS and LAMA/LABA PA criteria as this is no longer a funded diagnosis.

    ACTION: Motion to approve, 2nd, All in Favor of number 1. Majority in favor, one opposed to number two. Approved.

III. DUR New Business

A. Hepatitis C Direct-Acting Antivirals Policy Discussions (pages 43-54)
Dr. Herink presented the proposal of modifying the PA criteria.
    1. Prior authorization criteria
        i. Modify PA criteria to clarify the definition of type 2 diabetes and insulin resistance.
    2. Treatment of Hepatitis C in people who inject drugs presentation. Presented by Dr. Seaman, OHSU
    3. Public Comment
    4. Discussion of clinical recommendations to OHA

    ACTION: Modified proposed language in 8e to just type 2 diabetes mellitus and remove proposed insulin resistance definition. Requested staff bring back SUD question with evidence to September P&T meeting. Motion to approve, 2nd. Majority in favor, two opposed. Approved.

IV. Preferred Drug List New Business

A. Biologics for Autoimmune conditions class update (pages 55 - 74)
Dr. Page presented the proposal of updating the PA criteria to:

1. Modify PA Criteria as follows:
    a. Add new and updated indications to the approved indications table
    b. Add guselkumab and sarilumab to the PA criteria
    c. Remove natalizumab (Tysabri) from biologic PA criteria

ACTION: Recommended changing the table heading in PA criteria to approved and funded conditions. Motion to approve, 2nd. All in favor. Approved.

B. Vesicular Monoamine Transporter 2 Inhibitors Class Review (pages 108-134)
Dr. Sentena presented the proposal to update the PA criteria to:

1. Create a new PDL class for VMAT2 inhibitors.
2. Implement prior authorization criteria for valbenazine, deutetrabenazine and tetrabenazine to ensure appropriate use.
3. Due to limited efficacy and safety data, make all products non-preferred.

ACTION: Modify PA to remove question #10 concerning specific diagnoses. Motion to approve, 2nd. All in favor. Approved.

C. Oral First and Second Generation Antipsychotics Class Update (pages 135-162)
D.

ACTION: Deferred to the March meeting

E. PCSK-9 Inhibitors Class Update (pages 163-184)
Dr. Herink presented the class update
1. Continue to require prior authorization for approval of evolocumab and alirocumab to approve for high CV risk patients that have been included in clinical studies.
2. No changes to PDL recommended.

ACTION: Modify PA requirement for trial of high-intensity statin and ezetimibe to 3 months in question #4 and remove time restriction for a recent LDL-C. Modify definition for clinical atherosclerotic cardiovascular disease in question #3 to mirror inclusion criteria of clinical trials and require at least one additional major risk factor or 2 minor risk factors. Motion to approve, 2nd. All in favor. Approved.

V. DUR Activities

A. Quarterly Utilization Reports (pages 185-190)
B. ProDUR Report (pages 191-194)
C. RetroDUR Report (pages 195-198)

ACTION: Deferred to the March meeting

VI. EXECUTIVE SESSION

VII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Drugs for Ashtma and COPD Literature Scan (pages 10-42)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

B. Biologics for Autoimmune conditions class update (pages 55 - 74)
*__ACTION:__ Modify PA criteria to require trial and failure of preferred Humira or Enbrel products.
Motion, 2nd, All in Favor. Approved.

C. Vesicular Monoamine Transporter 2 Inhibitors Class Review (pages 108-134)
*__ACTION:__ No changes to the PMPDP. Refer to HERC for prioritization consideration and update PA criteria as needed.
Motion, 2nd, All in Favor. Approved.

D. PCSK-9 Inhibitors Class Update (pages 163-184)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

VIII. ADJOURN

Drug Use Research & Management Program
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Literature Scan: Antiepileptics

Date of Review: March 2018

Date of Last Review: July 2016
End Date of Literature Search: 12/11/2017

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

Conclusions:

- There are no new evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- Two Cochrane reviews included moderate to high quality evidence to evaluate carbamazepine safety and efficacy compared with lamotrigine or topiramate when used as monotherapy in patients with epilepsy.[1,2] Lamotrigine was significantly less likely to be withdrawn than carbamazepine, but the results for time to first seizure suggested that carbamazepine may be superior in terms of seizure control.[1] For individuals with focal onset seizures, there is evidence that 12-month remission will be achieved earlier with carbamazepine than with topiramate.[2]
- A systematic review evaluating the safety of levetiracetam in pediatric patients identified behavioral problems and somnolence as the most prevalent adverse events and the most common causes of treatment discontinuation.[4] In addition, children receiving levetiracetam in combination with other AEDs had a greater risk of adverse events than those receiving monotherapy with levetiracetam.[4]
- Five AED medications received expanded indications from the Food and Drug Administration (FDA) since the last AED class update. Fosphenytoin received approval for use in pediatric patients with status epilepticus from birth through 17 years of age.[5] Lacosamide and eslicarbazepine are now indicated for use in pediatric patients with focal onset seizures aged 4 years and older.[6,7] Only the oral formulations of lacosamide are approved for use in children; the intravenous (IV) product remains recommended for use only in adults.[6] Perampanel received an expanded indication for monotherapy for treatment of focal seizures with or without secondary generalized seizures in patients with epilepsy 12 years of age and older.[8] Brivaracetam received an expanded indication for monotherapy treatment in patients with focal seizures in patients 16 years of age and older with epilepsy.[9]
- The FDA expanded safety warnings for 4 AEDs since the last class update. The warnings and precaution labeling for perampanel and lacosamide were revised to include information about Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, associated with therapy.[6,8] DRESS may be fatal or life-threatening and patients should be evaluated immediately if they experience fever, rash, lymphadenopathy, and/or facial swelling. Labeling for levetiracetam was updated to include warnings and precautions describing the risk for anaphylaxis and angioedema associated with levetiracetam administration.[10] Measurement of serum sodium and chloride levels should be considered during maintenance treatment with eslicarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels, and should be performed if symptoms of hyponatremia develop.[7]

Recommendations:

- No further review or research needed at this time. Review comparative drug costs in the executive session

Previous Conclusions:

- The American Academy of Neurology and the American Epilepsy Society published evidence-based guidelines for starting AEDs in adults after a first seizure. The authors found moderate evidence that immediate AED therapy as compared with no treatment is likely to reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years.
- There is moderate quality evidence lacosamide is effective and well tolerated in the short term when used as add-on treatment for drug-resistant partial epilepsy in adults.
- There are insufficient data to address the risk-benefit balance of vigabatrin versus carbamazepine monotherapy for epilepsy in adults and children.
- There is moderate quality evidence that describes common adverse effects with lamotrigine therapy in pediatric patients. The most commonly reported adverse events include: rash, headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia. Children on lamotrigine monotherapy had lower incidences of adverse events compared to those taking multiple AEDs.
- There is low quality evidence that levetiracetam is effective in reducing neuropathic pain but it is associated with an increase in adverse events and premature discontinuation due to side effects.
- There is moderate quality evidence that discontinuing an AED in children prior to at least 2 seizure-free years is associated with a higher recurrence rate than waiting 2 or more seizure-free years. The optimal time of withdrawal is not clear due to insufficient evidence. There is no evidence to guide AED discontinuation in adults.
- For all the currently marketed AEDs, there is no evidence to support the use of any of them in treating migraines. Topiramate, sodium valproate and divalproex are effective prophylactic treatments for episodic migraine in adults. There is insufficient evidence to further support the use of gabapentin in migraine prophylaxis.
- There is low quality evidence that topiramate may be effective in reducing the frequency of binge eating in patients with binge-eating disorder

Previous Recommendations:

- No further review or research needed at this time. After the executive session, no changes to the PDL were made.

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 Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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

New Systematic Reviews:

Cochrane: Individual Participant Data Reviews

A series of Cochrane reviews evaluating pair-wise monotherapy comparisons of carbamazepine, phenobarbital, lamotrigine, topiramate, phenytoin and valproate were updated in 2016 and 2017.[1,2,11-13] Each of these updates compiled a meta-analysis of individual participant data (IPD), in which the raw individual level data for each study were obtained from the investigators and used for synthesis of the meta-analysis.[14] Traditional meta-analysis methods involve combining quantitative evidence from related studies to evaluate outcomes. The goal of IPD meta-analysis is to summarize the raw data on a specific clinical question from multiple related studies.[14] IPD analyses are time consuming to generate because the original investigators must be contacted to ask if they will share their raw data for the report. Only the updates that were based on moderate to high quality evidence will be described in detail for this class update. Three separate updates evaluated carbamazepine and phenobarbital, [11] carbamazepine and phenytoin,[13] and phenytoin with valproate,[12] but the recently published trials included in these updates were imprecise and may have misclassified seizure type, so the methodological quality of the evidence was rated as low by the Cochrane reviewers. Therefore, they are not included in this summary.

One of the Cochrane updates in this series evaluated new evidence published through October 2017 for head to head trials comparing lamotrigine to carbamazepine in people with focal or generalized onset seizures.[1] The authors used the IPD method to compile data for the meta-analysis. The primary outcome was time to withdrawal of allocated treatment. Secondary outcomes included time to first seizure, time to remission, and incidence of adverse events. Thirteen studies were identified for this update. IPD were available for 2572 participants out of 3394 individuals from 9 out of 13 trials, or 78% of the potential data.[1] The results of this review are applicable mainly to individuals with focal seizures as 88% of included individuals experienced seizures of this type at baseline.[1] The methodological quality of the included trials was generally good, but there is some evidence that the design choice of open-label treatment may have influenced the withdrawal rates of the trials.[1] Therefore, the quality of the evidence for the primary outcome of treatment withdrawal was judged as moderate for individuals with focal seizures and low for individuals with generalized seizures.[1] For efficacy outcomes (first seizure and remission), the quality of evidence was rated as high for individuals with focal seizures and moderate for individuals with generalized seizures.[1] For remission outcomes, a hazard ratio (HR) less than one indicated an advantage for carbamazepine, and for first seizure and withdrawal outcomes a HR less than one indicated an advantage for lamotrigine.[1] Results were pooled and adjusted for seizure type when HR were calculated. The main results showed a significant advantage for lamotrigine compared to carbamazepine for withdrawal but a significant advantage for carbamazepine compared to lamotrigine for first seizure and six-month remission [time to withdrawal of allocated treatment (HR 0.72, 95% CI 0.63 to 0.82); time to first seizure (HR 1.22, 95% CI 1.09 to 1.37); and time to six-month remission (HR 0.84, 95% CI 0.74 to 0.94)].[1] No difference was found between the 2 drugs for time to 12-month remission (HR 0.91, 95% CI 0.77 to 1.07) or time to 24-month remission (HR 1.00, 95% CI 0.80 to 1.25), however, only two trials included follow up for more than one year so the evidence is limited for this outcome.[1] The most commonly reported adverse events for both of the drugs across all of the included trials were dizziness, fatigue, gastrointestinal disturbances, headache and rash. The rate of adverse events was similar for the carbamazepine and lamotrigine.[1] Lamotrigine was significantly less likely to be withdrawn than carbamazepine, but the results for time to first seizure suggested that carbamazepine may be have improved seizure control up to 6 months.[1]

A second pairwise analysis with carbamazepine and topiramate evaluated comparative head to head evidence in patients with focal and generalized seizures through April 2016. The primary outcome was time to withdrawal of allocated treatment, and secondary outcomes were time to first seizure, time to remission, and incidence of adverse events. Three studies were identified and IPD were available for 1151 of 1239 eligible individuals from 2 of the 3 studies, or 93% of the

potential data.[2] Data from the third trial (n=88) was unavailable. A small proportion of individuals recruited into these trials had unclassified seizures so for analysis purposes these individuals were grouped with those with generalized onset seizures.[2] The results of this review are applicable mainly to individuals with focal onset seizures as 85% of included individuals experienced seizures of this type.[2] The methodological quality of the included trials was good; however, there was some evidence that the open label design of the larger of the two trials may have influenced the withdrawal rate from the trial.[2] Therefore, the evidence for the primary outcome of treatment withdrawal was rated as moderate for individuals with focal seizures and low for individuals with generalized seizures.[2] For efficacy outcomes (first seizure and remission), the authors judged the evidence from this review to be high quality for individuals with focal seizures and moderate quality for individuals with generalized or unclassified seizures.[2] For remission outcomes, a HR less than 1 indicated an advantage for carbamazepine, and for first seizure and withdrawal outcomes, a HR less than 1 indicated an advantage for topiramate.[2] There were no significant differences between carbamazepine and topiramate in time to withdrawal, time to first seizure or 6-month remission rates [time to withdrawal of allocated treatment (HR 1.16, 95% CI 0.98 to 1.38); time to first seizure (HR 1.11, 95% CI 0.96 to 1.29); and time to 6-month remission (HR 0.88, 95% CI 0.76 to 1.01)].[2] However, a trend toward improved remission with carbamazepine was shown for time to 12-month remission (HR 0.84, 95% CI 0.71 to 1.00) compared to topiramate.[2] The most commonly reported adverse events with both drugs were drowsiness or fatigue, tingling sensation, headache, gastrointestinal disturbance and anxiety or depression. The rate of adverse events was similar for topiramate and carbamazepine.[2] For individuals with focal onset seizures, there is evidence that 12-month remission will be achieved earlier with carbamazepine than with topiramate.[2]

Pediatrics

A 2016 systematic review evaluated adverse effects observed in children taking levetiracetam.[4] The literature search was conducted through February 2015. Sixty-seven articles involving 3174 patients ages 18 years or younger were identified. The identified literature included twenty prospective cohort studies, 21 retrospective cohort studies, 4 pharmacokinetic studies, 16 case reports, and 6 RCTs. Five of the 6 RCTs were evaluated as having a low risk of bias. One RCT had a high risk of bias due to uncertain blinding methods for outcome assessments and investigators.[4] A meta-analysis of the RCTs was completed to evaluate the association between levetiracetam and commonly reported adverse effects (AEs) or treatment discontinuation stratified by type of regimen (monotherapy vs. polytherapy). A total of 1,913 AEs were reported across all 67 studies.[4] The most common AEs were behavioral problems and somnolence, which accounted for 10.9% and 8.4% of all AEs in prospective studies.[4] In the prospective studies involving 1120 children, 47% of these children experienced AEs.[4] Significantly more children experienced AEs with polytherapy (64%) than monotherapy (22%) ($p<0.001$).[4]

New Guidelines: No new guidelines were identified since the last literature scan.

New Formulations or Indications:

Cerebyx® (fosphenytoin) (March 2017): Fosphenytoin received expanded approval for pediatric patients from birth to less than 17 years of age for the treatment of generalized status epilepticus.[5] Prior to this approval, fosphenytoin was not labeled for administration in pediatric patients. Pediatric dosing is different from adult dosing in that loading doses should be administered in the range of 10 to 15 mg phenytoin equivalents (PE) per kilogram (kg) followed by a maintenance dose of 2 to 4 mg PE/kg every 12 hours.[5] The recommended adult loading dose is 15 to 20 mg PE/kg followed by a maintenance dose of 4 to 6 mg PE/kg in divided doses.[5]

Fycompa® (perampanel) (July 2017): Perampanel received an expanded indication for monotherapy for treatment of focal seizures with or without secondary generalized seizures in patients with epilepsy 12 years of age and older.[8] The pediatric approval was based on FDA guidance that permits drug efficacy in adults to be extrapolated to pediatric patients.[15] Only efficacy data may be extrapolated; safety studies must still be conducted in pediatric populations. The original

FDA approved indication for perampanel in 2012 was as adjunctive therapy for treatment of focal seizures with or without secondarily generalized seizures in patients aged 12 years and older.

Briviact® (brivaracetam) (September 2017): Brivaracetam received an expanded indication for monotherapy treatment in patients with focal seizures in patients 16 years of age and older with epilepsy as of September 2017.[9] Brivaracetem was originally FDA approved in 2016 as adjunctive treatment for focal seizures in patients 16 years of age and older with epilepsy.

Aptiom® (eslicarbazepine) (September 2017): Eslicarbazepine received FDA approval for management of focal seizures in pediatric patients age 4 years or older.[7] The original approval of eslicarbazepine in 2013 was only in adults with focal seizures. Approval for use in children was based on FDA guidance that permits extrapolation of data to support pediatric use. Data from 3 clinical trials support the safety and tolerability of eslicarbazepine in children.[16]

Vimpat® (lacosamide) (November 2017): Lacosamide tablets and oral solution are now approved in pediatric patients aged 4 to 17 years.[6] The original FDA approval was only in adults with focal seizures. The injectable formulation continues to be only approved for use in adults aged 17 years and older.[6]

New FDA Safety Alerts:

Fycompa® (perampanel) (July 2017): The warnings and precautions labeling for perampanel was revised to include information about Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking perampanel.[8] DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection.[8] Eosinophilia is often present. If such signs or symptoms are present, the patient should be evaluated immediately. Perampanel should be discontinued if an alternative etiology for the signs or symptoms cannot be established.[8]

Vimpat® (lacosamide) (March 2017): Lacosamide warnings and precautions section was updated to include the risk of DRESS, a very serious adverse drug event which has been reported with other AEDs.[6]

Keppra® (levetiracetam) (April 2017): Labeling for levetiracetam updated to include warnings and precautions describing the risk for anaphylaxis and angioedema associated with levetiracetam administration.[10]

Aptiom® (eslicarbazepine) (September 2017): Clinically significant hyponatremia (sodium less than 125 mEq/L) can develop in patients taking eslicarbazepine. Measurement of serum sodium and chloride levels should be considered during maintenance treatment with eslicarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels, and should be performed if symptoms of hyponatremia develop (e.g., nausea/vomiting, malaise, headache, lethargy, confusion, irritability, muscle weakness/spasms, obtundation, or increase in seizure frequency or severity).[7] Cases of symptomatic hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported during postmarketing use. In clinical trials, patients whose treatment with eslicarbazepine was discontinued because of hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.[7]

Randomized Controlled Trials:

A total of 138 citations were manually reviewed from the initial literature search. After further review, 137 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 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
Baulac, et al[17]	Lacosamide titrated up to 600 mg/day via protocol vs. carbamazepine CR titrated up to 1200 mg/day via protocol Phase 3, RCT, DB, MC non-inferiority trial	Patients aged 16 years or greater with focal or generalized seizures N= 888	Proportion of patients who remained seizure free for 6 months after dose stabilization. The predefined non-inferiority criteria was lower limit of 95% CI of absolute difference greater than -12%	Proportion of patients with seizures after 6 months of treatment. Full analysis set: Lacosamide 89.8% (n=444) Carbamazepine CR 91.1% (n=442) Absolute treatment-difference: −1.3%, 95% CI −5.5 to 2.8 Per protocol set: Lacosamide 91.5% (n=408) Carbamazepine CR 92.8% (n=397) Absolute treatment-difference: −1.3%, 95% CI −5.3 to 2.7

Abbreviations: CI = Confidence Interval; CR = controlled release; DB = double blind; MC = multi center; RCT = randomized controlled trial

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2. Nolan SJ, Sudell M, Tudur Smith C, Marson AG. Topiramate versus carbamazepine monotherapy for epilepsy: an individual participant data review. *Cochrane Database Syst Rev.* 2016;12:CD012065.
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4. Egunsola O, Choonara I, Sammons HM. Safety of Levetiracetam in Paediatrics: A Systematic Review. *PLoS ONE.* 2016;11(3):e0149686.
5. Cerebyx® (Fosphenytoin) Prescribing Information. New York, NY; Pfizer, Inc.: March 2017.
6. Vimpat® (lacosamide) Prescribing Information. Smyrna, GA; UCB, Inc.: November 2017.
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8. Fycompa® (perampanel) Product Information. Woodcliff Lake, NJ: Eisai, Inc; July 2017.
9. Briviact® (brivaraceteam) Prescribing Information. Smyrna, GA: UCB, Inc.; September 2017.
10. Keppra® (levetiracetem) Prescribing Information. Smyrna, GA; UCB, Inc.: October, 2017.
11. Nolan SJ, Marson AG, Weston J, Tudur Smith C. Carbamazepine versus phenobarbitone monotherapy for epilepsy: an individual participant data review. *Cochrane Database Syst Rev.* 2016;12:CD001904.
12. Nolan SJ, Marson AG, Weston J, Tudur Smith C. Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures: an individual participant data review. *Cochrane Database Syst Rev.* 2016;4:CD001769.
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14. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj.* 2010;340.
15. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. *Pediatrics.* 2011.
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17. Baulac M, Rosenow F, Toledo M, et al. Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Neurology.* 2017;16(1):43-54.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
PHENOBARBITAL	PHENOBARBITAL	ORAL	ELIXIR	Y
PHENOBARBITAL	PHENOBARBITAL	ORAL	TABLET	Y
DIAZEPAM	DIASTAT	RECTAL	KIT	Y
DIAZEPAM	DIASTAT ACUDIAL	RECTAL	KIT	Y
PHENYTOIN SODIUM EXTENDED	DILANTIN	ORAL	CAPSULE	Y
PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	ORAL	CAPSULE	Y
PHENYTOIN SODIUM EXTENDED	PHENYTEK	ORAL	CAPSULE	Y
PHENYTOIN	DILANTIN-125	ORAL	ORAL SUSP	Y
PHENYTOIN	PHENYTOIN	ORAL	ORAL SUSP	Y
PHENYTOIN	DILANTIN	ORAL	TAB CHEW	Y
PHENYTOIN	PHENYTOIN	ORAL	TAB CHEW	Y
ETHOTOIN	PEGANONE	ORAL	TABLET	Y
VALPROIC ACID (AS SODIUM SALT)	DEPAKENE	ORAL	SOLUTION	Y
VALPROIC ACID (AS SODIUM SALT)	VALPROIC ACID	ORAL	SOLUTION	Y
VALPROIC ACID	DEPAKENE	ORAL	CAPSULE	Y
VALPROIC ACID	VALPROIC ACID	ORAL	CAPSULE	Y
DIVALPROEX SODIUM	DEPAKOTE SPRINKLE	ORAL	CAP DR SPR	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM	ORAL	CAP DR SPR	Y
DIVALPROEX SODIUM	DEPAKOTE	ORAL	TABLET DR	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM	ORAL	TABLET DR	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM	ORAL	TABLET DR	Y
DIVALPROEX SODIUM	DEPAKOTE ER	ORAL	TAB ER 24H	Y
DIVALPROEX SODIUM	DIVALPROEX SODIUM ER	ORAL	TAB ER 24H	Y
PRIMIDONE	MYSOLINE	ORAL	TABLET	Y
PRIMIDONE	PRIMIDONE	ORAL	TABLET	Y
METHSUXIMIDE	CELONTIN	ORAL	CAPSULE	Y
ETHOSUXIMIDE	ETHOSUXIMIDE	ORAL	CAPSULE	Y
ETHOSUXIMIDE	ZARONTIN	ORAL	CAPSULE	Y
ETHOSUXIMIDE	ETHOSUXIMIDE	ORAL	SOLUTION	Y
ETHOSUXIMIDE	ZARONTIN	ORAL	SOLUTION	Y
CARBAMAZEPINE	CARBAMAZEPINE	ORAL	ORAL SUSP	Y
CARBAMAZEPINE	TEGRETOL	ORAL	ORAL SUSP	Y
CARBAMAZEPINE	CARBAMAZEPINE	ORAL	TABLET	Y
CARBAMAZEPINE	EPITOL	ORAL	TABLET	Y
CARBAMAZEPINE	TEGRETOL	ORAL	TABLET	Y
CARBAMAZEPINE	CARBAMAZEPINE	ORAL	TAB CHEW	Y

CARBAMAZEPINE	CARBAMAZEPINE ER	ORAL	TAB ER 12H	Y
CARBAMAZEPINE	TEGRETOL XR	ORAL	TAB ER 12H	Y
LAMOTRIGINE	LAMICTAL	ORAL	TABLET	Y
LAMOTRIGINE	LAMOTRIGINE	ORAL	TABLET	Y
GABAPENTIN	GABAPENTIN	ORAL	CAPSULE	Y
GABAPENTIN	NEURONTIN	ORAL	CAPSULE	Y
GABAPENTIN	GABAPENTIN	ORAL	TABLET	Y
GABAPENTIN	NEURONTIN	ORAL	TABLET	Y
TOPIRAMATE	TOPAMAX	ORAL	TABLET	Y
TOPIRAMATE	TOPIRAMATE	ORAL	TABLET	Y
OXCARBAZEPINE	OXCARBAZEPINE	ORAL	ORAL SUSP	Y
OXCARBAZEPINE	TRILEPTAL	ORAL	ORAL SUSP	Y
OXCARBAZEPINE	OXCARBAZEPINE	ORAL	TABLET	Y
OXCARBAZEPINE	TRILEPTAL	ORAL	TABLET	Y
TIAGABINE HCL	GABITRIL	ORAL	TABLET	Y
TIAGABINE HCL	TIAGABINE HCL	ORAL	TABLET	Y
LEVETIRACETAM	KEPPRA	ORAL	TABLET	Y
LEVETIRACETAM	LEVETIRACETAM	ORAL	TABLET	Y
LEVETIRACETAM	ROWEEPRA	ORAL	TABLET	Y
LEVETIRACETAM	KEPPRA	ORAL	SOLUTION	Y
LEVETIRACETAM	LEVETIRACETAM	ORAL	SOLUTION	Y
ZONISAMIDE	ZONEGRAN	ORAL	CAPSULE	Y
ZONISAMIDE	ZONISAMIDE	ORAL	CAPSULE	Y
RUFINAMIDE	BANZEL	ORAL	TABLET	Y
LACOSAMIDE	VIMPAT	ORAL	TABLET	Y
LAMOTRIGINE	LAMICTAL	ORAL	TB CHW DSP	V
LAMOTRIGINE	LAMOTRIGINE	ORAL	TB CHW DSP	V
LAMOTRIGINE	LAMICTAL (BLUE)	ORAL	TAB DS PK	V
LAMOTRIGINE	LAMICTAL (GREEN)	ORAL	TAB DS PK	V
LAMOTRIGINE	LAMICTAL (ORANGE)	ORAL	TAB DS PK	V
LAMOTRIGINE	LAMICTAL ODT	ORAL	TAB RAPDIS	V
LAMOTRIGINE	LAMOTRIGINE ODT	ORAL	TAB RAPDIS	V
LAMOTRIGINE	LAMICTAL ODT (ORANGE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMOTRIGINE ODT (ORANGE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMICTAL ODT (BLUE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMOTRIGINE ODT (BLUE)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMICTAL ODT (GREEN)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMOTRIGINE ODT (GREEN)	ORAL	TB RD DSPK	V
LAMOTRIGINE	LAMICTAL XR	ORAL	TAB ER 24	V

LAMOTRIGINE	LAMOTRIGINE ER	ORAL	TAB ER 24	V
LAMOTRIGINE	LAMICTAL XR (BLUE)	ORAL	TB ER DSPK	V
LAMOTRIGINE	LAMICTAL XR (GREEN)	ORAL	TB ER DSPK	V
LAMOTRIGINE	LAMICTAL XR (ORANGE)	ORAL	TB ER DSPK	V
LAMOTRIGINE	LAMICTAL XR	ORAL	TAB ER 24	V
LAMOTRIGINE	LAMOTRIGINE ER	ORAL	TAB ER 24	V
GABAPENTIN	GRALISE	ORAL	TAB ER 24H	N
CARBAMAZEPINE	CARBAMAZEPINE ER	ORAL	CPMP 12HR	N
CARBAMAZEPINE	CARBATROL	ORAL	CPMP 12HR	N
VIGABATRIN	SABRIL	ORAL	POWD PACK	N
VIGABATRIN	SABRIL	ORAL	TABLET	N
FELBAMATE	FELBAMATE	ORAL	ORAL SUSP	N
FELBAMATE	FELBATOL	ORAL	ORAL SUSP	N
FELBAMATE	FELBAMATE	ORAL	TABLET	N
FELBAMATE	FELBATOL	ORAL	TABLET	N
GABAPENTIN	NEURONTIN	ORAL	SOLUTION	N
GABAPENTIN	GABAPENTIN	ORAL	SOLUTION	N
TOPIRAMATE	TOPAMAX	ORAL	CAP SPRINK	N
TOPIRAMATE	TOPIRAMATE	ORAL	CAP SPRINK	N
TOPIRAMATE	TROKENDI XR	ORAL	CAP ER 24H	N
TOPIRAMATE	QUDEXY XR	ORAL	CAP SPR 24	N
TOPIRAMATE	TOPIRAMATE ER	ORAL	CAP SPR 24	N
OXCARBAZEPINE	OXTELLAR XR	ORAL	TAB ER 24H	N
LEVETIRACETAM	KEPPRA XR	ORAL	TAB ER 24H	N
LEVETIRACETAM	LEVETIRACETAM ER	ORAL	TAB ER 24H	N
LEVETIRACETAM	SPRITAM	ORAL	TAB SUSP	N
PREGABALIN	LYRICA	ORAL	CAPSULE	N
PREGABALIN	LYRICA	ORAL	SOLUTION	N
RUFINAMIDE	BANZEL	ORAL	ORAL SUSP	N
LACOSAMIDE	VIMPAT	ORAL	SOLUTION	N
ESLICARBAZEPINE ACETATE	APTIOM	ORAL	TABLET	N
PERAMPANEL	FYCOMPA	ORAL	TABLET	N
PERAMPANEL	FYCOMPA	ORAL	ORAL SUSP	N
BRIVARACETAM	BRIVIACT	ORAL	SOLUTION	N
BRIVARACETAM	BRIVIACT	ORAL	TABLET	N
GABAPENTIN ENACARBIL	HORIZANT	ORAL	TABLET ER	N
CLOBAZAM	ONFI	ORAL	TABLET	N
CLOBAZAM	ONFI	ORAL	ORAL SUSP	N

Appendix 2: Abstracts of Comparative Clinical Trials

Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial.
Baulac, M., Rosenow, F., Toledo, M., et al.
Lancet Neurol. 2017 Jan; 16(1):43-54. doi: 10.1016/S1474-4422(16)30292-7.

BACKGROUND: Further options for monotherapy are needed to treat newly diagnosed epilepsy in adults. We assessed the efficacy, safety, and tolerability of lacosamide as a first-line monotherapy option for these patients.
METHODS: In this phase 3, randomised, double-blind, non-inferiority trial, patients from 185 epilepsy or general neurology centres in Europe, North America, and the Asia Pacific region, aged 16 years or older and with newly diagnosed epilepsy were randomly assigned in a 1:1 ratio, via a computer-generated code, to receive lacosamide monotherapy or controlled-release carbamazepine (carbamazepine-CR) twice daily. Patients, investigators, and trial personnel were masked to treatment allocation. From starting doses of 100 mg/day lacosamide or 200 mg/day carbamazepine-CR, up titration to the first target level of 200 mg/day and 400 mg/day, respectively, took place over 2 weeks. After a 1-week stabilization period, patients entered a 6-month assessment period. If a seizure occurred, the dose was titrated to the next target level (400 or 600 mg/day for lacosamide and 800 or 1200 mg/day for carbamazepine-CR) over 2 weeks with a 1-week stabilization period, and the 6-month assessment period began again. Patients who completed 6 months of treatment and remained seizure-free entered a 6-month maintenance period on the same dose. The primary efficacy outcome was the proportion of patients remaining free from seizures for 6 consecutive months after stabilization at the last assessed dose. The predefined non-inferiority criteria were -12% absolute and -20% relative difference between treatment groups. This trial is registered with ClinicalTrials.gov, number NCT01243177.
FINDINGS: The trial was done between April 27, 2011, and Aug 7, 2015. 888 patients were randomly assigned treatment. 444 patients taking lacosamide and 442 taking carbamazepine-CR were included in the full analysis set (took at least one dose of study treatment), and 408 and 397, respectively, were included in the per-protocol set. In the full analysis set, 327 (74%) patients in the lacosamide group and 308 (70%) in the carbamazepine-CR group completed 6 months of treatment without seizures. The proportion of patients in the full analysis set predicted by the Kaplan-Meier method to be seizure-free at 6 months was 90% taking lacosamide and 91% taking carbamazepine-CR (absolute treatment-difference: -1.3%, 95% CI -5.5 to 2.8 relative treatment difference: -6.0%). Kaplan-Meier estimates results were similar in the per-protocol set (92% and 93%; -1.3%, -5.3 to 2.7; -5.7%). Treatment-emergent adverse events were reported in 328 (74%) patients receiving lacosamide and 332 (75%) receiving carbamazepine-CR. 32 (7%) patients taking lacosamide and 43 (10%) taking carbamazepine-CR had serious treatment-emergent adverse events, and 47 (11%) and 69 (16%), respectively, had treatment-emergent adverse events that led to withdrawal.
INTERPRETATION: Treatment with lacosamide met the predefined non-inferiority criteria when compared with carbamazepine-CR. Therefore, it might be useful as first-line monotherapy for adults with newly diagnosed epilepsy.
FUNDING: UCB Pharma.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 5 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 11, 2017

1	Carbamazepine	11358
2	Diazepam/	18868
3	divalproex.mp. or Valproic Acid/	12820
4	Ethosuximide/	959
5	ethotoin.mp.	48
6	Anticonvulsants/ or gabapentin.mp.	54656
7	lacosamide.mp.	586
8	lamotrigine.mp.	5056
9	levetiracetam.mp.	2734
10	methsuximide.mp.	107
11	oxcarbazepine.mp.	1792
12	Phenobarbital/	18995
13	Phenytoin/	14221
14	Primidone/	1373
15	rufinamide.mp.	211
16	tiagabine.mp.	993
17	topiramate.mp.	4369
18	Valproic Acid/	12589
19	zonisamide.mp.	1239
20	brivaracetam.mp.	136
21	clobazam.mp.	886
22	esclicarbazepine.mp.	2
23	felbamate.mp.	761
24	perampanel.mp.	215
25	Pregabalin/	1784

26	Vigabatrin/	1721
27	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	113635
28	Epilepsy/	74323
29	27 and 28	20504
30	limit 29 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	138

Clobazam

Goal(s):

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

Length of Authorization:

- 12 months

Requires PA:

- Clobazam

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is 2 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Limitations of Use:

• Clobazam is not indicated for other epilepsy syndromes other than Lennox-Gastaut.

P&T Review: *3/18 (DM); 7/16; 3/15; 5/12*
Implementation: *8/16, 8/12*

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin

Covered Alternatives

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

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to # 4
4. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to # 5	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days
Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin
Funded	
Diabetic Neuropathy	X
Post herpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	X
Chemotherapy Induced Neuropathy	X
Non-funded	
Fibromyalgia	X

P&T Review: *3/18 (DM); 3/17*
Implementation: *4/1/17*

Topiramate

Goal(s):

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

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	

P&T Review: *3/18 (DM); 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: July 2016 - June 2017

Eligibility	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Total Members (FFS & Encounter)	1,018,479	1,005,560	991,736	990,652	980,593	969,749	956,495	953,093	978,100	991,147	991,908	994,823	985,195
FFS Members	145,488	143,283	149,942	155,740	139,906	142,728	144,554	140,575	146,756	144,374	130,857	135,409	143,301
OHP Basic with Medicare	32,597	32,574	32,707	32,844	32,823	32,859	32,850	32,815	33,065	33,156	33,179	33,308	32,898
OHP Basic without Medicare	13,155	13,263	13,490	13,382	12,478	12,602	12,851	12,507	12,526	12,803	12,559	12,546	12,847
ACA	99,736	97,446	103,745	109,514	94,605	97,267	98,853	95,253	101,165	98,415	85,119	89,555	97,556
Encounter Members	872,991	862,277	841,794	834,912	840,687	827,021	811,941	812,518	831,344	846,773	861,051	859,414	841,894
OHP Basic with Medicare	40,186	40,383	40,452	40,531	40,691	40,697	40,501	40,586	40,562	40,614	40,798	40,843	40,570
OHP Basic without Medicare	69,438	68,793	67,857	67,357	67,819	67,277	67,089	67,386	67,328	67,031	67,125	66,631	67,594
ACA	763,367	753,101	733,485	727,024	732,177	719,047	704,351	704,546	723,454	739,128	753,128	751,940	733,729

Gross Cost Figures for Drugs	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	YTD Sum
Total Amount Paid (FFS & Encounter)	$65,695,875	$71,045,169	$67,932,801	$68,305,053	$68,714,085	$69,401,753	$72,775,276	$68,974,502	$76,840,335	$68,821,689	$76,396,599	$75,200,797	$850,103,935
Mental Health Carve-Out Drugs	$7,818,910	$8,456,103	$7,889,079	$7,591,298	$7,800,551	$7,807,415	$8,125,700	$7,711,923	$8,462,436	$7,738,563	$8,401,378	$8,178,437	$95,981,792
OHP Basic with Medicare	$820	$373	$753	$571	$263	$1,066	$1,485	$1,159	$3,134	$954	$912	$37	$11,527
OHP Basic without Medicare	$3,258,374	$3,506,338	$3,345,002	$3,146,213	$3,328,153	$3,324,446	$3,427,491	$3,256,589	$3,538,296	$3,171,738	$3,442,054	$3,334,810	$40,079,505
ACA	$4,499,995	$4,876,500	$4,482,950	$4,387,007	$4,407,208	$4,420,839	$4,633,994	$4,391,280	$4,841,958	$4,494,255	$4,877,395	$4,769,262	$55,082,644
FFS Physical Health Drugs	$3,245,095	$3,778,350	$3,651,811	$3,616,107	$3,468,582	$3,231,382	$3,782,091	$3,457,219	$3,740,927	$3,268,691	$3,492,633	$3,151,258	$41,884,147
OHP Basic with Medicare	$206,008	$305,966	$214,518	$277,259	$295,141	$203,069	$302,332	$289,950	$264,349	$238,202	$242,693	$229,641	$3,069,128
OHP Basic without Medicare	$942,671	$1,121,245	$1,069,465	$1,039,983	$924,524	$880,054	$1,008,992	$927,660	$1,275,721	$1,053,864	$1,121,164	$953,861	$12,319,205
ACA	$2,013,202	$2,245,632	$2,261,235	$2,192,744	$2,148,451	$2,063,764	$2,353,455	$2,131,739	$2,080,046	$1,821,219	$2,001,873	$1,810,238	$25,123,595
FFS Physician Administered Drugs	$1,587,188	$1,632,454	$1,880,000	$1,700,895	$1,704,885	$2,359,990	$2,867,822	$2,718,693	$2,566,488	$1,830,721	$2,832,333	$2,819,792	$26,501,260
OHP Basic with Medicare	$303,285	$341,720	$416,386	$334,626	$319,948	$319,411	$372,932	$362,721	$436,844	$417,814	$419,963	$331,186	$4,376,835
OHP Basic without Medicare	$233,033	$213,973	$400,978	$339,971	$232,377	$208,845	$325,771	$390,043	$391,707	$250,690	$1,244,383	$1,215,063	$5,446,835
ACA	$755,402	$816,605	$818,262	$809,276	$925,521	$1,084,152	$1,708,004	$1,304,553	$1,294,759	$753,789	$865,876	$892,456	$12,028,656
Encounter Physical Health Drugs	$43,926,133	$46,535,689	$44,738,958	$45,134,356	$46,887,911	$46,114,101	$47,276,968	$44,575,689	$50,819,111	$45,744,555	$50,113,614	$49,318,231	$561,185,315
OHP Basic with Medicare	$122,115	$144,249	$133,938	$140,880	$130,960	$116,418	$122,050	$116,407	$121,947	$114,965	$116,185	$109,262	$1,489,377
OHP Basic without Medicare	$11,813,234	$12,960,709	$12,293,476	$12,371,263	$12,811,247	$12,921,889	$13,135,377	$12,453,291	$13,691,968	$12,354,008	$13,530,417	$13,221,665	$153,558,545
ACA	$31,602,017	$32,951,237	$31,837,171	$32,182,953	$33,424,599	$32,525,509	$33,478,420	$31,415,680	$36,379,351	$32,686,958	$35,768,840	$35,309,865	$399,562,602
Encounter Physician Administered Drugs	$9,118,548	$10,642,572	$9,772,953	$10,262,398	$8,852,156	$9,888,866	$10,722,696	$10,510,978	$11,251,374	$10,239,159	$11,556,640	$11,733,079	$124,551,421
OHP Basic with Medicare	$184,152	$258,921	$200,824	$180,667	$196,461	$213,738	$234,350	$221,576	$268,497	$198,767	$254,867	$202,240	$2,615,060
OHP Basic without Medicare	$2,273,968	$2,402,546	$2,098,821	$2,344,744	$2,180,027	$2,565,423	$2,575,473	$2,313,145	$2,186,454	$2,348,429	$2,515,050	$2,305,663	$28,109,741
ACA	$6,006,716	$7,315,541	$7,111,331	$7,299,530	$6,260,861	$6,862,349	$7,719,932	$7,728,968	$8,615,892	$7,522,674	$8,519,781	$9,057,324	$90,020,900

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

Last Updated: January 17, 2018

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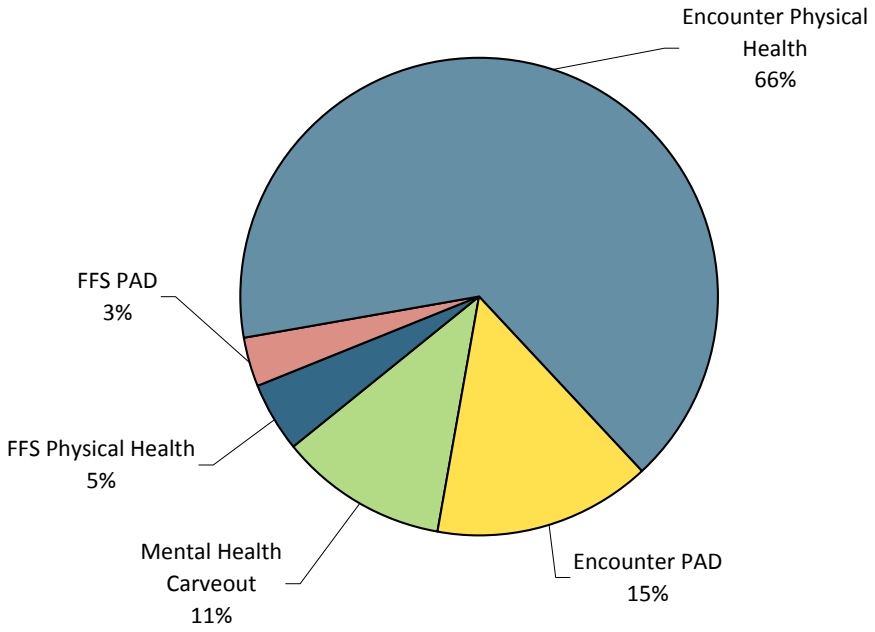
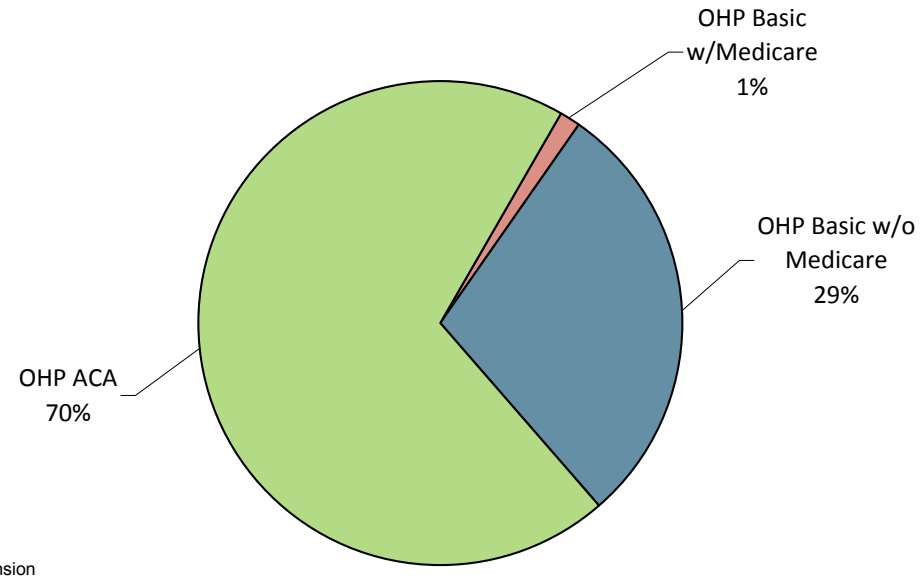
YTD Percent Paid Amounts





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

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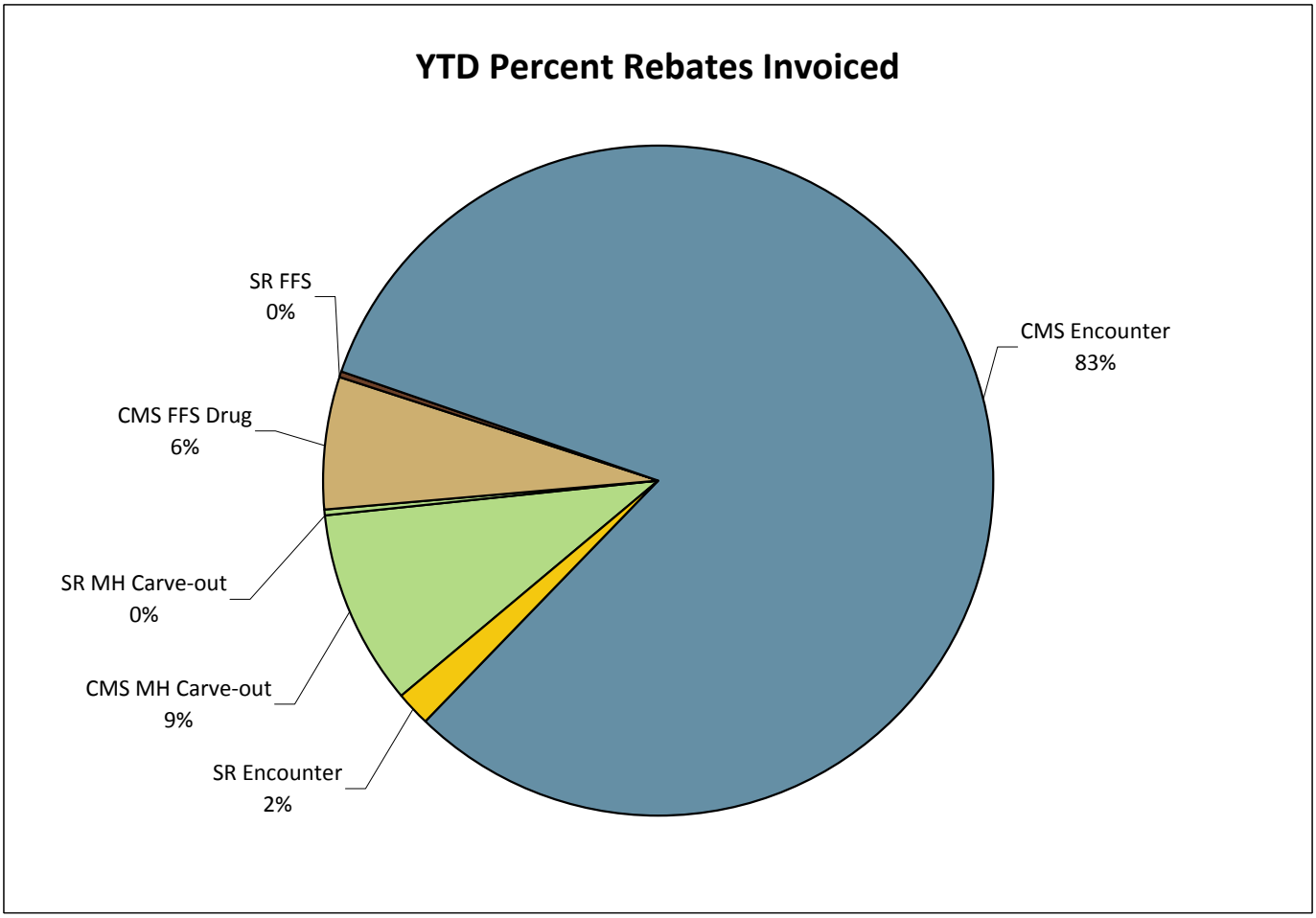
Pharmacy Utilization Summary Report: July 2016 - June 2017

Quarterly Rebates Invoiced	2016-Q3	2016-Q4	2017-Q1	2017-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$91,725,712	$100,306,583	$104,745,074	$146,298,846	$443,076,215
CMS MH Carve-out	$10,698,536	$9,516,452	$10,795,124	$10,313,237	$41,323,349
SR MH Carve-out		$512,346	$634,141	$595,005	$1,741,492
CMS FFS Drug	$5,905,328	$6,453,704	$7,981,325	$7,613,573	$27,953,930
SR FFS	$310,068	$275,999	$212,682	$219,390	$1,018,139
CMS Encounter	$73,587,961	$82,100,815	$83,010,368	$124,372,907	$363,072,051
SR Encounter	$1,223,820	$1,447,267	$2,111,433	$3,184,734	$7,967,254

Quaterly Net Drug Costs	2016-Q3	2016-Q4	2017-Q1	2017-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$112,948,133	$106,114,309	$113,845,039	$74,120,239	$407,027,720
Mental Health Carve-Out Drugs	$13,465,556	$13,170,465	$12,870,794	$13,410,136	$52,916,951
FFS Phys Health + PAD	$9,559,503	$9,352,138	$10,939,232	$9,562,465	$39,413,338
Encounter Phys Health + PAD	$89,923,074	$83,591,705	$90,035,014	$51,147,638	$314,697,431



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

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Pharmacy Utilization Summary Report: July 2016 - June 2017

Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$64.50	$70.65	$68.50	$68.95	$70.07	$71.57	$76.09	$72.37	$78.56	$69.44	$77.02	$75.59	$71.94
Mental Health Carve-Out Drugs	$7.68	$8.41	$7.95	$7.66	$7.95	$8.05	$8.50	$8.09	$8.65	$7.81	$8.47	$8.22	$8.12
FFS Physical Health Drugs	$22.30	$26.37	$24.35	$23.22	$24.79	$22.64	$26.16	$24.59	$25.49	$22.64	$26.69	$23.27	$24.38
FFS Physician Administered Drugs	$10.91	$11.39	$12.54	$10.92	$12.19	$16.53	$19.84	$19.34	$17.49	$12.68	$21.64	$20.82	$15.52
Encounter Physical Health Drugs	$50.32	$53.97	$53.15	$54.06	$55.77	$55.76	$58.23	$54.86	$61.13	$54.02	$58.20	$57.39	$55.57
Encounter Physician Administered Drugs	$10.45	$12.34	$11.61	$12.29	$10.53	$11.96	$13.21	$12.94	$13.53	$12.09	$13.42	$13.65	$12.33

Claim Counts	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Total Claim Count (FFS & Encounter)	973,754	1,037,962	995,151	1,009,290	1,006,948	988,262	1,032,861	972,753	1,093,763	1,009,960	1,076,783	1,025,121	1,018,551
Mental Health Carve-Out Drugs	145,016	156,001	146,047	146,342	146,382	144,472	148,825	138,430	156,070	146,682	158,908	152,231	148,784
FFS Physical Health Drugs	64,257	70,184	67,875	68,302	67,922	68,116	71,963	67,820	72,265	63,828	67,192	64,091	67,818
FFS Physician Administered Drugs	15,998	16,413	16,244	16,543	16,445	17,050	24,466	21,538	21,984	16,447	16,276	15,555	17,913
Encounter Physical Health Drugs	651,865	691,801	665,255	673,768	675,626	659,452	683,779	644,385	733,387	679,109	731,636	697,051	682,260
Encounter Physician Administered Drugs	96,618	103,563	99,730	104,335	100,573	99,172	103,828	100,580	110,057	103,894	102,771	96,193	101,776

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$67.47	$68.45	$68.26	$67.68	$68.24	$70.23	$70.46	$70.91	$70.25	$68.14	$70.95	$73.36	$69.53
Mental Health Carve-Out Drugs	$53.92	$54.21	$54.02	$51.87	$53.29	$54.04	$54.60	$55.71	$54.22	$52.76	$52.87	$53.72	$53.77
FFS Physical Health Drugs	$50.50	$53.83	$53.80	$52.94	$51.07	$47.44	$52.56	$50.98	$51.77	$51.21	$51.98	$49.17	$51.44
FFS Physician Administered Drugs	$99.21	$99.46	$115.74	$102.82	$103.67	$138.42	$117.22	$126.23	$116.74	$111.31	$174.02	$181.28	$123.84
Encounter Physical Health Drugs	$67.39	$67.27	$67.25	$66.99	$69.40	$69.93	$69.14	$69.18	$69.29	$67.36	$68.50	$70.75	$68.54
Encounter Physician Administered Drugs	$94.38	$102.76	$97.99	$98.36	$88.02	$99.71	$103.27	$104.50	$102.23	$98.55	$112.45	$121.97	$102.02

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$28.18	$27.85	$27.25	$26.84	$27.31	$27.81	$27.27	$27.24	$26.86	$26.16	$26.26	$26.57	$27.13
Mental Health Carve-Out Drugs	$37.55	$37.32	$36.54	$33.83	$33.80	$33.93	$34.24	$34.26	$33.25	$30.97	$30.21	$30.05	$33.83
FFS Physical Health Drugs	$24.27	$24.46	$23.64	$22.38	$23.23	$22.11	$23.85	$23.28	$22.65	$20.87	$21.20	$20.77	$22.73
Encounter Physical Health Drugs	$26.39	$25.96	$25.47	$25.70	$26.24	$27.00	$26.04	$26.09	$25.86	$25.57	$25.83	$26.30	$26.04

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$636.63	$630.84	$596.43	$588.51	$632.92	$634.05	$636.65	$649.24	$658.51	$655.34	$670.90	$685.66	$639.64
Mental Health Carve-Out Drugs	$728.43	$742.03	$754.62	$762.38	$781.59	$793.10	$800.67	$807.82	$808.01	$837.60	$852.43	$864.59	$794.44
FFS Physical Health Drugs	$423.92	$462.21	$451.14	$445.09	$425.89	$387.38	$421.88	$424.10	$444.00	$458.66	$468.93	$437.29	$437.54
Encounter Physical Health Drugs	$650.20	$638.95	$599.18	$590.10	$641.46	$646.22	$646.46	$659.43	$667.36	$658.64	$673.76	$692.38	$647.01

Multi-Source Drug Use Percentage	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Multi-Source Drug Use Percentage	94.1%	94.0%	93.5%	93.5%	93.7%	93.8%	93.7%	93.8%	93.9%	94.0%	94.0%	94.0%	93.8%
Mental Health Carve-Out Drugs	97.6%	97.6%	97.6%	97.5%	97.4%	97.4%	97.3%	97.2%	97.3%	97.3%	97.2%	97.2%	97.4%
FFS Physical Health Drugs	93.4%	93.3%	92.9%	92.8%	93.1%	93.1%	92.8%	93.1%	93.1%	93.1%	93.1%	93.2%	93.1%
Encounter Physical Health Drugs	93.4%	93.3%	92.7%	92.7%	93.0%	93.1%	93.1%	93.2%	93.2%	93.4%	93.4%	93.3%	93.1%

Preferred Drug Use Percentage	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Preferred Drug Use Percentage	85.98%	85.77%	85.54%	85.45%	85.15%	85.11%	86.67%	86.67%	86.64%	86.57%	86.43%	86.30%	86.0%
Mental Health Carve-Out Drugs	75.18%	75.02%	75.01%	76.23%	76.04%	76.02%	75.89%	75.79%	75.67%	75.64%	75.29%	75.09%	75.6%
FFS Physical Health Drugs	95.33%	95.37%	95.19%	95.26%	95.56%	95.45%	95.42%	95.35%	95.33%	95.17%	95.28%	95.25%	95.3%
Encounter Physical Health Drugs	87.42%	87.18%	86.87%	86.48%	86.11%	86.05%	88.09%	88.10%	88.12%	88.14%	88.01%	87.89%	87.4%

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

Last Updated: January 17, 2018

Drug Use Research & Management Program
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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2017

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$4,804,682	14.6%	4,408	$1,090	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,919,745	5.8%	1,051	$1,827	V
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$969,861	2.9%	544	$1,783	Y
4	REXULTI	Antipsychotics, 2nd Gen	$807,316	2.4%	798	$1,012	V
5	FLUOXETINE HCL	Antidepressants	$593,290	1.8%	30,651	$19	Y
6	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$575,297	1.7%	1,510	$381	V
7	ATOMOXETINE HCL	ADHD Drugs	$572,473	1.7%	4,429	$129	Y
8	SAPHRIS	Antipsychotics, 2nd Gen	$516,262	1.6%	829	$623	Y
9	VRAYLAR	Antipsychotics, 2nd Gen	$510,286	1.5%	484	$1,054	V
10	DULOXETINE HCL	Antidepressants	$493,629	1.5%	28,158	$18	V
11	SERTRALINE HCL	Antidepressants	$462,241	1.4%	40,037	$12	Y
12	INVEGA TRINZA	Antipsychotics, Parenteral	$457,814	1.4%	85	$5,386	V
13	VENLAFAXINE HCL ER	Antidepressants	$437,538	1.3%	1,985	$220	V
14	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$434,742	1.3%	501	$868	Y
15	TRAZODONE HCL	Antidepressants	$417,856	1.3%	36,872	$11	
16	BUPROPION XL	Antidepressants	$400,990	1.2%	20,216	$20	V
17	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$399,222	1.2%	1,717	$233	V
18	MAKENA*	Progestational Agents	$330,257	1.0%	138	$2,393	Y
19	VIIBRYD	Antidepressants	$318,001	1.0%	1,320	$241	V
20	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$301,425	0.9%	13,566	$22	V
21	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$276,321	0.8%	1,868	$148	
22	TRINTELLIX	Antidepressants	$276,166	0.8%	809	$341	V
23	QUETIAPINE FUMARATE ER*	Antipsychotics, 2nd Gen	$268,551	0.8%	2,845	$94	V
24	AMITRIPTYLINE HCL	Antidepressants	$268,187	0.8%	15,715	$17	Y
25	LAMOTRIGINE	Antiepileptics (oral & rectal)	$257,541	0.8%	21,424	$12	Y
26	ESCITALOPRAM OXALATE	Antidepressants	$248,100	0.8%	21,663	$11	Y
27	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$244,988	0.7%	15,797	$16	
28	CITALOPRAM HBR	Antidepressants	$234,679	0.7%	24,168	$10	Y
29	ARISTADA	Antipsychotics, Parenteral	$221,329	0.7%	129	$1,716	Y
30	Unclassified Drugs Or Biolog	Physican Administered Drug	$213,573	0.6%	18	$11,865	
31	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$203,888	0.6%	629	$324	V
32	HUMIRA PEN*	Biologics for Autoimmune Conditions	$198,353	0.6%	63	$3,148	Y
33	VENLAFAXINE HCL ER	Antidepressants	$194,216	0.6%	14,143	$14	Y
34	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$186,649	0.6%	14,307	$13	Y
35	LANTUS	Diabetes, Insulins	$181,449	0.5%	541	$335	Y
36	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$167,378	0.5%	48	$3,487	Y
37	FETZIMA	Antidepressants	$163,717	0.5%	449	$365	V
38	CLOZAPINE	Antipsychotics, 2nd Gen	$160,123	0.5%	2,843	$56	Y
39	BUPROPION HCL SR	Antidepressants	$156,407	0.5%	10,560	$15	Y
40	GENVOYA	HIV	$152,409	0.5%	78	$1,954	Y
		Top 40 Aggregate:	**$19,996,950**		**337,396**	**$1,032**	
		All FFS Drugs Totals:	**$33,019,364**		**651,665**	**$445**	

*** Drug requires Prior Authorization**

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

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2017

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	MAKENA*	Progestational Agents	$330,257	3.0%	138	$2,393	Y
2	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$276,321	2.5%	1,868	$148	
3	Unclassified Drugs Or Biolog	Physican Administered Drug	$213,573	2.0%	18	$11,865	
4	HUMIRA PEN*	Biologics for Autoimmune Conditions	$198,353	1.8%	63	$3,148	Y
5	LANTUS	Diabetes, Insulins	$181,449	1.7%	541	$335	Y
6	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$167,378	1.5%	48	$3,487	Y
7	GENVOYA	HIV	$152,409	1.4%	78	$1,954	Y
8	METHYLPHENIDATE ER*	ADHD Drugs	$152,199	1.4%	1,111	$137	N
9	Infliximab Not Biosimil 10mg	Physican Administered Drug	$149,778	1.4%	89	$1,683	
10	ORKAMBI*	Cystic Fibrosis	$146,452	1.3%	10	$14,645	N
11	ADVATE	Antihemophilia Factors	$140,680	1.3%	10	$14,068	
12	ADVAIR DISKUS	Corticosteroids/LABA Combination, Inhaled	$129,655	1.2%	436	$297	Y
13	TRIUMEQ	HIV	$124,486	1.1%	54	$2,305	Y
14	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$122,719	1.1%	2,038	$60	Y
15	Factor Viii Recombinant Nos	Physican Administered Drug	$115,301	1.1%	5	$23,060	
16	VENTOLIN HFA	Beta-Agonists, Inhaled Short-Acting	$105,259	1.0%	1,953	$54	Y
17	NUVARING	STC 63 - Oral Contraceptives	$96,520	0.9%	468	$206	
18	Inj Pembrolizumab	Physican Administered Drug	$94,934	0.9%	25	$3,797	
19	LANTUS SOLOSTAR*	Diabetes, Insulins	$94,640	0.9%	288	$329	Y
20	VYVANSE	ADHD Drugs	$92,650	0.9%	631	$147	Y
21	PULMOZYME	Cystic Fibrosis	$87,117	0.8%	56	$1,556	Y
22	SPIRIVA	Anticholinergics, Inhaled	$86,813	0.8%	259	$335	Y
23	Rituximab Injection	Physican Administered Drug	$86,736	0.8%	57	$1,522	
24	TRUVADA	HIV	$83,110	0.8%	70	$1,187	Y
25	NOVOLOG	Diabetes, Insulins	$82,121	0.8%	255	$322	Y
26	Factor Viii Pegylated Recomb	Physican Administered Drug	$80,367	0.7%	3	$26,789	
27	Drugs Unclassified Injection	Physican Administered Drug	$76,521	0.7%	4,258	$18	
28	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$74,987	0.7%	314	$239	Y
29	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$74,789	0.7%	3	$24,930	Y
30	QVAR	Corticosteroids, Inhaled	$74,010	0.7%	580	$128	Y
31	ZEPATIER*	Hepatitis C, Direct-Acting Antivirals	$72,839	0.7%	4	$18,210	Y
32	Etonogestrel Implant System	Physican Administered Drug	$72,117	0.7%	112	$644	
33	NOVOLOG FLEXPEN	Diabetes, Insulins	$71,716	0.7%	174	$412	Y
34	Aflibercept Injection	Physican Administered Drug	$70,828	0.7%	131	$541	
35	FLOVENT HFA	Corticosteroids, Inhaled	$70,800	0.7%	427	$166	Y
36	ONFI*	Antiepileptics (oral & rectal)	$70,034	0.6%	137	$511	N
37	HUMALOG	Diabetes, Insulins	$69,709	0.6%	249	$280	Y
38	LEVEMIR FLEXTOUCH*	Diabetes, Insulins	$67,997	0.6%	156	$436	Y
39	Mirena, 52 Mg	Physican Administered Drug	$63,835	0.6%	115	$555	
40	Factor Ix Recombinant Nos	Physican Administered Drug	$61,929	0.6%	1	$61,929	
		Top 40 Aggregate:	**$4,583,389**		**17,233**	**$5,621**	
		All FFS Drugs Totals:	**$10,873,248**		**199,875**	**$453**	

*** 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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Last updated: January 17, 2018

ProDUR Report for October through December 2017

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Set alert/Pay claim	19	7	0	12	0.01%	36.84%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,622	386	0	1,236	1.43%	23.80%
DD (Drug/Drug Interaction)	Set alert/Pay claim	156	51	0	105	0.13%	32.69%
ER (Early Refill)	Set alert/Deny claim	75,999	15,294	170	60,517	68.60%	20.12%
ID (Ingredient Duplication)	Set alert/Pay claim	22,898	6,379	15	16,488	20.63%	27.86%
LD (Low Dose)	Set alert/Pay claim	717	177	0	533	0.60%	24.69%
LR (Late Refill/Underutilization)	Set alert/Pay claim	5	4	0	1	0.00%	80.00%
MC (Drug/Disease Interaction)	Set alert/Pay claim	895	228	0	666	0.77%	25.47%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	726	188	1	536	0.63%	25.90%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	54	24	0	30	0.01%	44.44%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,622	2,441	2	5,166	6.83%	32.03%
	Totals	**110,713**	**25,179**	**188**	**85,290**	**99.66%**	**22.74%**

ProDUR Report for October through December 2017

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,252	218	1,034	11,101	11.3%	17.4%
ER	Hydrocodone/APAP	62	19	43	4,233	1.5%	30.6%
ER	Oxycodone	98	35	63	2,402	4.1%	35.7%
ER	Oxycodone/APAP	16	4	12	1,280	1.3%	25.0%
ER	Tramadol	24	5	19	1,106	2.2%	20.8%
ER	Buspirone (Buspar)	2,179	346	1,832	21,668	10.1%	15.9%
ER	Lorazepam	705	165	540	16,119	4.4%	23.4%
ER	Alprazolam	506	103	403	11,661	4.3%	20.4%
ER	Diazepam	284	64	220	6,599	4.3%	22.5%
ER	Lamictal (Lamotrigine)	3,987	851	3,136	33,824	11.8%	21.3%
ER	Abilify (Aripiprazole)	2,096	397	1,698	20,574	10.2%	18.9%
ER	Seroquel (Quetiapine)	2,459	585	1,869	25,162	9.8%	23.8%
ER	Risperdal (Risperidone)	1,120	307	813	13,559	8.3%	27.4%
ER	Wellbutrin (Bupropion)	4,368	784	3,584	46,308	9.4%	17.9%
ER	Zoloft (Sertraline)	5,279	990	4,289	53,633	9.8%	18.8%
ER	Prozac (Fluoxetine)	3,788	621	3,167	41,570	9.1%	16.4%
ER	Celexa (Citalopram)	2,656	426	2,230	31,827	8.3%	16.0%

ProDUR Report for October through December 2017
Top Drugs in Early Refill

DUR Alert	Drug Name	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	218	13	11	33	0	161	0
ER	Hydrocodone/APAP	19	0	0	8	0	11	0
ER	Oxycodone	35	0	1	14	0	20	0
ER	Oxycodone/APAP	4	0	0	3	0	1	0
ER	Tramadol	5	0	0	0	0	5	0
ER	Buspirone (Buspar)	346	11	15	82	0	238	0
ER	Lorazepam	165	5	4	37	1	118	0
ER	Alprazolam	103	5	5	17	0	76	0
ER	Diazepam	64	0	4	15	0	45	0
ER	Lamictal (Lamotrigine)	851	31	37	196	0	587	0
ER	Abilify (Aripiprazole)	397	20	26	83	0	268	0
ER	Seroquel (Quetiapine)	585	14	25	144	0	402	0
ER	Risperdal (Risperidone)	307	2	8	51	0	246	0
ER	Wellbutrin (Bupropion)	784	58	52	93	1	580	0
ER	Zoloft (Sertraline)	990	35	39	313	2	601	0
ER	Prozac (Fluoxetine)	621	32	28	153	2	406	0
ER	Celexa (Citalopram)	426	27	25	77	2	295	0
	Totals =	**5,920**	**253**	**280**	**1,319**	**8**	**4,060**	**0**

ProDUR Report for October through December 2017 (Approx. 1,015,995 Enrolled Recipients)

DUR Alert	Drug Name	# Alerts	# Overrides	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lorazepam	705	165	16,119	4.4%	23.4%
ER	Alprazolam	506	103	11,661	4.3%	20.4%
ER	Diazepam	284	64	6,599	4.3%	22.5%
	4Q2017 Total =	**1,495**	**332**	**34,379**		

ProDUR Report for October through December 2015 (Approx. 1,074,781 Enrolled Recipients)

DUR Alert	Drug Name	# Alerts	# Overrides	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lorazepam	1,731	390	27,267	6.3%	22.5%
ER	Alprazolam	1,247	219	20,641	6.0%	17.6%
ER	Diazepam	685	152	11,988	5.7%	22.19%
	4Q2015 Total =	**3,663**	**761**	**59,896**		

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

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	50	131	121	86
		Total Faxes Successfully Sent	37	31	23	22
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	14	14	8	5
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	4	3	2
		Prescriptions Unchanged after 3 Months of Fax Sent	16	11	12	
		Safety Monitoring Profiles Identified	1	2		4
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$86,626	$55,262	$7,207	$2,006

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified	21			
		Profiles Sent	5			
		Responses Received	0			
		Response Rate	0%			
		Information Useful or Will Change Practice	0			
		Patient Not With Office	0			
		Already Scheduled	0			
		Will Not Schedule	0			
		Requested No Future Notifications	0			
	Antipsychotic Metabolic Monitoring	Members Identified	658			
		Profiles Sent	649			
		Members With Response	18			
		Response Rate	3%			
		Newly Scheduled	12			
		Provider Contacted	247			
		Provider Responses	11			
		Provider Agreed with Recommendation	5			
		Patient Not With Office	5			

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

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	90	91	92	46
		Estimated Savings				
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	8	18	19	8
		Estimated Savings				
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	92	97	119	47
		Estimated Savings				
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	14	14	17	13
		Estimated Savings				
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed		3	2	1
		Estimated Savings				
	Lock-In	RetroDUR_Profiles Reviewed	51	26	20	10
		RetroDUR_Letters Sent To Providers	3	2	1	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
		Locked In	13	2	1	0
		Estimated Savings	$3,446	$512	$153	
	Polypharmacy	RetroDUR_Profiles Reviewed		48	41	12
		RetroDUR_Letters Sent To Providers		1		2
		Provider Responses		0		0
		Provider Agreed / Found Info Useful		0		0
		Estimated Savings				

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	ICS/LABA	Disqualified	1	5	21	27
		Disqualified - No Provider Info	1			
		Disqualified - Erroneous denial		5	21	27
		Faxes Sent	5	4	6	2
		Fax Sent - Combination Inhaler	1	3	2	
		Fax Sent - SABA	1		2	
		Fax Sent - Controller	2	1	2	
		No Subsequent Pulmonary Claims	1			2

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Marketing Claims of Newer Drugs and the Evidence

Kathy Sentena, PharmD, and Megan Herink, PharmD, BCPS, Both with Drug Use Research and Management, Oregon State University College of Pharmacy

Marketing new drug therapies is a major focus of pharmaceutical companies, with many of the largest pharmaceutical companies spending more money on drug marketing than on research and development.[1]

Thirty-four new molecular entities have been approved this year by the Food and Drug Administration (FDA).[2] As market competition increases, the promotion of drugs to prescribers and consumers often follows. The time it takes to evaluate the evidence to validate claims of improved efficacy, safety, and convenience of new therapies can be burdensome. With the pressure to generate sales and profits, pharmaceutical marketing messages may not be an accurate or complete reflection of the data available. This newsletter will review recent drug marketing statements and provide perspective on the evidence behind these claims.

Insulin Degludec (Tresiba) Comparative Efficacy

Marketing Angle: "Are you Tresiba ready?" Marketing promotes use of a once-daily insulin that lasts longer than 24 hours to lower hemoglobin A1C (A1C).[3]
Evidence Fact: Evidence has not demonstrated that insulin degludec (Tresiba) is superior to other long-acting insulin in lowering A1C and is much more expensive.[4]

Insulin degludec (Tresiba) is a long-acting insulin approved by the FDA in 2015.[5] There is evidence that insulin degludec can be given at different times of the day without compromising efficacy due to a half-life of approximately 25 hours, other long-acting insulins, such as insulin glargine, have a half-life of 12 hours.[5,6] The longer duration of action has not been shown to translate into improved A1C lowering. A Drug Effectiveness Review Project (DERP) report found that in an analysis of 4,434 patients there was moderate evidence of no difference between insulin degludec and insulin glargine in the number of patients with type 2 diabetes mellitus (T2DM) that were able to obtain an A1C less than 7% (pooled risk ratio 0.96; 95% CI, 0.90 to 1.03) and there was low quality evidence of no difference in A1C lowering in patients with type 1 diabetes (T1DM), based on 3 trials.[4] The risk of nocturnal hypoglycemia, defined by most studies as a reading less than 56 mg/dL between the hours of 1 am to 6 am, has been shown to be less with insulin degludec compared to insulin glargine in patients with T1DM and T2DM.[4] Studies lasting 52 weeks found a small absolute risk reduction (ARR) of 2.0% (number needed to harm [NNH] 50) in patients with T1DM and a mean ARR of 4.2% (NNH of 43) in studies of patients with T2DM.[4] The risk of severe hypoglycemia was not different between insulin degludec and insulin glargine in patients with T1DM or T2DM. These results are most applicable to patients with T1DM and an average age of 44 years and a 19 year history of T1DM and to patients with T2DM with an average age of 59 years and an 11 year history of diabetes. The mean A1C was 8.5% in patients with T1DM and T2DM. Patients with diabetes complications were excluded from most studies. The cost of insulin degludec is approximately $5 more per mL based on the national average actual acquisition cost (AAAC).[7]

OHP FFS policy allows for insulin glargine (Lantus) vials and pens without prior authorization. Insulin degludec requires prior authorization approval.

Empagliflozin (Jardiance) and Cardiovascular Effects

Marketing Angle: "For adults with type 2 diabetes and heart disease Jardiance is the only type 2 diabetes pill with a lifesaving cardiovascular benefit."[8]
Evidence Fact: In a subgroup analysis of the trial described below, there was no reduction in cardiovascular (CV) deaths in Europe and North America (representing 61% of the global study population). This makes it uncertain if there is a benefit in the Oregon Health Plan (OHP) fee-for -service (FFS) population. In addition, the primary event rate of CV death was not measured appropriately, as 40% of the CV deaths reported in the trial were not CV in origin, but were 'non-assessable'. [9] Baseline characteristics of patient included in the trial demonstrate that results are most applicable to patients with a diabetes diagnosis of at least 10 years, an average age of 63 years and living outside North America and Europe.[10]

The evidence from an industry sponsored study demonstrated that empagliflozin reduced the composite endpoint of death from CV causes, nonfatal myocardial infarction (MI) and nonfatal stroke when compared to placebo (ARR 1.6%/number needed to treat [NNT] 63) over 3.1 years in patients with underlying CV disease, when all study sites were imcluded.[10] There was no statistically significant differences between empagliflozin and placebo in incidence of non-fatal MI or non-fatal stroke. [1] The reduction in CV events was driven by a decreased risk of death related to CV causes with empagliflozin compared to placebo, 5.9% vs. 3.7%, respectively (HR 0.62; 95% CI, 0.49 to 0.77; P<0.001).[1] This translates to a relative risk reduction of 38% in death from CV causes, which is only a 2.2% absolute difference between empagliflozin and placebo.[10] Absolute risk reduction is often a better way to evaluate the clinical difference between treatment groups as it reflects the actual magnitude of change. Statistically significant reductions due to death from any cause favored empagliflozin over placebo, 8.3% vs. 5.7%, respectively (HR 0.68; 95% CI, 0.57 to 0.82; P<0.001).[10]

It is unknown if the risk reduction in CV endpoints seen with empagliflozin would be seen in T2DM patients *without* preexisting CV disease. This is important because currently we only have evidence of CV benefits in older patients with CV disease and a multi-drug approach to managing their diabetes and other comorbidities. Lastly, the risk of ketoacidosis and serious urinary tract infections seen with empagliflozin need to be balanced with its benefits.[11]

OHP FFS policy requires prior authorization approval for empagliflozin and other SGLT-2 inhibitors.

Non-vitamin K Oral Anticoagulants Comparative Efficacy

Marketing Angle: Consumer commercials advertise "Pradaxa is proven better than warfarin at reducing stroke."[12] Other marketing focuses on non-vitamin K oral anticoagulants (NOAC) being more convenient than warfarin due to lack of dietary interactions and lack of blood monitoring.[13,14]

Evidence Fact: Subgroup analysis of patients with atrial fibrillation (AF) demonstrate that superior efficacy of NOACs over warfarin is valid only for those patients who are consistently unable to maintain a therapeutic international normalized ratio (INR).[14] Appropriate patient selection for NOAC treatment warrants consideration. NOACs have a potential for significant drug interactions with combinations of P-glycoprotein and CYP 3A4 inhibitors and inducers. Dosing adjustments based on renal function is required for all NOACs.

Advertising promotes the use of NOACs, such as dabigatran and apixaban, at being superior to warfarin at reducing the risk of stroke in patients with AF. Numerically, both these treatments were superior to warfarin for the overall findings. However, a DERP report found that the efficacy of NOACs was not superior to warfarin in patients who were taking warfarin with an INR in the therapeutic range at least 66% of the time.[15] This finding was illustrated in the open-label study comparing dabigatran (Pradaxa) to warfarin. Results found an ARR for the primary endpoint of stroke or systemic embolism to be 0.60% and a number needed to treat of 167 with dabigatran compared to warfarin.[16] However only 64% of patients taking warfarin were in the therapeutic range, suggesting sub-optimal warfarin management. The open-label study design imparts a high risk of performance bias with the potential to influence the results.

A reduction in risk of hemorrhagic stroke, lack of laboratory monitoring and less food and drug interactions compared to warfarin have been cited as some of the benefits of NOACs. A less emphasized risk of NOAC therapy is the potential for increased risk of bleeding when combined with other drugs that share the same metabolic pathways (CYP3A4 and P-glycoprotein). Apixaban and rivaroxaban have warnings against concomitant use with other drugs that are metabolized by the CYP3A4 metabolic pathway and apixaban, dabigatran and rivaroxaban have warnings against use with P-glycoprotein inducers/competitors. Edoxaban should not be used with the P-glycoprotein inducer, rifampin, but does not undergo metabolism via the other shared metabolic pathways. NOAC efficacy and safety studies often exclude patients who take drugs that may alter the plasma concentrations of NOACs. Evidence regarding concomitant use of NOACs with drugs with similar metabolic pathways often comes from animal models with limited evidence available from human studies. A retrospective cohort study in 91,330 patients taking either apixaban, dabigatran, or rivaroxaban for atrial fibrillation (AF) found an increased adjusted risk of major bleeding (hospitalization or emergency room visit with primary diagnosis of intracranial hemorrhage or gastrointestinal, urogenital, or other bleeding) when NOACs were used in combination with amiodarone, fluconazole, rifampin or phenytoin (Table 1).[17] Diltiazem and amiodarone were prescribed in 22.7% and 21.1%, respectively, of patients taking NOACs despite warnings against these combinations.[17]

In addition to drug interactions, renal function should be considered. All NOACs have recommendations for dosing adjustments based on reduced renal function. Warfarin is recommended for patients with severe renal impairment (CrCl <15 mL/min). NOAC trials also excluded patients with chronic kidney disease, who are at increased risk of stroke, preventing efficacy conclusions in this population.[16,18–20] Additionally, edoxaban use in patients with CrCl greater than 95 mL/min is not recommended.

Tolerability, based on withdrawal rates, was higher in clinical trials with some NOACs compared to warfarin. Twice-daily dosing may pose adherence concerns in some patients and the shorter half-lives of NOACs compared to warfarin, putting patients at a higher risk of thrombosis if a dose is missed.

Table 1. Adjusted incidence Rates of Major Bleeding per 1000 person-years[17]*

Combinations	Increased Risk with Combination Therapy
NOAC + Amiodarone	13.94 (99% CI, 9.76 to 18.13)
NOAC + Fluconazole	138.46 (99% CI, 80.96 to 195.97)
NOAC + Rifampin	36.90 (99% CI, 1.59 to 72.22)
NOAC + Phenytoin	52.31 (99% CI, 32.18 to 72.44)

* Apixaban, edoxaban and rivaroxaban included

OHP FFS policy allows coverage of warfarin, apixaban, dabigatran, edoxaban and rivaroxaban without a PA

Hepatitis C Treatment Candidates

Marketing Angle: Marketing claims imply new hepatitis C direct-acting antivirals (DAA) cure 99% of hepatitis C cases and treatment is appropriate for all patients that "are ready".[17]

Evidence Fact: There are limitations to the evidence demonstrating sustained viral response (SVR) rates of up to 99% with DAA therapy. Important safety concerns and lack of evidence for important health outcomes requires diligent prescribing of DAAs to the most appropriate patients.

There is widespread marketing promoting the use of DAAs for the treatment and potential cure of hepatitis C. While these new treatments offer significant improvements in SVR over control (ARR 30.3%; NNT 4), limitations to the evidence remain. Chronic hepatitis C is a slowly progressing disease over decades and it is unknown if delaying treatment in those with mild disease (F0-F2 fibrosis) results in poorer outcomes.[18] Additionally, SVR is a non-validated surrogate outcome. There is recent data suggesting that treatment with DAAs improves patient reported outcomes compared to placebo[21] and evolving evidence on other clinically significant long term outcomes. However, due to the time to progress to complications, there is insufficient direct evidence that treatment of hepatitis C with DAAs improves complications including ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, or liver transplantation with long-term use.[18] Additionally, there is evidence of up to a 30% incidence of spontaneous viral clearance within the first 6 to12 months of acute hepatitis C infection.[22,23]

Patient exclusion criteria and reliance on short-term data are also limitations to understanding the full treatment effect of DAAs. Trials excluded patients with hepatitis B infection, which have led to post-

marketing reports of reactivation of latent hepatitis B infection in patients receiving DAAs in the general population.[19] In response, the FDA has issued a Boxed Warning to be added to all DAAs to inform practitioners of this risk. Additional safety concerns regarding serious and life-threatening symptomatic bradycardia in patients taking sofosbuvir (Sovaldi) or ledipasvir/sofosbuvir (Harvoni) who were also taking other DAAs and amiodarone have been reported.[20] The FDA recommends that patients avoid sofosbuvir or ledipasvir/sofosbuvir in combination with DAAs and amiodarone. Successful evaluation of the most appropriate candidates for hepatitis C treatment will increase the chance of a successful outcome and minimize the risk of inappropriate prescribing.

Conclusion

While newer therapies may present an advantage in certain populations, the evidence needs to be carefully considered before universally applying these benefits to all patients. While numeric superiority may exist, it is also important to consider the number of patients that need to be treated and for what duration of time to receive treatment benefits. An additional concern is that most new drug studies are conducted by the manufacturer, which presents an inherent risk of bias due to conflicts of interest. Most importantly, treatment selection needs to represent a clinically meaningful benefit to the patient.

Complete evidence reviews are available at www.orpdl.org/drugs/.

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Current Landscape of the Antidepressant Class: First Line Agents, Newer Agents, and Safety Risks

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The antidepressants class is comprised of a variety of agents with different clinical characteristics and within the past few years three new agents have been approved by the United States Food and Drug Administration (FDA). Generally, second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are the most commonly utilized and recommended medications for the management of major depressive disorder (MDD) due to their safety profile.[1-4] However, the choice of antidepressant should be individualized for each patient based on evidence for safety and efficacy while taking cost into consideration.[2,4] The purpose of this newsletter is to review first line agents, evaluate comparative data for newer agents, and assess safety risks with SSRIs in pediatric patients.

Guidelines

The National Institute for Health and Care Excellence (NICE) guidelines for treatment of depression in adults recommend generic SSRIs as first line treatment for most patients.[2] In addition to SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion are also recommended as first line options by the American Psychiatric Association and the Department of Veterans Affairs (VA) and Department of Defense (DoD) MDD guidelines.[3,4] Patient-specific considerations of safety risks and drug interactions are also emphasized in the guidelines.[2-4]

Oregon Health Plan Policy

Drugs for mental health conditions in Oregon Health Plan (OHP) Medicaid patients are exempt from the traditional Preferred Drug List (PDL) and prior authorization requirements. Therefore, OHP relies on prescribers to voluntarily prescribe antidepressants with high value. Preferred agents are listed below and have demonstrated safety and efficacy (Table 1).

Table 1. Preferred Agents on Voluntary Mental Health PDL

Preferred Agents		
Atypical	Bupropion tablets & 12H ER tablets	Mirtazapine tablets & rapidly disintegrating tablets
SNRI	Venlafaxine tablets & 24H ER capsules	
SSRI	Citalopram tablets & solution	Escitalopram tablets
	Fluoxetine capsules, tablets & solution	Fluvoxamine tablets
	Paroxetine tablets	Sertraline tablets & oral concentrate
Tricyclic	Amitriptyline tablets	Anafranil™ (brand only) capsules
	Desipramine tablets	Doxepin capsules & oral concentrate
	Imipramine tablets	Maprotiline tablets
	Nortriptyline capsules & solution	Protriptyline tablets
	Trimipramine capsules	

Abbreviations: ER = extended release; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; 12H = 12-hour; 24H = 24-hour

Newer Agents Compared to Other Second Generation Antidepressants

Levomilnacipran, vilazodone, and vortioxetine are three newer agents approved by the FDA for the treatment of MDD between 2011 and 2013.[5-7]

In April 2017, the Drug Effectiveness Review Project (DERP) published a review on second-generation antidepressants with an emphasis on levomilnacipran, vilazodone, and vortioxetine.[1] The report focused on MDD and generalized anxiety disorder in adults and seven head-to-head trials were included.[1] A pre-specified network meta-analysis studying response to treatment on the Hamilton Depression Rating Scale was also completed which utilized 119 placebo- and active comparator-controlled randomized controlled trials (RCTs).[1] All trials included in the network meta-analysis were double-blinded and focused on the outpatient MDD population.[1] However, as the network meta-analysis reflects indirect evidence, results should be interpreted with caution.

For MDD, limited direct comparative evidence is available for levomilnacipran, vilazodone, or vortioxetine compared with other second-generation antidepressants.[1] Moderate quality evidence shows similar response rates for both vilazodone and citalopram as well as vortioxetine and venlafaxine XR, and vortioxetine had similar or lower response rates compared to duloxetine depending on the trial.[1]

Low quality network meta-analyses showed overall similar response rates for all three agents versus other second-generation antidepressants.[1]

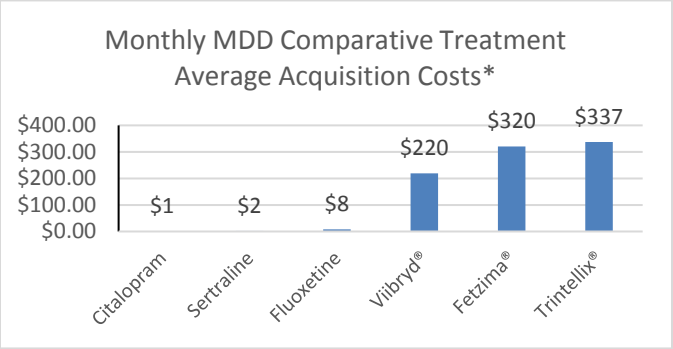
Safety outcomes were evaluated in the DERP report as well.[1] Low strength of evidence found differences in adverse effects which included higher rates of diarrhea (26.5% vs. 10.6%) and vomiting (6.6% vs. 1.8%) with vilazodone versus citalopram (one fair quality RCT; n=580), statistically non-significant yet numerically lower rates of discontinuation due to adverse events with vortioxetine versus venlafaxine XR (7.0% vs. 14.2%; one fair quality RCT; n=320), and significantly lower rates of sexual dysfunction (25% vs. 46% and 36% vs. 53%; two fair quality RCTs; n=288) and somnolence (5% vs. 12%; one fair quality RCT; n=310) with vortioxetine versus duloxetine.[1] Meta-analyses demonstrated lower risks with vortioxetine compared to duloxetine for dry mouth (9.6% vs. 13.1%; RCT=3).[1] Other safety outcomes evaluated in the DERP report demonstrated no statistically significant difference between levomilnacipran, vilazodone, or vortioxetine and other second-generation antidepressants.[1]

Levomilnacipran, vilazodone, and vortioxetine are voluntary non-preferred agents on the Oregon Medicaid voluntary mental health PDL.

Cost Comparison

The newer agents of levomilnacipran (Fetzima®), vilazodone (Viibryd®), and vortioxetine (Trintellix®) have significantly higher costs per 30 days of MDD treatment compared to common SSRIs which are recommended as first line treatment for most patients (Chart 1).[2-4] Many patients can be treated with older, more established agents for the same cost of treating one patient with a newer agent.

Chart 1: Comparative Costs of Common SSRIs & Newer Agents



*Based on commonly prescribed maintenance doses

Safety Reminder: SSRIs in Pediatric Patients

When prescribing antidepressants in pediatric or young adult patients, special consideration should be given to the potential safety risks. Antidepressants have a boxed warning regarding the increased risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.[8] In SSRIs specifically, dose-related safety risks have been demonstrated.[9]

One large, well-designed retrospective cohort study (n=21,305) from 2014 revealed a dose-related increase in deliberate self-harm among pediatric, adolescent, and young adult patients initiated on high-dose SSRIs for MDD.[9] The risk of deliberate self-harm in the high dose group was found to be approximately double that of the modal dose group (HR 2.2; 95% CI, 1.6-3.0).[9] As a result of this study, a 2014 Oregon Medicaid drug use evaluation was completed which found that 27% of patients aged 5-24 years were initiated on high-dose SSRI therapy, potentially putting them at risk for deliberate self-harm.[10]

To improve safety for pediatric patients initiating on SSRI therapy, it is recommended to prescribe SSRIs at recommended initial doses or not higher than the age-specific maximum initiation doses (Table 2). Additionally, patients should be monitored closely for clinical worsening, suicidality, and unusual changes in behavior, especially in the initial few months of therapy and at times of dose changes.[8]

Table 2. Recommended Initial SSRI Doses in Younger Patients

SSRI	Recommended initial dose (mg)*[11]	Age – specific maximum initiation dose (mg)**[10]			
		Age range [years]			
		5 – 9	10 – 15	16 – 19	20 – 24
escitalopram	5 – 10	5	10	10	10
fluoxetine	5 – 20	10	10	10	20
sertraline	12.5 – 50	25	25	50	50

*Doses for MDD or depression were used if listed and other indication doses were used if no MDD or depression dose was available. Citalopram excluded due to lack of FDA-approved pediatric indications.[12] Paroxetine excluded due to lack of FDA-approved pediatric indications as well as safety and efficacy concerns in this population.[13,14]
**Based on modal doses determined in a 2014 Oregon Medicaid drug use evaluation.[10]

Avoid high doses to limit risk of deliberate self-harm when prescribing initial antidepressant therapy with SSRIs in pediatric, adolescent, or young adult populations and evaluate risks versus benefits.

Conclusion

Levomilnacipran, vilazodone, and vortioxetine lack established efficacy or safety advantages over first line MDD agents that have been in clinical use for many years yet have significantly higher comparative costs. Evidence shows these drugs are similar or less effective than other second generation antidepressants and as they are still relatively new, the full long term safety profile may not be established. Safety concerns in the antidepressants class such as high initial doses of SSRIs in pediatric patients also continue to be of importance. Risks and clinical need with any treatment should be weighed and evaluated. If multiple agents are determined to be equally appropriate for a patient, utilizing the most cost-effective medication can assist in managing Oregon Medicaid resources in the most effective manner possible.

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Drug Class Update with New Drug Evaluation: Bone Metabolism Agents for Osteoporosis or Paget Disease

Date of Review: November 2017
Date of Last Review: July 2016
Generic Name: Abaloparatide

End Date of Literature Search: July 7, 2017
Brand Name (Manufacturer): Tymlos™ (Radius Health)
Dossier Received: yes

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

Purpose for Class Update:
To define place in therapy for a new parathyroid hormone analog (abaloparatide) recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women at high risk for fracture. In addition, new comparative evidence for existing bone metabolism agents for management of osteoporosis and Paget disease will be reviewed.

Research Questions:
- Is there new comparative evidence that bone metabolism agents differ in efficacy or effectiveness for osteoporosis or Paget Disease?
- Is there any new comparative evidence the bone metabolism agents differ in harms?
- Are there specific subpopulations (gender, fracture risk) for which one agent is better tolerated or more effective than other available agents?

Conclusions:
- Two new systematic reviews and two updated clinical guidelines were identified for this class update.[1-4]
- There is no new comparative evidence to evaluate the comparative safety and efficacy or effectiveness of the bone metabolism agents.
- One systematic review evaluated the use of bisphosphonates in men and provides moderate quality evidence that bisphosphonates reduce fracture risk for men with osteoporosis. Further studies are needed to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.[3]
- The Institute for Clinical and Economic Review (ICER) evaluated the effectiveness of anabolic therapies for osteoporosis in postmenopausal women. Currently, there are no head-to-head trials that compare abaloparatide to teriparatide so there is insufficient evidence to assess the comparative clinical effectiveness of the two anabolic therapies on reduction of fractures in patients with osteoporosis. Teraparatide and abaloparatide are both administered via subcutaneous injection once daily and have similar adverse effect profiles.[1]

Author: Deanna Moretz, PharmD, BCPS Date: March 2018

- The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) and American College of Physicians (ACP) continue to recommend alendronate, risedronate, zoledronic acid, or denosumab as first-line treatment options for postmenopausal osteoporosis in their clinical practice guideline due to these agent's evidence for reducing risk of fractures (spine, hip, and nonvertebral fracture risk).[2]
- In one randomized, placebo-controlled trial, abaloparatide significantly reduced the risk of new vertebral fractures in postmenopausal women compared to placebo over 18 months (relative risk (RR) 0.14, 95% confidence interval (CI) 0.05 to 0.39, p<0.001, absolute risk reduction (ARR) 3.6%, number-needed-to-treat (NNT) 28).[5] The risk of nonvertebral fractures, a secondary endpoint for this trial, was also reduced when abaloparatide was compared to placebo over 18 months (hazard ratio (HR) 0.57; 95% CI 0.32 to 1.00, p<0.049, ARR 2%, NNT 50).[5]
- Rates of serious treatment-emergent adverse events between abaloparatide, open-label teriparatide, and placebo were similar in the same trial (9.7%, 10.0%, and 11% respectively).[5] The most common adverse effects that led to treatment discontinuation with abaloparatide included nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%).[5]
- The duration of therapy for abaloparatide is limited to 2 years due to the risk of osteosarcoma noted in rats with systemic exposure 4 to 28 times the exposure in humans receiving recommended doses.[6] Teriparatide also has a risk of osteosarcoma, and duration of therapy is limited to 2 years.[7] Abaloparatide also carries risks of orthostatic hypotension (17.1%), hypercalcemia (3.4 %), and hypercalciuria (11.3%) as described in the phase 3 randomized controlled trial.[5]
- There was no new evidence for the use of bone metabolism agents in managing Paget disease.
- Xgeva® (denosumab) received an expanded indication to include prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.[8] This indication is only for the Xgeva® branded formulation of denosumab, not the other branded formulation of denosumab known as Prolia®.
- The warnings and precautions section of the denosumab labeling was revised to include the risk of embryo-fetal toxicity based on data from animal studies.[8]

Recommendations:
- Maintain abaloparatide as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Update clinical PA criteria for bone metabolism agents to include abaloparatide.
- Evaluate costs in executive session.

Previous Conclusions:
Efficacy
- The Endocrine Society recommends IV zoledronic acid 5 mg in a single dose for most patients with active Paget disease who are at risk for complications unless contraindications exist.
- One systematic review and meta-analysis found no statistically significant and consistent difference in vertebral and nonvertebral fracture risk reduction between bisphosphonates, denosumab, or teriparatide.
- Denosumab had lower rates of nonvertebral fracture compared to other bisphosphonates or placebo in one systematic review and meta-analysis.[3] On the contrary, two systematic reviews and meta-analyses found that denosumab had an increased risk for infections.
- A systematic review and meta-analysis found no benefit in terms of vertebral or nonvertebral fracture risk with bisphosphonate use at 12 months in patients with cystic fibrosis, though a significant increase in percent change in bone mineral density (BMD) of the lumbar spine, hip and femur.

- In patients with osteogenesis imperfecta, oral alendronate and IV pamidronate showed no difference in fracture incidence. A significant increase was seen in Z score BMD between patients dosed 0.2 mg/kg versus 2 mg/kg of IV risedronate.[5] No difference was seen in patients treated with zoledronic acid versus pamidronate in change in number of fractures.
- Bisphosphonate-treated patients with inflammatory bowel disease had improvements in BMD at the lumbar spine and total hip and lower rates of vertebral and nonvertebral fractures when compared to active controls.
- Early breast cancer patients scheduled to receive aromatase inhibitors had a greater increase in BMD in the lumbar spine in terms of percent change and absolute change in bisphosphonate treated groups compared to groups treated with oral calcium, oral vitamin D or cholecalciferol with or without placebo.[7]
- Patients with Parkinson disease and previous stroke had reduced rates of hip fractures when treated with bisphosphonates compared to controls.[8]

Safety
- Raloxifene was not found to prevent nonvertebral fractures and is associated with a significant rate of severe side effects including thromboembolic events, pulmonary embolism, and fatal strokes.
- Cases of osteonecrosis of the jaw have been reported with bisphosphonate use but are associate much more significantly with IV bisphosphonates versus oral formulations and in patients being treated for malignant conditions.

Previous Recommendations:
- Consider inclusion of zoledronic acid due to the Endocrine Society's recommendation for use as first-line for Paget's disease.
- Consider inclusion of bazedoxifene on preferred list due to superiority over other bisphosphonates in patients at high risk for fractures (FRAX score ≥20%).
- Consider inclusion of denosumab, zoledronic acid, risedronate, alendronate in various routes and dosing schedules for osteoporosis treatment based upon cost.
- Include at least one nitrogen-containing bisphosphonate for Paget disease (zoledronic acid, pamidronate, risedronate, alendronate or ibandronate).
- Make calcitonin, raloxifene and teriparatide non-preferred due to limited evidence to reduce nonvertebral and hip fracture risk in post-menopausal women. Calcitonin has limited evidence for Paget disease.
- Make tiludronate non-preferred as it is only indicated for Paget disease, is not a nitrogen containing bisphosphonate and it has insufficient evidence for osteoporosis treatment.

Background:
Osteoporosis is characterized by low bone mass, deterioration of bone tissue, compromised bone strength, and increased risk of fracture.[9] Osteoporosis occurs as part of the aging process or secondary to nutritional deficiency, metabolic disorders, or utilization of certain medications.[9] Long-term intake of anticoagulants, antiepileptics, aromatase inhibitors, gonadotropin releasing-hormones, glucocorticoids, lithium, thiazolidinediones, or proton pump inhibitors are also associated with increased risk for osteoporosis.[9] Lifestyle factors that adversely impact the risk for osteoporosis include low calcium intake, vitamin D deficiency, excess vitamin A intake, inadequate physical activity, smoking and alcohol abuse.[9] Other patients at high risk for osteoporosis include those with low body weight (<57.6 kg), rheumatic disease, hyperparathyroidism, multiple myeloma, malabsorption, diabetes, or inflammatory bowel disease.[10] Throughout life, older bone is resorbed by osteoclasts and replaced with new bone made by osteoblasts.[11] This process is known as remodeling and is orchestrated and targeted to a particular site that is in need for repair by osteocytes.[11] When this system is out of balance, bone loss occurs. In the past decade, the master signals that regulate this process have been defined. The receptor activator of nuclear factor kappa-B ligand (RANKL) is a key signal that increases bone loss and has become a target for the treatment of osteoporosis with the monoclonal antibody denosumab.

The estimated prevalence of osteoporosis in the US is 10.3%, or approximately 10.2 million older adults using 2010 population estimates.[12] One study estimated that 7.7 million non-Hispanic White, 0.5 million non-Hispanic Black, and 0.6 million Mexican American adults had osteoporosis and another 33.8, 2.9, and 2.0 million had low bone mass, respectively.[12] Although most of the individuals with osteoporosis or low bone mass were non-Hispanic white women, a substantial number of men and women from other racial/ethnic groups also had osteoporosis or low bone mass.[12]

Bone mineral density (BMD) assessed with dual x-ray absorptiometry (DXA) is a surrogate marker used to diagnose osteoporosis. A patient is considered to have osteoporosis with a BMD T-score of less than 2.5 standard deviations below the average of a young adult.[9] BMD can be used in conjunction with the World Health Organization fracture-risk assessment tool (FRAX) to estimate an individual's 10-year risk of sustaining a hip fracture or major osteoporotic fractures.[13] The life-time fracture risk of a patient with osteoporosis can be as high as 40% and fractures of the hip, spine or wrist are the most common locations. [9] The primary goal of osteoporosis management is to reduce fracture risk. Fractures are associated with decreased quality of life, reduced independence, and increased morbidity and mortality.[14] The US Preventative Services Task Force (USPSTF) recommends screening average-risk women with a bone density measurement at age 65 years and screening younger women whose fracture risk is equal to or greater than that of a 65-year old white woman with no additional risk factors.[15] The USPSTF concluded that there is insufficient evidence to assess the balance of benefits and harms for screening for osteoporosis in men.[15]

Drugs to treat osteoporosis fall into two groups: the anti-resorptive drugs, which slow down bone resorption, and anabolic drugs, which stimulate bone formation. The anti-resorptive drugs include bisphosphonates, raloxifene, calcitonin, and denusomab, which suppresses the RANKL pathway. Teriparatide and abaloparatide are recombinant forms of parathyroid hormone which stimulate osteoblasts to form new bone. Teriparatide is approved for use up to 2 years in the US due to concerns that prolonged use may cause osteosarcoma based on data from rat studies. All drugs require adequate serum levels of calcium and vitamin D for optimum effect. Bisphosphonates are considered first line therapy, but short-term tolerability and potential long-term risk of atypical femur fracture, osteonecrosis of the jaw and esophageal cancer may limit their utilization. Dosing recommendations of the bone metabolism agents for osteoporosis and Paget disease are presented in **Table 1.**

Paget disease is a disorder of bone metabolism that includes an accelerated rate of bone remodeling, resulting in overgrowth of bone at selected sites and impaired integrity of affected bone.[16] It is a finding in aging bone, with estimates ranging from 2.3 to 9% in patients older than 55 years.[16] Many patients with Paget disease are asymptomatic but others exhibit joint pain and deformities. Most frequently affected areas are the pelvis, femur, lumbar spine, skull, and tibia.[16] Paget disease that affects the skull may result in hearing loss. Fractures, bone tumors, neurologic disease, cardiac disease, and abnormalities in calcium and phosphate balance can also occur.[16] Diagnosis of Paget disease is confirmed by x-ray or bone scintigraphy in addition to an elevated serum total alkaline phosphatase (ALP) level that is not due to hepatic dysfunction. The goals of treatment are to reduce pain, normalize bone remodeling and slow disease progression.[17] The nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, and alendronate) are first-line agents for the treatment of Paget disease.[16,17] Bisphosphonate therapy may resolve bone pain, reduce ALP levels, and slow bone turnover; however, there is insufficient evidence to demonstrate improved clinical outcomes or reduced complications with bisphosphonate therapy.[16] Analgesics, nonsteroidal anti-inflammatory drugs, or antineuropathic agents may control pain that does not respond to bisphosphonates. In one comparative study, bisphosphonate therapy did not reduce the risk of fracture or need for orthopedic surgery more than analgesics or anti-inflammatory agents.[18]

Fee-for-service (FFS) utilization of bone metabolism drugs in the third quarter of 2017 (July 1, 2017 through September 30, 2017) included a total of 63 paid claims for preferred bisphosphonates. Eighty-eight percent were for alendronate, 6% were for risedronate, and 5% were for ibandronate. One paid claim was received for the nonpreferred agent teriparatide. There was no utilization of calcitonin or raloxifene during this quarter.

Table 1. Bone Metabolism Agent Dosing in Osteoporosis and Paget Disease[19]

Anti-Resorptive Agents				
		Osteoporosis Dosing		
Generic Name (Brand Name)	**Drug Class**	**Prevention**	**Treatment**	**Paget Disease Dosing**
Alendronate (Fosamax)	Bisphosphonate	5 mg orally once daily 35 mg orally once a week	10 mg orally once daily 70 mg orally once a week	40 mg orally once daily for 6 months
Risedronate (Actonel, Atelvia)	Bisphosphonate	5 mg orally once daily 35 mg orally once a week 150 mg orally once a month	5 mg orally once daily 35 mg orally once a week 150 mg orally once a month	30 mg orally once daily for 2 months
Ibandronate (Boniva)	Bisphosphonate	2.5 mg orally once daily 150 mg orally once a month	2.5 mg orally once daily 150 mg orally once a month 3 mg IV once every 3 months	-
Pamidronate (Aredia)	Bisphosphonate	-	-	30-60 mg IV once daily for 3 consecutive days
Zoledronic Acid (Reclast)	Bisphosphonate	5 mg IV every 2 years	5 mg IV once a year	5 mg IV as a single dose
Denosumab (Prolia)	RANKL inhibitor	-	60 mg SC every 6 months	-
Raloxifene (Evista)	Selective estrogen receptor modulator (SERM)	60 mg orally once daily	60 mg orally once daily	-
Calcitonin (Miacalcin)	Hormone	-	100 units IM or SC once daily 200 units intranasal in one nostril once daily	100 units IM or SC once daily
Anabolic Agents				
Teriparatide (Forteo)	Parathyroid hormone analog	-	20 mcg SC once daily	-
Abaloparatide (Tymlos)	Parathyroid hormone analog	-	80 mcg SC once daily	-

Abbreviations: IM = intramuscular; IV = intravenous; SC = subcutaneous

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of this review 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:
Anabolic Therapy in Osteoporosis
The Institute for Clinical and Economic Review (ICER) evaluated the effectiveness of anabolic therapies for osteoporosis in postmenopausal women.[1] Two placebo controlled trials evaluated the effectiveness of teraparatide or abaloparatide in reducing vertebral fractures.[5,20] Both drugs were significantly better than placebo in reducing the proportion of women with vertebral fractures. No head to head randomized controlled trials that compare the efficacy of teraparatide to abaloparatide have been published. Both drugs are administered via a once daily subcutaneous injection. The adverse effects of both drugs are similar as they are both associated with injection site reactions and hypercalcemia. Duration of therapy with both drugs is limited to two years due to evidence that rats developed osteosarcoma after being treated with teriparatide or abaloparatide. This adverse effect has not been observed in humans. In summary, although teraparatide and abaloparatide appear similar in efficacy, dosing and adverse effects, there is insufficient evidence to assess the comparative clinical effectiveness of the two anabolic therapies to manage osteoporosis.

Osteoporosis in Men
A systematic review and meta-analysis published in 2017 evaluated the efficacy of treatment options to reduce osteoporotic fracture risk in men.[21] FDA approved osteoporosis treatments for men include alendronate, risedronate, zoledronic acid, teriparatide, and denosumab. A total of 3802 studies published between 1998 and 2013 were reviewed. Twenty-two studies (including 4,868 male participants) met inclusion criteria. Very few studies had active comparators and most agents were compared to placebo. Most of the studies were supported by pharmaceutical company funding. The quality of the evidence was rated by the reviewers as low to moderate due to unclear bias in selection, performance, detection, attrition, and reporting domains. Separate meta-analysis were completed to assess the outcome of vertebral fractures for alendronate, calcitonin, denosumab and risedronate; nonvertebral fractures for alendronate; and clinical fractures with zoledronic acid. The bisphosphonates were also analyzed as treatment category to evaluate outcomes of vertebral, nonvertebral and clinical fractures. Fixed-effects meta-analyses demonstrated significantly lower risk of vertebral fractures with alendronate (relative risk (RR) = 0.328, 95% CI = 0.155–0.692) and risedronate (RR = 0.428, 95% CI = 0.245–0.746) but not with calcitonin (RR = 0.272, 95% CI = 0.046–1.608) or denosumab (RR = 0.256, 95% CI = 0.029–2.238) than in controls.[21] The meta-analysis findings for individual treatment options did not demonstrate significantly lower risk of nonvertebral fractures with alendronate (RR = 0.751, 95% CI = 0.352–1.602) or clinical fractures with zoledronic acid (RR = 0.742, 95% CI = 0.436–1.263) than in controls.[21] For bisphosphonates as a treatment category, meta-analyses demonstrated significantly lower risk of vertebral fractures (RR = 0.368, 95% CI = 0.252–0.537) and nonvertebral fractures (RR = 0.604, 95% CI = 0.404–0.904) than in controls.[21] In conclusion, this systematic review supports the use of bisphosphonates to reduce

fracture risk for men with osteoporosis. Further studies are needed to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.[21]

New Guidelines:

American Association of Clinical Endocrinologists and American College of Endocrinology

In 2016 the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) updated clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis.[2] The panel of subject matter experts evaluated available literature and graded the evidence using AACE protocols which are based on the Grades of Recommendation, Development and Evaluation (GRADE) approach developed by Guyatt et al.[22,23] Randomized controlled trials (RCTs) and meta-analysis of RCTs are considered strong evidence while case series and case reports are rated as weak evidence. Only evidence graded as "A" (benefit far outweighs risk) with best level evidence "1" (strong) is reported below.

- Pharmacologic therapy is recommended for the following patients:
  - Osteopenia or low bone mass and a history of fragility fracture of the hip or spine [2]
  - T-score of -2.5 or lower in the spine, femoral neck, total hip, or 33% radius.[2]
- First-line of treatment of postmenopausal osteoporosis include alendronate, risedronate, zoledronic acid, and denosumab due to their evidence for reducing risk of fractures (spine, hip, and nonvertebral fractures).[2]
- Injectable agents such as teriparatide, denosumab, and zoledronic acid are recommended first-line for treatment of patients with high fracture risk (e.g., older women who have had multiple vertebral fractures or hip fractures, or who have very low T-scores), upper gastrointestinal (GI) problems, lower GI problems or poor compliance to oral medications.[2]
- Ibandronate and raloxifene are considered appropriate treatment for patients at high risk for spine fracture but not at risk for hip or nonvertebral fractures. Raloxifene also reduces the risk for breast cancer.[2]
- Denosumab is the treatment of choice for patients with renal insufficiency but is not recommended for patients on dialysis or those with stage 5 kidney disease due to the risk of hypocalcemia.[2]
- Treatment with teriparatide should be limited to 2 years.[2]
- Treatment with teriparatide should always be followed by anti-resorptive agents to prevent bone density decline and loss of fracture efficacy.[2]

American College of Physicians

Updated guidelines from the American College of Physicians (ACP) for the treatment of low bone density or osteoporosis to prevent fractures in men and women were published in 2017.[4] The evidence review was conducted by the Agency for Healthcare Research and Quality (AHRQ) Southern California Evidence-Based Practice Center. The recommendations were graded by the quality of evidence using the GRADE methodology.[23] Only 2 of the 6 recommendations are based on moderate to high quality evidence. Both ACP and AACE/ACE agree the choice of first-line agents to manage osteoporosis should include alendronate, risedronate, zoledronic acid, or denosumab. The ACP guidelines do not address the use of anabolic agents such as teriparatide or abaloparatide. Although AACE/ACE recommends raloxifene as appropriate treatment for patients at high risk for spinal fracture, ACP does not recommend using estrogen or raloxifene for the treatment of osteoporosis in postmenopausal women due to increased risk of adverse events with these drugs. Also, ibandronate is not recommended in the ACP guidelines due to insufficient data regarding its effects on reducing the risk for hip fracture. The recommendations are as follows:

- Clinicians should offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)

- ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)[21]
- Clinicians should offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)[21]
- ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence).[22]
- ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)[22]
- Estrogen therapy, estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in post-menopausal women is not recommended due to the increased risk of cerebrovascular accidents and venous thromboembolism with these therapies. (Grade: strong recommendation; moderate-quality evidence)[21]

New Formulations or Indications:
Xgeva (denosumab) (January 2018). The FDA approved indications for denosumab were expanded to include prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.[8] The expanded indication only applies to the Xgeva® branded formulation of denosumab 120 mg injection. Prolia®, the 60mg formulation of denosumab is only indicated for treatment of postmenopausal men or women with osteoporosis at high risk for fracture, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, or to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.[24]

New FDA Safety Alerts:
Xgeva (denosumab) (January 2018). The warnings and precautions section of the denosumab labeling was revised to include the risk of embryo-fetal toxicity based on data from animal studies.[8] In animal reproduction studies, administration of denosumab to cynomolgus monkeys throughout pregnancy at a dose 25-fold higher than the recommended human dose of denusomab based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth and decreased neonatal growth.[8] Pregnant women or females of reproductive potential should be advised that exposure to denosumab during pregnancy or within 5 months prior to conception can result in fetal harm.

Randomized Controlled Trials:
A total of 160 citations were manually reviewed from the initial literature search. After further review, 160 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Abaloparatide (Tymlos™)

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.

Abaloparatide is a synthetic analog of human parathyroid hormone-related protein (PThrP 1-34) and has binding selectivity to the RG conformation of the parathyroid hormone receptor Type 1 (PTHR1).[6] Abaloparatide was approved by the FDA for the treatment of postmenopausal women with osteoporosis at high risk for fracture. It is an anabolic agent that stimulates bone formation similar to teriparatide. However, abaloparatide and teriparatide differ in their conformational binding to PTH1 receptors. Teriparatide binding results in prolonged signaling, while the binding of abaloparatide causes a more transient response.[25] The transient response appears to cause an anabolic effect on bone with fewer bone resorptive effects. Teriparatide initially increases bone formation, but also increases bone resorption over time, which limits its nets anabolic effect. The FDA approved abaloparatide on the results of one phase 2 dose finding trial and one phase 3 randomized controlled trial.[5,26]

Clinical Efficacy:
The Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) trial randomized 2,463 post-menopausal women to daily subcutaneous injections of abaloparatide 80 mcg, teriparatide 20 mcg, or identical placebo and followed them for 18 months.[5] The teriparatide arm was open label due to proprietary labeling which prevented dispensing teriparatide in other devices besides the prefilled pen. The teriparatide arm was not sufficiently powered to compare efficacy with abaloparatide. The participants were aged 49 to 86 years and had at least one moderate or two mild vertebral fractures or other fragility fractures in the previous 5 years and BMD T-scores between -2.5 and -5.0, or were women at least 65 years of age without a history of a fragility fracture with BMD T-scores between -3.0 and -5.0.[5] At baseline, the mean T-score at the total hip was -1.9 and 63% of subjects had a history of fracture. The primary outcome was the percentage of patients with new vertebral fractures at 18 months. Secondary end points included change in BMD at total hip, femoral neck, and lumbar spine and percentage of patients with nonvertebral fracture. Hypercalcemia was a prespecified safety end point in abaloparatide-treated versus teriparatide participants.

New vertebral fractures occurred in 0.6% (n=4) of women in the abaloparatide group, 0.8% (n=6) of women in the teriparatide group, and 4.2% (n=30) of women in the placebo group over the 18 month trial (abaloparatide RR 0.14, 95% CI 0.05 to 0.39, $p < 0.001$, NNT 28; teriparatide RR 0.20, 95% CI 0.08 to 0.47, $p < 0.001$, NNT 26, both vs. placebo).[5] Nonvertebral fractures event rates estimated using Kaplan-Meier estimates were 2.7% of women in the abaloparatide group, 3.3% of women in the teriparatide group and 4.7% of women in the placebo group (abaloparatide hazard ratio (HR) 0.57, 95% CI 0.32 to 1.00, $p = 0.049$; teriparatide HR 0.72, 95% CI 0.42 to 1.22, $p = 0.22$ both vs. placebo).[5] The HR for abaloparatide versus teriparatide was 0.79 (95% CI 0.43 to 1.45; p=0.44) for nonvertebral fractures.[5] BMD at 18 months was improved with abaloparatide compared to placebo at the hip (4.2% vs. -0.1%), femoral neck (3.6% vs. -0.4%) and lumbar spine (11.2% vs. 0.6%).[5] Incidence of hypercalcemia was lower with abaloparatide (3.4%) versus teriparatide (6.4%) (risk difference [RD], −2.96 [95% CI, −5.12 to −0.87]; $p = 0.006$).[5] In this trial, abaloparatide significantly reduced the risk of new fractures in postmenopausal women compared to placebo.

One limitation of this study is that 63% of participants had a prior fracture. The impact of abaloparatide on reducing fracture in women with lower risk for fracture cannot be determined from this trial. The trial was only conducted over 18 months; therefore, it is not clear how long the reduction in fracture risk with abaloparatide will persist using data from this trial. The trial was not powered to detect differences in efficacy between abaloparatide and teriparatide. The trial was not sufficiently powered to detect the effects of abaloparatide on hip fracture. Finally, the open label arm of teriparatide and lack of blinding may have

resulted in bias because subjects and investigators were aware of the treatment which may have affected adverse reaction reporting or adherence. This trial may have limited applicability to Medicaid patients, who are primarily under the age of 65 years.

Patients in both the abaloparatide and placebo groups of the ACTIVE trial were offered an additional two years of follow-up receiving open-label oral alendronate 70 mg weekly and 92% (n=1139) of eligible patients agreed to participate.[27] The 6-month follow-up results reported lower rates of vertebral fractures (HR 0.13, 95% CI 0.04-0.41) and nonvertebral fractures (HR 0.48, 95% CI 0.26-0.89) for abaloparatide followed by alendronate compared to placebo followed by alendronate when analyzed from the beginning of the ACTIVE trial.[27] However, the number of new fractures in the extension trial was low in both the abaloparatide/alendronate and placebo/alendronate groups (vertebral 0 vs. 7; nonvertebral 3 vs. 7, respectively).[27] These data suggests that alendronate therapy can preserve the fracture reduction benefits of abaloparatide.

Clinical Safety:
During the ACTIVE trial, discontinuation of the study drug due to adverse events was higher in the abaloparatide group (9.9% vs. teriparatide 6.8% and placebo 6.1%).[5] However, rates of serious treatment-emergent adverse events were similar when abaloparatide, teriparatide, and placebo were evaluated in this trial (9.7%, 10.0%, and 11% respectively).[5] Most common adverse effects that led to treatment discontinuation with abaloparatide included nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%).[5] Hypercalcemia was more common in the parathyroid hormone analog groups than placebo (3.4% abaloparatide, 6.4% teriparatide, 0.4% placebo).[5] Other significant adverse effects of abaloparatide in the ACTIVE trial were orthostatic hypotension (17.1%) and hypercalciuria (11.3%).[5] The safety profile of abaloparatide compared to placebo as described in the ACTIVE trial is presented in **Table 2**.[5]

Abaloparatide labeling contains a black box warning about the possible risk of osteosarcoma is based on an increased incidence in rats with systemic exposure 4-28 times the exposure in humans receiving recommended doses.[6] It is unknown if abaloparatide causes osteosarcoma in humans. Teriparatide contains a similar warning.[7] Use of abaloparatide greater than 2 years during a patient's lifetime is not recommended per the manufacturer's prescribing information.[6]

Table 2. Safety Profile of abaloparatide compared to placebo from the ACTIVE trial[5]

Common Adverse Events	**Abaloparatide N = 822**	**Placebo N = 820**
Hypercalciuria	11.3%	9%
Dizziness	10%	6.1%
Arthralgia	8.6%	9.8%
Headache	8%	6%
Nausea	8.3%	3%
Upper Respiratory Tract Infection	8.3%	7.7%
Serious Adverse Events	**Abaloparatide**	**Placebo**

Orthostatic Hypotension	17.1%	16.4%
Hypercalcemia	3.4%	0.4%
Tachycardia	2%	1%

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

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Human parathyroid hormone related peptide (PTHrP1-34) analog which results in an anabolic effect on bone
Bioavailability	Bioavailability of an 80 mcg subcutaneous dose was 36%
Distribution and Protein Binding	Volume of distribution is 50 liters. Protein binding is 70%
Elimination	Peptide fragments are primarily eliminated through renal elimination
Half-Life	Mean half-life is 1.7 hours
Metabolism	No specific metabolism or excretion studies have been performed with abaloparatide

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:

1) Percentage of patients with new vertebral fractures
2) Percentage of patients with new non-vertebral fractures
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percentage of patients with new vertebral fractures over 18 months

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. Miller et al[5] RCT, DB, PC, MC, Phase 3	1. Abaloparatide 80 mcg SC once daily 2. Placebo SC daily 3.Teriparatide 20 mcg once daily (open label due to	Demographics: -Mean age: 69 years -Mean femoral neck T score = -2.1 -White = 80% -Asian = 16% -Black = 3%	ITT: 1.824 2.821 3.818 mITT	Primary Endpoint: Percentage of patients with new vertebral fractures: ABL: 0.58% PBO: 4.2% RR 0.14 (95% CI, 0.05 to 0.39; P < 0.001)	3.6/28	Hypercalcemia (corrected Ca >10.7 mg/dL): ABL 3.4% TPTD 6.4% RD -2.96 (95% CI,	2.96/33	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW - Randomized 1:1:1 using permuted-blocks design with a block size of 6. Patients were sequentially assigned a treatment number and allocated to each group using a centralized IVRS system. The IVRS system recorded site number, subject number, and kit/randomization number and

	proprietary packaging of teriparatide) 18 months	-History of prior fracture: 63% -No prior fracture: 37% Key Inclusion Criteria: -Women who were postmenopausal for at least 5 years -Age 49-86 years -BMD T score ≤ -2.5 and > -5.0 at the lumbar spine or femoral neck AND radiologic evidence ≥ 2 mild or ≥ 1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years -Women aged 65 years with T score ≤ -2.0 and > 5.0 or with fracture criteria OR T score ≤ -3.0 and > -5.0 without fracture criteria Key Exclusion Criteria: -> 4 mild, moderate or severe vertebral fractures -< 2 evaluable lumbar vertebrae -unevaluable hip BMD	1.711 2.690 3.717 Attrition: 1.26% 2.22% 3.20%	TPTD: 0.84% PBO: 4.2% RR 0.20 (95% CI 0.08 to 0.47; p < 0.001) Secondary Endpoints: Nonvertebral fractures: ABL 2.7% PBO 4.7% HR 0.57 (95% CI, 0.32 to 1.00; p < 0.049) TPTD: 3.3% PBO 4.7% HR 0.72 (95% CI, 0.42 to 1.22; P = 0.22)	3.38/26	-5.12 to - 0.87; p= 0.006) All TEAE: ABL: 89.4% PBO: 87.6% TPTD: 88.9% Serious TEAE: ABL: 9.7% PBO: 11% TPTD: 10%		details were blinded to investigators. Baseline characteristics similar among treatment groups. Performance Bias: HIGH- Double blinded arms for abaloparatide and placebo (participant, provider, investigator, radiologists). Teriparatide arm was blinded until after randomization, then open label to participant, provider and investigator. Primary endpoint compared to placebo for both drugs. Detection Bias: LOW – All radiologists assessing radiographs were blinded to treatment. A second radiologist reviewed radiographs to confirm reading of incident fracture. Attrition Bias: HIGH - Attrition similar between groups. Data from 2118 subjects was analyzed using mITT analysis for all patients who had pre-treatment and end of treatment evaluable spine x-rays. Missing data was imputed using a logistic regression model that used 5 data sets combined with the final results. Reporting Bias: LOW – Detailed study protocol is available in supplemental publication. All endpoints reported as stated a priori. Funded by manufacturer. Study design and statistical analysis completed by manufacturer. **Applicability**: Patient: Mean age of patients in this study was 69 years with a mean T score of -2.1. Sixty-three percent of subjects had prior fracture (vertebral and nonvertebral combined). These demographics may not represent OHP population. Intervention: FDA approved doses were used in the study for both abaloparatide and teriparatide. Patients were taught to self-administer the drug. If they could not self-administer, a trained family member could

		-Evidence of metabolic bone disease -Use of bisphosphonates > 3 months within the past 5 years or denosumab within the past year -history of osteosarcoma -Treatment with anticonvulsants that affect Vitamin D metabolism or with chronic heparin with the 6 months prior to screening period -Daily treatment with corticosteroids within the previous 12 months						assist with administration. Adherence was assessed by patient diaries, cartridge accountability, and site-assessment of remaining drug content of returned cartridges. Comparator: Only powered to detect differences between abaloparatide and placebo in order to establish efficacy of the drug. Not powered to detect a difference between abaloparatide and teriparatide, which would have been a more meaningful comparison. Outcomes: Primary outcome was an appropriate assessment for treatment of osteoporosis. Fracture rate was smaller than anticipated given the incidence predicted in the population of postmenopausal women. Setting: 28 International sites including in 10 countries including US, Denmark, China, and Brazil. Most patients were from Europe (56%) and South America (27%). Only 39 patients (1.6%) were from the US.
Abbreviations [alphabetical order]: ABL = abaloparatide; ALN = alendronate; ARR = absolute risk reduction; BMD = bone mineral density; DB = double blind; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; IVRS = interactive voice response system; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PBO = placebo; PC = Placebo controlled; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SC = subcutaneously; TD = treatment difference; TEAE + treatment-emergent adverse event; TPTD = teriparatide								

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Appendix 1: Current Preferred Drug List

Brand	Generic	PDL	Route	Formulation
ACTONEL	RISEDRONATE SODIUM	Y	ORAL	TABLET
ALENDRONATE SODIUM	ALENDRONATE SODIUM	Y	ORAL	TABLET
BONIVA	IBANDRONATE SODIUM	Y	ORAL	TABLET
FOSAMAX	ALENDRONATE SODIUM	Y	ORAL	TABLET
IBANDRONATE SODIUM	IBANDRONATE SODIUM	Y	ORAL	TABLET
RISEDRONATE SODIUM	RISEDRONATE SODIUM	Y	ORAL	TABLET
MIACALCIN	CALCITONIN,SALMON,SYNTHETIC	N	INJECTION	VIAL
BONIVA	IBANDRONATE SODIUM	N	INTRAVEN	SYRINGE
IBANDRONATE SODIUM	IBANDRONATE SODIUM	N	INTRAVEN	SYRINGE
CALCITONIN-SALMON	CALCITONIN,SALMON,SYNTHETIC	N	NASAL	SPRAY/PUMP
ALENDRONATE SODIUM	ALENDRONATE SODIUM	N	ORAL	SOLUTION
ETIDRONATE DISODIUM	ETIDRONATE DISODIUM	N	ORAL	TABLET
FOSAMAX PLUS D	ALENDRONATE SODIUM/VITAMIN D3	N	ORAL	TABLET
RALOXIFENE HCL	RALOXIFENE HCL	N	ORAL	TABLET
ATELVIA	RISEDRONATE SODIUM	N	ORAL	TABLET DR
RISEDRONATE SODIUM DR	RISEDRONATE SODIUM	N	ORAL	TABLET DR
BINOSTO	ALENDRONATE SODIUM	N	ORAL	TABLET EFF
FORTEO	TERIPARATIDE	N	SUB-Q	PEN INJCTR
PROLIA	DENOSUMAB	N	SUB-Q	SYRINGE
RECLAST	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PGGYBK BTL
ZOLEDRONIC ACID	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PGGYBK BTL
ZOMETA	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PGGYBK BTL
ZOLEDRONIC ACID	ZOLEDRONIC AC/MANNITOL/0.9NACL		INTRAVEN	PIGGYBACK
ZOLEDRONIC ACID	ZOLEDRONIC ACID/MANNITOL-WATER		INTRAVEN	PIGGYBACK
IBANDRONATE SODIUM	IBANDRONATE SODIUM		INTRAVEN	VIAL
PAMIDRONATE DISODIUM	PAMIDRONATE DISODIUM		INTRAVEN	VIAL
ZOLEDRONIC ACID	ZOLEDRONIC ACID		INTRAVEN	VIAL
ZOMETA	ZOLEDRONIC ACID		INTRAVEN	VIAL
XGEVA	DENOSUMAB		SUB-Q	VIAL

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 4 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 03, 2017

1.	Paget Disease, Extramammary/ or pagets disease.mp.	3262
2.	Osteoporosis, Postmenopausal/ or Osteoporosis/ or osteoporosis.mp.	57969
3.	Risedronate Sodium/	1056
4.	Alendronate/	3183
5.	ibandronate.mp.	922
6.	Etidronic Acid/	1672
7.	calcitonin/	6175
8.	Raloxifene Hydrochloride/	2390
9.	Teriparatide/	1144
10.	Denosumab/	982
11.	zoledronic acid.mp.	3872
12.	pamidronate.mp.	2395
13.	1 or 2	60780
14.	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	20054
15.	abaloparatide.mp.	33
16.	14 or 15	20082
17.	13 and 16	6638
18.	limit 17 to (english language and humans and yr="2016 -Current")	160

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

TYMLOS™ (abaloparatide) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: RISK OF OSTEOSARCOMA
See full prescribing information for complete boxed warning.

- **Abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma, a malignant bone tumor, in male and female rats. It is unknown whether TYMLOS will cause osteosarcoma in humans. (5.1, 13.1)**
- **Use of TYMLOS is not recommended in patients at increased risk for osteosarcoma. (5.1)**
- **Cumulative use of TYMLOS and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended. (5.1)**

----------INDICATIONS AND USAGE----------
TYMLOS is a human parathyroid hormone related peptide [PTHrP(1-34)] analog indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose is 80 mcg subcutaneously once daily; patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. (2.1)
- Administer as a subcutaneous injection into periumbilical region of abdomen. (2.2)
- Administer initially where the patient can sit or lie down in case symptoms of orthostatic hypotension occur. (2.2, 5.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 3120 mcg/1.56 mL (2000 mcg/mL) in a single-patient-use prefilled pen. The prefilled pen delivers 30 daily doses of 80 mcg abaloparatide in 40 mcL of sterile, clear, colorless solution. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Orthostatic Hypotension: Instruct patients to sit or lie down if symptoms develop after dose administration. (5.2)
- Hypercalcemia: Avoid use in patients with pre-existing hypercalcemia and those known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism. (5.3)
- Hypercalciuria and Urolithiasis: Monitor urine calcium if preexisting hypercalciuria or active urolithiasis are suspected. (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥2%) are hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain and vertigo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Radius Health, Inc. at 1-855-672-3487 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2017

Bone Resorption Inhibitors and Related Agents

Goal(s):

To ensure appropriate drug use and safety of bone resorption suppression agents by authorizing utilization in specified patient populations.

Length of Authorization:

- 12 to 24 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded condition?	**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? Note: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Is the request for raloxifene?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Is the patient pregnant and/or at increased risk for thromboembolism or stroke?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: inform prescriber of pregnancy category X and boxed warning for venous thromboembolism and stroke.	**No:** Approve for up to 12 months
6. Is the request for teriparatide and is the patient at high risk for fractures? Examples include: • Postmenopausal women with osteoporosis and T-score ≤ 2.5 or history of fracture • Men with primary or hypogonadal osteoporosis* • Men or women with osteoporosis associated with sustained glucocorticoid therapy	**Yes:** Go to #8	**No:** Pass to RPh. Go to #7
7. Is the request for abaloparatide and is the patient a postmenopausal woman at high risk for fractures? • Postmenopausal women with osteoporosis and T-score ≤ 2.5 or history of fracture	**Yes:** Go to #8	**No:** Pass to RPh. Go to #9
~~7.~~8. Does the patient meet one of the following conditions: • Concomitant bisphosphonate; or • Pediatric or young adult with open epiphyses; or • History of osteosarcoma or skeletal malignancies; or • Metabolic bone disease; or • Underlying hypercalcemic disorders; or • Unexplained elevated alkaline phosphatase levels?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 24 months (depending on when therapy was initiated. These two agents are only FDA approved for a total duration of therapy of 2 years.)

Approval Criteria		
~~8.~~9. RPh only: All other indications need to be evaluated as to whether they are funded by the OHP or not.	If funded and clinic provides supporting literature, approve for up to 12 months	If non-funded, deny; not funded by the OHP

P&T Review: *3/18 (DM); 7/16; 9/10*
Implementation: *TBD; 8/16, 1/1/11*

* FDA approved osteoporosis treatments for men include alendronate, risedronate, zoledronic acid, teriparatide, and denosumab.

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Class Update: Oral Antipsychotics

Date of Review: March 2018

Date of Last Review: May 2016
End Date of Literature Search: 10/27/2017

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

Purpose for Class Update:
Evidence for the comparative effectiveness of first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in May 2016. Comparative effectiveness of parenteral antipsychotic products were reviewed in September 2017. This review examines recently published comparative evidence of oral first and second generation antipsychotics. In addition, data regarding new expanded indications and one new formulation are summarized.

Research Questions:
1. Is there new comparative evidence of meaningful difference in clinical efficacy or effectiveness between oral first- or second-generation antipsychotic agents, or between oral antipsychotic agents compared to parenteral antipsychotic agents (first- or second-generation) for schizophrenia, bipolar mania, or major depressive disorder?
2. Is there new comparative evidence of meaningful difference in harms between oral antipsychotic agents (first- or second-generation) or compared to parenteral antipsychotic agents?
3. Is there new comparative evidence of meaningful difference in effectiveness or harms in certain subpopulations based on demographic characteristics (age, gender, or comorbidities), treatment history (treatment naive or treatment resistant), or concomitant medications?

Conclusions:
Schizophrenia
- In adults, no single SGA was superior to other SGAs for multiple clinically relevant outcomes.[1] Similarly, there was no difference in efficacy between FGAs and SGAs.[1] Results for individual efficacy and safety outcomes are reported in **Table 1**.[1] There was insufficient evidence for other comparisons or other outcomes.
- Subgroup analyses demonstrated no difference in efficacy or harms based on age, sex, or prior treatment history.
- There is insufficient evidence assess efficacy of combination antipsychotic treatment with clozapine compared to clozapine monotherapy.

- In children and adolescents, there was low quality evidence of no difference in symptom improvement, response rate, or global impressions of severity between risperidone and olanzapine.[2] There was insufficient evidence for comparisons of other agents for the treatment of schizophrenia.[2]

Bipolar Disorder

- There was no difference in efficacy outcomes (including remission rates, mania symptoms or treatment discontinuation) between olanzapine monotherapy and divalproex or valproate for acute mania in adults with bipolar I (low quality evidence from 4 RCTs [n=867]).[3]
- There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania. There was low quality evidence from a single study (n=488) which reported greater response rate with asenapine compared to olanzapine but no difference in remission rate between therapies.[3]
- In children and young adults, there was insufficient evidence of a difference in clinical outcomes for bipolar disease.

Other Diagnoses

- There is no new evidence for the treatment of other mental health conditions including major depressive disorder. New evidence for the treatment conditions including borderline personality disorder and aggression is insufficient to form meaningful conclusions on comparative efficacy or safety.
- In children and adolescents, there is insufficient direct comparative evidence for FGAs or SGAs for bipolar disorder, autism spectrum disorder, ADHD or other conduct disorders, major depressive disorder, eating disorders, or tic disorders.

Harms

- Since the last review, there have been 4 new Food and Drug Administration (FDA) safety labeling updates for FGAs and SGAs.[4] In 2017, the FDA updated warnings for all SGAs and haloperidol to include risk for falls. Clozapine labeling was updated to include warnings for severe and life-threatening hepatotoxicity, and olanzapine labeling was updated to include a warning for drug reaction with eosinophilia and systemic symptoms. Warnings for pathological gambling and other compulsive behaviors were added to labeling for aripiprazole.
- There was moderate quality evidence that haloperidol was associated with a greater number of withdrawals due to adverse events compared to aripiprazole, olanzapine, risperidone, or ziprasidone in adults with schizophrenia (number needed to harm [NNH] 14 to 52).[1] Comparative evidence for other outcomes was insufficient.
- There was insufficient comparative evidence to determine differences in safety or harms for adults with bipolar disorder.
- In children or young adults, there was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (absolute risk reduction [ARR] 25%, NNH 4; RR 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.[2] There was moderate quality evidence of no difference in mortality upon comparison of SGAs and placebo.[2]
- In children and adolescents, there was low quality evidence based on a large retrospective cohort study that use of SGAs for over 1 year increases risk of diabetes compared to patients not treated with antipsychotics (HR 2.89, 95% CI 1.64 to 5.10; 25.3 vs. 7.8 cases per 10,000 person-years follow-up corresponding to an approximate NNH of 572 over 1 year).[2]

Recommendations:

- No changes to the PDL are recommended for oral antipsychotics based on efficacy or safety data. There is a lack of evidence to recommend any new safety edits for the antipsychotic medications.
- Evaluate comparative costs in executive session.

Previous Conclusions (May 2016):

- There is insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms between antipsychotic agents for schizophrenia, bipolar mania or MDD.
- There is insufficient evidence to determine if brexpiprazole and cariprazine offer superior efficacy or safety to other antipsychotic agents for schizophrenia.
- There is insufficient evidence to determine if brexpiprazole offers superior efficacy or safety to other antipsychotic agents for MDD.
- There is insufficient evidence to determine if cariprazine offers superior efficacy or safety to other antipsychotic agents for bipolar mania.
- There is insufficient evidence to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents generally.

Previous Recommendations:

- Designate Rexulti (brexpiprazole), Vraylar (cariprazine), and new formulations of aripiprazole (Aristada) and paliperidone (Invega Trinza) voluntary non-preferred (no PA required) based on limited data.
- After executive session, make Latuda (lurasidone), Saphris (asenapine) and Abilify Maintena (aripiprazole) preferred and make chlorpromazine voluntary non-preferred (no PA required).

Background:

Antipsychotic medications are typically categorized as FGAs and SGAs. **Appendix 1** lists the oral FGAs and SGAs which are currently available. Antipsychotic medications are indicated for a variety of conditions including schizophrenia and schizoaffective disorder, bipolar disorder (acute and maintenance treatment), adjunct treatment for depression, autism, and Tourette's syndrome.[5] They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression and nausea or vomiting.[5]

Schizophrenia is characterized by presence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms. Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of at least 2 of these symptoms (one must be either delusions, hallucinations or disorganized speech) for longer than 6 months. Symptoms are commonly categorized as positive symptoms (delusions and hallucinations) or negative symptoms (blunted affect, alogia, asociality, anhedonia, and avolition).[6] Onset of schizophrenia occurs most commonly in early adulthood and can have a significant impact on quality of life. Approximately 20% of patients remain relapse-free after a first psychotic episode.[1] However, the majority of patients experience relapse or continued symptoms which can decrease quality of life and create social or occupational difficulties. Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, and slow or early disease onset at less than 18 years of age.[1] Schizophrenia has been associated with increased risk of mortality, and is often also associated with increased cannabis use, substance abuse, and higher rates of depression.[1] Treatment indicated for schizophrenia includes both FGAs and SGAs. First-generation antipsychotics are generally associated with higher incidence of extrapyramidal side effects whereas second-generation antipsychotics may have increased risk for long-term cardiovascular adverse effects.[1] Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also often combined with pharmacological therapy.[1] Initial medication selection is often dependent on effectiveness and risks for adverse effects.

Bipolar disorder is characterized by episodes of mania and episodes of depression or hypomania and is estimated to occur in approximately 2% of the world population.[7] Initial diagnosis is most common in patients less than 25 years of age.[7] It is classified as bipolar I disorder (characterized by at least one manic

episode) or bipolar II disorder (primarily characterized by history of depressive and hypomanic episodes).[7] It can be further classified as rapid cycling with at least 4 episodes of mania, hypomania or depression per year, mania with mixed features, or mania with psychotic features (including hallucinations or delusions).[7] Frequently bipolar disorder is associated with other mental health conditions including anxiety disorder, ADHD and substance use disorders.[7] First-line treatment for bipolar disorder is medication therapy including antipsychotics or mood stabilizers such as lithium, divalproex, or lamotrigine.[7] Goals of treatment include resolution of acute symptoms and long-term prevention of recurrent mania or depressive episodes.[3] Typically, if acute symptoms do not resolve with treatment, the patient is switched to an alternative medication or an additional medication is added.[7] Other treatments include electroconvulsive therapy (ECT), psychoeducational therapy, cognitive behavioral therapy and social therapy. The American Psychiatric Association and the National Institute for Health and Clinical Excellence (NICE) recommends ECT as an option for patients with life-threatening suicidality, psychosis or refusal to eat.[7] ECT may also be considered with severe or treatment-resistant bipolar depression and as a first-line option for pregnant women with severe depression.[7]

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The Clinical Global Impression Scale (CGI) evaluates disease severity and improvement using a 7 point analogue scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimum clinically important difference.[3,6] The Positive and Negative Syndrome Scale (PANSS) evaluates 30 items in schizophrenic patients each scored on a 7 point scale with lower scores indicating less severe symptoms (range 30-210). This scale can also be sub-divided to assess general psychopathology, positive symptoms, or negative symptoms. Typically response to treatment is defined as greater than 20% improvement in the PANSS score though this definition can vary among trials.[1,8] There is no established minimum clinically important difference for the PANSS, though improvements of 4-8 points have been correlated to increases in employment and improvements of 10 points have been correlated with reduced hospitalization. Negative symptoms of schizophrenia may also be assessed using the Scale for Assessment of Negative Symptoms (SANS) score which assesses negative symptoms including alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attention impairment. Each item is assessed on a 0-5 point scale with higher scores indicating more severe symptoms (range 0-125). The Brief Psychiatric Rating Scale (BPRS) assesses schizophrenia symptom severity via assessment of 16-18 items (each assessed on a 7-point scale with a total score of 0 to 126). Similarly, quality of life and functional improvement may be assessed using a variety of metrics. The Global Assessment Scale of Functioning (GAF) scale is commonly used for patients with schizophrenia and assesses functional improvement on a 0 to 100 scale. Clinically important improvements in function have been correlated to changes of at least 10 points.[1]

For patients with bipolar disorder, symptom improvement is commonly evaluated using the 11-item Young Mania Rating Scale (YMRS). Using this scale, changes of at least 6 points have been correlated with clinically significant improvements.[3,9] Symptom improvement and severity for patients with bipolar disorder may also be evaluated using the CGI scale (range 1-7 with a minimum clinically important difference of 1 point).[3]

In the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (PDL) and PA requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use and for pimavanserin to promote safe use in patients with Parkinson's disease psychosis. The majority of antipsychotic use is for SGAs. Each quarter, approximately 25,000 patients receive a prescription for a SGA and 1700 patients have claims for a FGA. This review will assess new evidence for the use of oral antipsychotics.

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), the Cochrane Collaboration, National Institute for

Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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

New Systematic Reviews:

Schizophrenia

An AHRQ report examining the effectiveness of first or second generation antipsychotic medications for the treatment of adults with schizophrenia was published in 2017.[1] First generation antipsychotics included in the review were fluphenazine, haloperidol, and perphenazine. Second-generation antipsychotics included aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Trials and systematic reviews were included if they had a minimum duration of 12 weeks, were conducted in an outpatient setting, and had fair to good methodological quality.[1] Trials not applicable to a US population, trials reporting only placebo comparisons, trials including only comparisons to older antipsychotic drugs and trials reporting only intermediate outcomes were excluded. Overall, one systematic review (n=47,189) and 24 RCTs (n=6,672) were included which compared differences between second generation antipsychotics.[1] One systematic review (n=118,503) and 5 RCTs (n=1,055) were included which compared first generation to second generation antipsychotics.[1] The majority of patients included in these trials were 25 to 50 years of age with moderate to severe disease and most included studies were 6 to 12 weeks in duration.[1] In trials assessing first-episode schizophrenia, the mean age was 26 years. Few studies assessed long-term outcomes up to 1 to 2 years.[1]

Results are reported in **Table 1**. There was little evidence which assessed newer second-generation antipsychotics and direct comparative evidence regarding other outcomes (including relapse rate, symptom improvement, overall treatment discontinuation, cardiovascular outcomes, diabetes, ketoacidosis and sexual function) was inconsistent between studies and insufficient to draw definitive conclusions between treatment groups.[1] Overall results for subgroup analyses were similar to the general population when analyzed based on study duration, dose, treatment-resistant population, or patients with first-episode psychosis (low quality evidence).[1] Similarly, there was no difference between olanzapine and risperidone in treatment discontinuation, quality of life, symptom improvement when stratified by age or sex. Upon comparison of clozapine to olanzapine, more women had symptom improvement compared to men (using the CGI or EQ-5D visual analog scale).[1]Women and younger patients (<40 years of age) had a higher risk of new onset diabetes than older or male patients when treated with olanzapine or risperidone compared to FGAs.[1] The exact rate of new onset diabetes remains unclear.[1]

Table 1. Outcomes and results of AHRQ report[1]

Outcome	**Comparators**	**Quality of evidence**	**Result**
Social or functional status	Risperidone, olanzapine, quetiapine, perphenazine, or ziprasidone	Low	No difference at 18 months
Quality of life	Olanzapine vs. risperidone Olanzapine vs. ziprasidone Olanzapine vs. quetiapine	Moderate Moderate Low	No difference at up to 12 months

	Risperidone vs. quetiapine or ziprasidone Ziprasidone vs. haloperidol Olanzapine vs. haloperidol Perphenazine vs. olanzapine, quetiapine, risperidone or ziprasidone	Low Low Low Low	
Treatment response*	Olanzapine vs. haloperidol Haloperidol vs. risperidone Haloperidol vs. aripiprazole or quetiapine	Low Moderate Low	52.6% vs. 46.5%;[10] RR 0.86, 95% CI 0.78 to 0.96 No difference No difference
Core symptom improvement	FGAs vs. SGAs	Low	No difference
Negative symptom improvement	Olanzapine vs. haloperidol Aripiprazole or risperidone vs. haloperidol Other FGAs vs. SGAs	Moderate Low Low	No clinical difference; MD 2.56, 95% CI 0.94 to 4.18 (SANS score) No clinical difference; MD 0.80, 95% CI 0.14 to 1.46 (PANSS scale) No difference
Remission (complete symptom resolution)	Olanzapine vs. haloperidol Risperidone vs. haloperidol	Low Low	RR 0.64, 95% CI 0.45 to 0.94 (favors olanzapine; ARR not reported) No difference
All-cause mortality or cardiovascular mortality	SGA comparisons	Low	No difference; range 0% to 1.17% at 4 to 24 months
Suicide at 2 years 1. Hospitalization to prevent suicide or suicide attempt 2. Symptoms of suicidality	Clozapine vs. olanzapine	Low Low	1. ARR 8%;[11] HR 0.76, 95% CI 0.58 to 0.97; NNT 12 (favors clozapine) 2. ARR 8.4%;[11] HR 0.78, 95% CI 0.61 to 0.99; NNT 12 (CGI-S - Suicidality scale; favors clozapine)
Overall adverse effects	SGA comparisons		No difference in overall rate of adverse events upon comparison of SGAs; For most studies, the proportion of patients with adverse effects was greater than 60%.
Withdrawals due to adverse events	Haloperidol vs. aripiprazole Haloperidol vs. olanzapine Haloperidol vs. risperidone Haloperidol vs. ziprasidone Haloperidol vs. clozapine or quetiapine	Moderate Moderate Moderate Moderate Low	16.2% vs. 14.3%; NNH 52; RR 1.25, 95% CI 1.07 to 1.47 11.6% vs. 6.0%; NNH 17; RR 1.89; 95% CI 1.57 to 2.27 11.1% vs. 8.4%; NNH 37; RR 1.32; 95% CI 1.09 to 1.60 16.0% vs. 9.2%; NNH 14; RR 1.68, 95% CI 1.26 to 2.23 No difference
Clinically important weight gain of >7%	Olanzapine vs aripiprazole Olanzapine vs. clozapine Olanzapine vs. quetiapine Olanzapine vs. risperidone Olanzapine vs. ziprasidone	Moderate Moderate Moderate Moderate Moderate	RR 2.31; 95% CI 1.96 to 2.72 (olanzapine more weight gain) RR 1.71; 95% CI 1.47 to 1.99 (olanzapine more weight gain) RR 1.82; 95% CI 1.34 to 2.46 (olanzapine more weight gain) RR 1.81; 95% CI 1.34 to 2.46 (olanzapine more weight gain) RR 5.76; 95% CI 3.46 to 9.59 (olanzapine more weight gain) Absolute values were not reported though mean differences in weight gain ranged from 1-7 kg over 3.7 to 24 months with larger weight gain generally associated with longer use.

Abbreviations: ARR = absolute risk reduction; CGI-S = Clinical Global Impression of Severity; CI = confidence interval; FGA = first generation antipsychotic; HR = hazard ratio; MD = mean difference; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; PANSS = positive and negative syndrome scale; RR = relative risk; SANS = scale for assessment of negative symptoms; SGA = second generation antipsychotic
*Treatment response most commonly defined as greater than 20% improvement in the PANSS.[1] Other definitions included improvement of more than 20% on BPRS with either CGI-S score of less than or equal to 3 or BPRS less than 35; 30%, 40%, and 50% improvements in PANSS or BPRS; or a score of less than or equal to 3 on all PANSS items and less than 3 on the CGI-S.[1]

A 2017 Cochrane review examined the safety and efficacy of antipsychotic combination treatments to antipsychotic monotherapy for patients with schizophrenia and schizoaffective disorders.[6] Of the 62 studies included in the review (n=4833), 31 studies compared combination treatment with clozapine to clozapine monotherapy.[6] Most trials had moderate to high risk of bias due to unclear allocation concealment, randomization and blinding methods. In addition, the majority of trials examined treatment durations of less than 12 weeks and only 7 studies examined long-term treatment for greater than 26 weeks.[6] Most trials included populations who had previously failed monotherapy antipsychotics and approximately half of the studies included patients admitted to a facility.[6] Outcomes assessed included clinical response to treatment, relapse, early study discontinuation, hospital admission, change in hospital status, serious adverse events or adverse events requiring treatment discontinuation, and quality of life.

- For all outcomes, with the exception for early study discontinuation, evidence was assessed as either insufficient or very low quality limiting the ability to draw meaningful conclusions.[6]
- Early study discontinuation was not statistically significant between patients on combination antipsychotic treatment versus monotherapy antipsychotic use (low quality evidence; RR 0.90, 95% CI 0.76 to 1.07, n=3137).[6] Data were limited by high risk or bias in included studies, high heterogeneity, lack of reported outcomes of interest, and short trial duration.

Combination treatment was also assessed in a 2016 report from CADTH which included 4 systematic reviews, 8 RCTs, and 2 evidence-based guidelines.[12] Upon comparison of combination treatment with aripiprazole and clozapine versus clozapine monotherapy, results of trials were mixed and there was insufficient evidence to determine differences in symptom improvement.[12] Additionally, symptom improvement was not significantly different upon clozapine augmentation with risperidone (n=255) or augmentation with haloperidol or aripiprazole (n=106) compared to clozapine monotherapy.[12] Data were limited by small populations, limited duration (<3 months), high heterogeneity between trials, and lack of reported randomization or blinding methods.[12] Guidelines included in the review recommend a 10-week trial of combination antipsychotic regimens only for patients who previously failed a dose-optimized clozapine regimen.[12]

In patients with treatment-resistant schizophrenia, a 2017 Cochrane review examined efficacy and safety of combination antipsychotic treatment with clozapine.[13] Three trials were identified which evaluated antipsychotics including aripiprazole versus haloperidol (n=105), risperidone versus ziprasidone (n=24), and ziprasidone versus quetiapine (n=63) when used in combination with clozapine.[13] For most outcomes, evidence was graded as very low quality, limiting confidence in the treatment effect.[13] There was no difference in mental state, clinically significant response, clinically significant symptom improvement, or treatment discontinuation upon comparison of aripiprazole to haloperidol or risperidone to ziprasidone (very low to low quality evidence).[13] There was low quality evidence from a single RCT that more patients treated with the combination of ziprasidone plus clozapine had a 50% reduction in PANSS score (MD 39%; RR 0.54, 95% CI 0.35 to 0.81) and global severity as assessed by CGI-Score (MD -0.70, 95% CI -1.18 to -0.22) compared to combination treatment with clozapine and quetiapine.[13]

<u>Bipolar Disorder</u>

At the time of this review, a 2017 draft AHRQ report was available which examines the effectiveness of drugs for the treatment of adults with bipolar disorder.[3] Drugs included in the review included second-generation antipsychotics, anticonvulsants (carbamazepine, divalproex, and lamotrigine), chlorpromazine, and lithium.[3] Direct comparisons for treatment of acute mania were limited.

- There was no difference in efficacy outcomes (including remission rates, mania symptoms or treatment discontinuation) between olanzapine monotherapy and divalproex or valproate for acute mania in adults with bipolar I (low quality evidence from 4 RCTs [n=867]).[3] One study noted that clinically important weight gain of at least 7% was more common in patients treated with olanzapine, though statistical significance weight gain was not documented in all studies.[3] There was low quality evidence from a single study (n=488) which reported greater response rate with asenapine compared to olanzapine but no difference in remission rate between therapies.[3]
- There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania.[3] Similarly, there was insufficient evidence for any treatment and all outcomes for bipolar depression or maintenance treatment.[3]

A 2016 CADTH rapid response report examined aripiprazole use as monotherapy or adjunct therapy in combination with lithium or divalproex.[14] A single systematic review (n=2505) and 3 evidence-based guidelines provided clinical evidence for the report. Relevant comparators included haloperidol, lithium and valproic acid.[14] Outcomes included response rate, treatment discontinuation and adverse effects. Overall, response rate with greater than 50% improvement in symptom score, symptom improvement, and treatment discontinuation were similar between aripiprazole and other traditional treatments for bipolar disorder including lithium, divalproex, and haloperidol.[14] Comparisons to individual agents were not evaluated and there was high heterogeneity among analyses.[14]

Another rapid response report published by CADTH in 2016 found no published literature regarding the use of combination second-generation antipsychotics for adults or adolescents with bipolar disorder.[15]

<u>Antipsychotic Treatment for Pediatric and Young Adult Patients</u>

An AHRQ report published in 2016 examined efficacy and safety of FGA and SGA use in children and young adults (less than 25 years of age).[2] The report included 135 studies which primarily compared antipsychotic use to placebo.[2] Direct comparative evidence (which will be the focus of this summary) was generally of insufficient or low quality particularly for clinical outcomes.

- There was low quality evidence of no difference between FGAs and SGAs for improvement of negative symptoms, positive symptoms, response rate, and global impression of illness severity for patients with schizophrenia or related psychosis.[2] For the comparison of olanzapine and risperidone, there was no difference in symptom improvement, response rate, or global impressions of severity (low quality evidence based on 6 studies).[2]
- There was insufficient evidence for comparisons of other agents for the treatment of schizophrenia.[2]
- There were no studies identified which examined direct comparative efficacy or safety of either FGAs or SGAs in patients with bipolar disorder, autism spectrum disorder, ADHD or other conduct disorders, depression, eating disorders, or tic disorders.[2] There was insufficient evidence regarding efficacy or safety of SGAs in patients with obsessive-compulsive disorder.[2]
- There was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (MD 25 %, NNH 4; RR 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.[2] Regarding long-term serious adverse events, there was moderate quality evidence of no difference in mortality upon comparison of SGAs and placebo.[2]
- There was low quality evidence based on a large retrospective cohort study that use of SGAs for over 1 year increases risk of diabetes compared to patients not treated with antipsychotics (HR 2.89, 95% CI 1.64 to 5.10; 25.3 vs. 7.8 cases per 10,000 person-years follow-up corresponding to an approximate NNH of 572 over 1 year).[2] Subgroup analyses demonstrated no difference in efficacy or harms based on age, sex, or prior treatment history. Duration of treatment

did have a slight effect on weight gain, with longer treatment durations associated with larger increases in weight over time (0.04 kg/week; 95% CI 0.014 to 0.071).[2] Overall, these analyses were limited by the populations enrolled in the included studies. Few trials enrolled young adults or children less than 8 years of age and many excluded patients with mild symptom severity or patients with comorbidities. In addition, the majority of studies were of short duration (<6 months) which limits estimates of long-term efficacy and adverse effects.

In May 2017, an AHRQ report was published which examined medical treatment for children with autism spectrum disorder.[16] Only 4 of these studies included direct comparative evidence between agents. Upon comparison of aripiprazole to risperidone in 3 small studies, there was no difference in challenging behavior or general improvement between groups at 8 weeks, 24 weeks, or up to 1-2 years (low quality evidence).[16] There was insufficient evidence for other comparisons.[16] The most common adverse effects associated with treatment included weight gain, increased appetite, and drowsiness. All antipsychotic treatments were associated with increased weight gain over time, but differences were not statistically different between groups.[16]

CADTH published a rapid response report in 2016 including 9 systematic reviews which examined antipsychotic use in pediatric patients (<18 years of age).[17] Overall, direct comparative evidence was limited. Two systematic reviews including patients with Tourette's syndrome or tic disorders provided evidence of no difference in symptom severity upon comparison of aripiprazole and haloperidol or risperidone.[17] For children with psychosis or schizophrenia, available evidence from 2 systematic reviews demonstrated no difference in efficacy between individual antipsychotic agents or between FGAs and SGAs.[17] There was no comparative evidence for efficacy and safety of antipsychotics in children with other conditions including disruptive behavior disorders or autism spectrum disorders.[17] Evidence regarding adverse events was mixed. The most common adverse events associated with treatment were weight gain, drowsiness, increased appetite, and extrapyramidal adverse effects.[17] In patients with schizophrenia, increased weight gain was observed with olanzapine compared to risperidone (MD 6.1 ± 3.6 kg vs. 3.6 ± 4 kg, p-value not reported), but there was no difference upon comparison of clozapine and olanzapine.[17] Other trials report no difference in adverse effects between agents, though the ability to detect differences between groups was limited by small population sizes, large heterogeneity, and poor quality of trials included in these systematic reviews.[17]

Other Conditions

In 2017, CADTH published a rapid response report assessing available evidence of aripiprazole treatment for borderline personality disorder.[18] First-line treatment for borderline personality disorder is psychotherapy though pharmacotherapy (including off-label use of antipsychotics, antidepressants and mood stabilizers) may be used as adjunct treatment.[18] Only 2 RCTs (one with direct comparative evidence to olanzapine and one with only placebo comparisons) were included in the review, and evidence was insufficient to assess efficacy, safety, or generalizability to a broader population. Data were limited by small population size (n=76), lack of reported randomization or blinding methods, and inadequate reporting of baseline population characteristics or concomitant medications use.[18]

A Cochrane review published in 2016 attempted to evaluate evidence for haloperidol as a treatment for long-term or persistent aggression in patients with psychosis.[19] Only one low-quality RCT (n=110) with high risk of bias was identified which compared haloperidol to olanzapine or clozapine.[19] There was low quality evidence of no difference in discontinuation rate between treatment groups.[19] Data for other outcomes including treatment efficacy was limited by unclear randomization, allocation concealment or blinding methodology, high attrition rate, and high risk of reporting bias.[19]

Several other systematic reviews and meta-analyses were not included due to poor methodological quality, because the evidence available for the analysis was of poor quality, or evidence was not applicable to the OHP population.[8,20-37]

New Guidelines:
Guidelines from the Department of Veterans Affairs and Department of Defense were updated in 2016 for the management of major depressive disorder.[38] Recommended first-line pharmacological treatments for mild to moderate major depressive disorder include SSRIs (except fluvoxamine), SNRIs, mirtazapine, or bupropion (strong recommendation).[38] Treatment selection is recommended based on patient preference, safety and adverse effect profile, history of prior treatment response, family history of response to a medication, concurrent comorbidities or medications, cost and provider training.[38] In patients with only partial response or no response to initial treatment, treatment should be switched to another treatment or augmented with another medication or psychotherapy. Similarly, for patients with severe depression, combination psychotherapy and pharmacotherapy is recommended (strong recommendation).[38] Medication augmentation strategies include addition of bupropion, buspirone, lithium, liothyronine, or SGAs to first-line pharmacotherapy.[38] Due to the significant potential of adverse effects with SGAs, they are recommended only when other strategies have failed.[38] Recommendation was based on 2 systematic reviews demonstrating aripiprazole, olanzapine, quetiapine, and risperidone improved remission rates compared to placebo.[38] However, there was fair quality evidence that adverse effects including akathisia were statistically more common with aripiprazole, and sedation were more common with olanzapine and quetiapine.[38] Aripiprazole, olanzapine, quetiapine and risperidone were also more commonly associated with weight gain compared to placebo (fair quality evidence).[38]

The Department of Veterans Affairs and Department of Defense also updated guidelines for the management of post-traumatic stress disorder (PTSD) in 2017.[39] Briefly, second-generation antipsychotics are not recommended as monotherapy or as augmentation therapy for the treatment of PTSD due to a lack of evidence regarding efficacy in this population and known adverse effects associated with treatment (weak recommendation).[39]

In 2016, the American Psychiatric Association updated guideline recommendations for the use of antipsychotics in patients with dementia.[40] The majority of guideline committee members reported no conflicts of interest. Only one member reported receiving funding from industry and government which could be perceived as a conflict of interest, and this member abstained from voting on medication-related recommendations.[40] Most recommendations focus on use of antipsychotics in the nonemergency setting. Overall, evidence was based on low to moderate quality evidence and few recommendations were made for specific antipsychotic regimens. Recommendations for specific medications are discussed here. Haloperidol is not recommended as a first-line nonemergency medication in patients with dementia and without delirium (strong recommendation; moderate quality evidence).[40] In addition, long-acting injectable antipsychotic medications are not recommended unless used for patients with concomitant chronic psychotic disorders (strong recommendation; moderate quality evidence).[40]

New Formulations or Indications:
In May 2016, Fanapt® (iloperidone) received an expanded indication for maintenance treatment of schizophrenia. It had previously been indicated only for short-term treatment. In addition, Saphris® (asenapine) was approved for pediatric patients 10 to 17 years with bipolar I disorder, and Latuda® (lurasidone) received approval from the FDA for treatment of schizophrenia in adolescents aged 13 to 17 years.

In November 2017, the FDA approved Abilify Mycite®, a new formulation of aripiprazole oral tablets with a sensor.[41] This formulation is a drug-device combination product with an ingestible event marker sensor which is intended to track whether the tablet is consumed.[41] Approval was based on prior efficacy and safety analysis of aripiprazole tablets. Abilify Mycite is indicated for treatment of adults with schizophrenia, adjunct treatment of adults with MDD, and acute or maintenance treatment of bipolar I disorder (as monotherapy or in combination with lithium or valproate).[41] The sensor embedded in the tablet activates upon contact with gastric fluid and sends a signal to a Mycite® Patch which is worn by the patient.[41] This patch then transmits the data to a smartphone app for the patient and/or web-based portal for healthcare providers. Labeling specifies that improved compliance with this formulation has not been

established, and that tracking drug ingestion in "real-time" or during an emergency is not recommended because detection of sensors may be delayed or not occur.[41]

New FDA Safety Alerts:
In 2017, the FDA updated warnings for all SGAs and haloperidol to include risk for falls. Labeling specifies that antipsychotics have been associated with somnolence, postural hypotension, and motor or sensory instability which may lead to falls. A complete fall risk assessment is advised upon initiation of these medications and intermittently for patients on long-term therapy.[4]

In February 2017, the FDA updated clozapine labeling to include warnings for severe and life-threatening hepatotoxicity. Reports of hepatotoxicity occurred in post-marketing studies of clozapine and the exact incidence or frequency of hepatotoxicity is unclear. Monitoring is recommended for signs and symptoms of hepatotoxicity including fatigue, nausea, jaundice, and hepatic encephalopathy.[4]

In October 2016, olanzapine labeling was updated to include a warning for drug reaction with eosinophilia and systemic symptoms. Discontinuation of treatment is recommended if symptoms are observed.[4]

Labeling for aripiprazole was updated in 2016 to include warnings for pathological gambling and other compulsive behaviors. Compulsive urges, particularly for gambling, have been reported in post-marketing experience. Dose reduction or treatment discontinuation should be considered if symptoms are present.[4]

Randomized Controlled Trials:
A total of 344 citations were manually reviewed from the initial literature search. After further review, 340 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical or exploratory). Only trials reporting new comparative evidence were considered for inclusion, and trials which offered no new additional information from sources already in the review were excluded. The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Mohamed S, et al.[42] AC, single-blind, MC, PG, RCT N=1522 Duration: 36 weeks	1. Switch to bupropion 150-400 mg daily 2. Add bupropion 150-400 mg daily 3. Add aripiprazole 5-15 mg daily Doses titrated based on tolerability and treatment effect	Veterans with MDD unresponsive to at least one antidepressant	Remission at 12 weeks defined as a score of ≤5 on the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C16) score	1. 114/511 (22.3%) 2. 136/506 (26.9%) 3. 146/505 (28.9%) 1 vs. 3: ARR: 6.6%; RR 1.30 (95% CI 1.05-1.60); *p*= 0.02 1 vs. 2 and 2 vs. 3 were not significant

Cheon E, et al.[43] AC, MC, OL, PG, RCT N=103 Duration: 6 weeks	1. Addition of aripiprazole 2.5 to 20 mg daily (mean 2.99 mg/day) 2. Addition of bupropion 150 to 300 mg daily (mean 199 mg/day)	MDD unresponsive to SSRI treatment of at least 4 weeks	Mean change in the Montgomery Asberg Depression Rating Scale total score from baseline to 6 weeks	1. -13.77 (SD 8.59) 2. -9.45 (SD 9.45) Difference between groups was not significant
Nierenberg A, et al.[44] MC, PG, Single-blind RCT N=482 Duration: 6 months	1. Lithium (mean dose 1007 mg) 2. Quetiapine (mean dose 345 mg) Medication titrated to maximum tolerated dose. Treatment given in combination with adjunctive personalized treatment which could include any medication except SGAs or lithium.	Bipolar I or II disorder	Clinical Global Impressions-Efficacy Index (range -3 [no benefit, significant harms] to +3 [significant benefit, no harm]) Necessary clinical adjustments (defined as the number of changes necessary in adjunctive treatment due to new, persistent or worsened symptoms or adverse effects)	Clinical Global Impressions-Efficacy Index 1. 1.58 (95% CI 1.32 to 1.84) 2. 1.52 (95% CI 1.26 to 1.78) MD 0.06 (95% CI -0.16 to 0.29); p=0.59 Average number of necessary clinical adjustments per month 1. 0.8 (SD 0.8) per month 2. 0.9 (SD 1.0) per month P=0.15
Lamberti M, et al.[45] OL, RCT N=44 Duration: 24 weeks	1. Risperidone 0.25 to 3 mg daily 2. Aripiprazole 1.25 to 15 mg daily Dose titrated based on clinical response	Italian patients with autism spectrum disorder and ADHD	Change in ADHD-rating scale (18 questions evaluating symptom improvement) or CGI-I (range 1-7) rating scales from baseline	ADHD-RS at 24 weeks 1. 19.1 (SD 3) 2. 26.7 (SD 7.8) P=0.842 CGI-I at 24 weeks 1. 2.7 (SD 0.7) 2. 3.0 (SD 1.2) P=0.356

Abbreviations: AC = active comparator; ADHD = attention-deficit/hyperactivity disorder; FGA = first generation antipsychotic; MC = multicenter; MD = mean difference; MDD = major depressive disorder; OL = open label; PG = parallel-group; RCT = randomized clinical trial; RR = relative risk; SD = standard deviation; SGA = second generation antipsychotic

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Appendix 1: Current Preferred Drug List

ROUTE	FORM	BRAND	GENERIC	PDL	CARVEOUT
FIRST GENERATION ORAL ANTIPSYCHOTICS					
ORAL	ELIXIR	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	ORAL CONC	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	HALOPERIDOL	HALOPERIDOL	Y	Y
ORAL	ORAL CONC	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
ORAL	CAPSULE	LOXAPINE	LOXAPINE SUCCINATE	Y	Y
ORAL	TABLET	PERPHENAZINE	PERPHENAZINE	Y	Y
ORAL	TABLET	THIORIDAZINE HCL	THIORIDAZINE HCL	Y	Y
ORAL	CAPSULE	THIOTHIXENE	THIOTHIXENE	Y	Y
ORAL	TABLET	TRIFLUOPERAZINE HCL	TRIFLUOPERAZINE HCL	Y	Y
ORAL	TABLET	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	V	Y
ORAL	TABLET	ORAP	PIMOZIDE	V	Y
ORAL	TABLET	PIMOZIDE	PIMOZIDE	V	Y
SECOND GENERATION ORAL ANTIPSYCHOTICS					
SUBLINGUAL	TAB SUBL	SAPHRIS	ASENAPINE MALEATE	Y	Y
ORAL	TABLET	CLOZAPINE	CLOZAPINE	Y	Y
ORAL	TABLET	LATUDA	LURASIDONE HCL	Y	Y
ORAL	TABLET	OLANZAPINE	OLANZAPINE	Y	Y
ORAL	TABLET	ZYPREXA	OLANZAPINE	Y	Y
ORAL	TABLET	QUETIAPINE FUMARATE	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	SEROQUEL	QUETIAPINE FUMARATE	Y	Y
ORAL	SOLUTION	RISPERDAL	RISPERIDONE	Y	Y
ORAL	SOLUTION	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERDAL	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	SOLUTION	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ABILIFY	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TABLET	REXULTI	BREXPIPRAZOLE	V	Y
ORAL	CAP DS PK	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	CAPSULE	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	ORAL SUSP	VERSACLOZ	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	CLOZAPINE	V	Y

ORAL	TAB RAPDIS	FAZACLO	CLOZAPINE	V	Y
ORAL	TABLET	FANAPT	ILOPEIDONE	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	OLANZAPINE	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	OLANZAPINE	V	Y
ORAL	TAB ER 24	INVEGA	PALIPERIDONE	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	PALIPERIDONE	V	Y
ORAL	TABLET	NUPLAZID	PIMAVANSERIN TARTRATE	V	Y
ORAL	TAB ER 24H	QUETIAPINE FUMARATE ER	QUETIAPINE FUMARATE	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	QUETIAPINE FUMARATE	V	Y
ORAL	TAB RAPDIS	RISPERDAL M-TAB	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	RISPERIDONE	V	Y
ORAL	CAPSULE	GEODON	ZIPRASIDONE HCL	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ZIPRASIDONE HCL	V	Y

Appendix 2: Abstracts of Comparative Clinical Trials

1. Cheon E-J, Lee K-H, Park Y-W, et al. Comparison of the Efficacy and Safety of Aripiprazole Versus Bupropion Augmentation in Patients With Major Depressive Disorder Unresponsive to Selective Serotonin Reuptake Inhibitors: A Randomized, Prospective, Open-Label Study. *Journal of clinical psychopharmacology.* 2017;37(2):193-199.

   PURPOSE: The purpose of this study was to compare the efficacy and safety of aripiprazole versus bupropion augmentation in patients with major depressive disorder (MDD) unresponsive to selective serotonin reuptake inhibitors (SSRIs)., METHODS: This is the first randomized, prospective, open-label, direct comparison study between aripiprazole and bupropion augmentation. Participants had at least moderately severe depressive symptoms after 4 weeks or more of SSRI treatment. A total of 103 patients were randomized to either aripiprazole (n = 56) or bupropion (n = 47) augmentation for 6 weeks. Concomitant use of psychotropic agents was prohibited. Montgomery Asberg Depression Rating Scale, 17-item Hamilton Depression Rating scale, Iowa Fatigue Scale, Drug-Induced Extrapyramidal Symptoms Scale, Psychotropic-Related Sexual Dysfunction Questionnaire scores were obtained at baseline and after 1, 2, 4, and 6 weeks of treatment., RESULTS: Overall, both treatments significantly improved depressive symptoms without causing serious adverse events. There were no significant differences in the Montgomery Asberg Depression Rating Scale, 17-item Hamilton Depression Rating scale, and Iowa Fatigue Scale scores, and response rates. However, significant differences in remission rates between the 2 groups were evident at week 6 (55.4% vs 34.0%, respectively; P = 0.031), favoring aripiprazole over bupropion. There were no significant differences in adverse sexual events, extrapyramidal symptoms, or akathisia between the 2 groups. CONCLUSIONS: The present study suggests that aripiprazole augmentation is at least comparable to bupropion augmentation in combination with SSRI in terms of efficacy and tolerability in patients with MDD. Both aripiprazole and bupropion could help reduce sexual dysfunction and fatigue in patients with MDD. Aripiprazole and bupropion may offer effective and safe augmentation strategies in patients with MDD who are unresponsive to SSRIs. Double-blinded trials are warranted to confirm the present findings.

2. Lamberti M, Siracusano R, Italiano D, et al. Head-to-Head Comparison of Aripiprazole and Risperidone in the Treatment of ADHD Symptoms in Children with Autistic Spectrum Disorder and ADHD: A Pilot, Open-Label, Randomized Controlled Study. *Paediatric drugs.* 2016;18(4):319-329.

   BACKGROUND: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are frequently overlapping neurodevelopmental disorders. Individuals in whom the disorders are comorbid show more severe impairment because of deficits in the processing of social situations, adaptive functioning, and executive control than individuals with either disorder alone., OBJECTIVE: This open-label pilot study aimed to evaluate and compare the efficacy and tolerability of risperidone and aripiprazole for treating ADHD symptoms in patients with both ASD and ADHD over the course of 24 weeks of treatment., METHODS: Patients (n = 44) were randomly assigned to start treatment with risperidone (22 patients) or aripiprazole (22 patients). Children were evaluated before starting treatment (T0), and after 12 weeks (T1) and 24 weeks (T2) of treatment. At each visit, specific psychiatric clinical scales were administered to assess the efficacy of the two drugs. RESULTS: The mean age was 8.4 +/- 2.9 years in the aripiprazole group and 7.8 +/- 2.3 years in the risperidone group. A total of 37 children (29 boys and 8 girls) completed the study (18 in the aripiprazole group and 19 in the risperidone group). Aripiprazole and risperidone appeared to have similar benefits in terms of efficacy and tolerability, although there were slight differences between the two drugs. Both groups showed a significant improvement in ADHD symptoms after 24 weeks of treatment (ADHD Rating Scale, Conners Parent Rating Scale-Hyperactivity, and Clinical Global Improvement-Severity Scale). No significant difference between the two drugs on any parameters at 24 weeks were found. Prolactin levels were decreased in the aripiprazole group. Both drugs were well tolerated, with no serious adverse events detected. CONCLUSIONS: Our study confirms the efficacy of both aripiprazole and risperidone in ameliorating ADHD symptoms of children also presenting with ASD.

3. Mohamed S, Johnson GR, Chen P, et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *Jama.* 2017;318(2):132-145.

   Importance: Less than one-third of patients with major depressive disorder (MDD) achieve remission with their first antidepressant., Objective: To determine the relative effectiveness and safety of 3 common alternate treatments for MDD., Design, Setting, and Participants: From December 2012 to May 2015, 1522 patients at 35 US Veterans Health Administration medical centers who were diagnosed with nonpsychotic MDD, unresponsive to at least 1 antidepressant course meeting minimal

standards for treatment dose and duration, participated in the study. Patients were randomly assigned (1:1:1) to 1 of 3 treatments and evaluated for up to 36 weeks., Interventions: Switch to a different antidepressant, bupropion (switch group, n=511); augment current treatment with bupropion (augment-bupropion group, n=506); or augment with an atypical antipsychotic, aripiprazole (augment-aripiprazole group, n=505) for 12 weeks (acute treatment phase) and up to 36 weeks for longer-term follow-up (continuation phase)., Main Outcomes and Measures: The primary outcome was remission during the acute treatment phase (16-item Quick Inventory of Depressive Symptomatology-Clinician Rated [QIDS-C16] score <=5 at 2 consecutive visits). Secondary outcomes included response (>=50% reduction in QIDS-C16 score or improvement on the Clinical Global Impression Improvement scale), relapse, and adverse effects. Results: Among 1522 randomized patients (mean age, 54.4 years; men, 1296 [85.2%]), 1137 (74.7%) completed the acute treatment phase. Remission rates at 12 weeks were 22.3% (n=114) for the switch group, 26.9% (n=136) for the augment-bupropion group, and 28.9% (n=146) for the augment-aripiprazole group. The augment-aripiprazole group exceeded the switch group in remission (relative risk [RR], 1.30 [95% CI, 1.05-1.60]; P=.02), but other remission comparisons were not significant. Response was greater for the augment-aripiprazole group (74.3%) than for either the switch group (62.4%; RR, 1.19 [95% CI, 1.09-1.29]) or the augment-bupropion group (65.6%; RR, 1.13 [95% CI, 1.04-1.23]). No significant treatment differences were observed for relapse. Anxiety was more frequent in the 2 bupropion groups (24.3% in the switch group [n=124] vs 16.6% in the augment-aripiprazole group [n=84]; and 22.5% in augment-bupropion group [n=114]). Adverse effects more frequent in the augment-aripiprazole group included somnolence, akathisia, and weight gain. Conclusions and Relevance: Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. Given the small effect size and adverse effects associated with aripiprazole, further analysis including cost-effectiveness is needed to understand the net utility of this approach.

4. Nierenberg AA, McElroy SL, Friedman ES, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. *The Journal of clinical psychiatry.* 2016;77(1):90-99.

   BACKGROUND: Bipolar disorder is among the 10 most disabling medical conditions worldwide. While lithium has been used extensively for bipolar disorder since the 1970s, second-generation antipsychotics (SGAs) have supplanted lithium since 1998. To date, no randomized comparative-effectiveness study has compared lithium and any SGA. METHOD: Within the duration of the study (September 2010-September 2013), participants with bipolar I or II disorder (DSM-IV-TR) were randomized for 6 months to receive lithium (n = 240) or quetiapine (n = 242). Lithium and quetiapine were combined with other medications for bipolar disorder consistent with typical clinical practice (adjunctive personalized treatment [APT], excluding any SGA for the lithium + APT group and excluding lithium or any other SGA for the quetiapine + APT group). Coprimary outcome measures included Clinical Global Impressions-Efficacy Index (CGI-EI) and necessary clinical adjustments, which measured number of changes in adjunctive personalized treatment. Secondary measures included a full range of symptoms, cardiovascular risk, functioning, quality of life, suicidal ideation and behavior, and adverse events. RESULTS: Participants improved across all measures, and over 20% had a sustained response. Primary (CGI-EI, P = .59; necessary clinical adjustments, P = .15) and secondary outcome changes were not statistically significantly different between the 2 groups. For participants with greater manic/hypomanic symptoms, CGI-EI changes were significantly more favorable with quetiapine + APT (P = .02). Among those with anxiety, the lithium + APT group had fewer necessary clinical adjustments per month (P = .02). Lithium was better tolerated than quetiapine in terms of the burden of side effects frequency (P = .05), intensity (P = .01), and impairment (P = .01)., CONCLUSIONS: Despite adequate power to detect clinically meaningful differences, we found outcomes with lithium + APT and quetiapine + APT were not significantly different across 6 months of treatment for bipolar disorder.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 3 2017, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013 to Daily Update

1	exp Fluphenazine/	463
2	exp Haloperidol/	7642
3	exp Loxapine/	276
4	exp Perphenazine/	373
5	exp Thioridazine/	620
6	exp Thiothixene/	37
7	exp Trifluoperazine/	889
8	exp Chlorpromazine/	2727
9	exp Pimozide/	443
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9/	12619
11	limit 10 to english language/	11856
12	limit 11 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	3121
13	limit 12 to yr="2016 -Current"	158
14	remove duplicates from 13	71

1	exp aripiprazole/ or exp clozapine/ or exp paliperidone palmitate/ or exp quetiapine fumarate/ or exp risperidone/	18070
2	paliperidone.mp.	1521
3	ziprasidone.mp.	2279
4	pimavanserin.mp.	153
5	olanzapine.mp.	10231
6	cariprazine.mp.	171
7	brexpiprazole.mp.	151
8	exp Lurasidone Hydrochloride/	292
9	asenapine.mp.	488
10	iloperidone.mp.	246
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	27310
12	limit 11 to english language	25863
13	limit 12 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	8300
14	limit 13 to yr="2016 -Current"	722
15	limit 14 to humans	633

Appendix 4: Safety Edits

Low Dose Quetiapine

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

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

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

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto PA approvals for :
  - Patients with a claim for a second generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	F3010; F302; F3160-F3164; F3177-3178; F319	
Major Depressive Disorder	F314-315; F322-323; F329; F332-333; F339; F3130	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	F205; F209; F2081; F2089	

Bipolar Mania	F3010; F339; F3110-F3113; F312	
Bipolar Depression	F3130	

Table 2. Pediatric FDA-approved indications

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *11/17 (SS) 9/15; 9/10; 5/10*
Implementation: *1/1/18; 10/15; 1/1/11*

Pimavanserin (Nuplazid™) Safety Edit

Goals:

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

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

Covered Alternatives:

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

Approval Criteria		
5. What diagnosis is being treated?	Record ICD10 code	
6. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
7. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
8. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
9. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
10. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

P&T Review: *01/2017 (SS)*
Implementation: *4/1/17*

Drug Use Research & Management Program
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New Drug Evaluation: Voretigene neparvovec-rzyl intraocular suspension for subretinal injection

Date of Review: March 2018
Generic Name: voretigene neparvovec-rzyl

End Date of Literature Search: 01/10/2018
Brand Name (Manufacturer): Luxturna (Spark Therapeutics)
Dossier Received: Yes

Research Questions:

1. What is the efficacy of voretigene neparvovec compared to placebo or currently available treatments of inherited retinal dystrophy due to retinal pigment epithelium-specific 65 kDa (RPE65) protein mutations?
2. Is voretigene neparvovec safe for treatment of inherited retinal dystrophy due to RPE65 mutations?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with voretigene neparvovec?

Conclusions:

- There is insufficient evidence to determine if voretigene neparvovec has any significant impact on functional status or disease progression. Similarly, there was no difference in visual acuity at 1 year compared to placebo (mean difference [MD] 0.16 logMAR; 95% Confidence Interval [CI] -0.14 to 0.08, p=0.17).[1]
- There is insufficient evidence that voretigene neparvovec improves patient's ability to navigate in low light environments. Mean improvement in MLMT score was 1.6 (95% CI 0.72 to 2.41, p=0.0013) and was maintained up to 2 years.[1] Evidence was downgraded based on high or unclear risk of bias, indirectness with use of a surrogate endpoint and small number of patients studied, and inconsistency based on only a single published phase 3 trial with small treatment effect. Because the MLMT is a relatively new test developed to study voretigene neparvovec, there is insufficient evidence that this change in score correlates with a real-world ability to navigate in low light environments.
- Evaluations of functional vision and visual fields demonstrate similar trends 1 year after treatment. The mean change in the full-field light sensitivity threshold testing (FST) was -2.11 (95% CI -3.19 to -1.04 log10 cd.s/m^2).[1] FST evaluates visual function and uses light flashes at varying intensities to determine the luminance at which the patient is able to perceive light.[2] A change of 1 log measurement is considered by the FDA to be clinically significant.[1]
- Upon evaluation of quality of life using an unvalidated patient questionnaire with a range of 0 to 250 points, there was little impact on patient's perceived quality of life or ability to complete daily tasks (MD of 2.6 to 3.9-point improvement from baseline compared to -0.2 to 0.2-point change in the control group; p=0.001).[1] It is unlikely that this change, which corresponds to a difference of less than 2% on this scale, represents a clinically important difference in daily function or quality of life.
- There is insufficient evidence to evaluate long-term safety of voretigene neparvovec. Ocular adverse events occurred in 66% of patients, and were generally consistent with the type and incidence of adverse events observed after vitrectomy surgery.[2] The most common adverse events included conjunctival hyperemia (22%), cataracts (20%), increased intraocular pressure (15%), retinal tear (10%), macular hole (7%), eye irritation, eye pain, and maculopathy (5% each).[2]

- Serious treatment-related ocular events (endophthalmitis and permanent vision loss) occurred in 2 patients (4.8%) following administration of voretigene neparvovec.[2]
- There is insufficient evidence to evaluate differences in subpopulations, though no differences in efficacy or safety were observed in post-hoc analyses based on age or sex.[2]

Recommendations:
- Recommend implementation of prior authorization criteria to limit use in the population studied (**Appendix 2**).

Background:
In late 2016, the Food and Drug Administration (FDA) approved voretigene neparvovec, the first gene therapy indicated for patients with confirmed biallelic RPE65 mutation-associated hereditary retinal diseases.[3] Inherited retinal diseases are a significant cause of blindness and decreased visual acuity in children and young adults and can be caused by a wide variety of genetic mutations. The RPE65 gene codes for the retinal pigment epithelium-specific 65 kDa (RPE65) protein, a protein responsible for regeneration of light reacting proteins in the retina.[4] Biallelic mutations in RPE65 gene are associated with several conditions including type 2 Leber congenital amaurosis, early onset severe retinal dystrophy, severe early childhood-onset retinal dystrophy, and retinitis pigmentosa type 20.[4] Mutations in the RPE65 gene lead to formation of misfolded or non-functional RPE65 proteins. Without a functional RPE65 protein, retinal cells are unable to convert light to electrical signals resulting in the inability of photoreceptors to respond to light. In addition, patients with RPE65 mutations have progressive degeneration of retinal epithelial cells.[3,4] The exact mechanism of retinal deterioration is unknown, but is thought to be associated with cytotoxic effects resulting from accumulation of nonfunctional RPE65 proteins.[4] Patients with two recessive mutations in the RPE65 gene have progressively decreasing visual acuity. Disease progression is highly variable, poorly characterized in available literature, and the rate and extent of visual loss varies based on the type of mutation. Biallelic mutations are typically associated with significant reduction in visual acuity during childhood (sometimes as early as 6 months of age) through early adulthood.[4] For example, adult patients with Leber congenital amaurosis due to biallelic RPE65 mutations commonly have a visual acuity of less than 20/20,000 and are unable to see hand motion.[4] Patients with early onset severe retinal dystrophy or severe early childhood-onset retinal dystrophy may have milder visual impairment, though all patients with biallelic RPE65 gene mutations typically have impaired visual acuity in low light environments.[4] Visual impairment typically begins with deceased peripheral and night vision (associated with rod photoreceptors) and progresses to involvement of cone photoreceptors which are responsible for color and visual acuity.[4]

The exact incidence of inherited retinal disease associated with biallelic RPE65 mutations is unknown, though estimates from the manufacturer of voretigene neparvovec indicate that biallelic RPE65 mutations occur in 3 to 10 per 1 million patients (corresponding to about 1000 to 3000 current patients in the United States with an estimated 14 to 40 new patients per year).[4,5] Currently, approximately 20 fee-for-service Oregon Health Plan (OHP) patients and 140 patients enrolled in coordinated care organizations have a diagnosis of *unspecified* hereditary retinal dystrophy. It is unclear from claims data how many of these OHP patients may have biallelic RPE65 mutations. Because diagnosis based on clinical symptoms of visual impairment can be difficult, and often different mutations can have a similar clinical presentation, the American Academy of Ophthalmology does recommend genetic testing for patients with inherited retinal diseases.[4,6]

Prior to approval of voretigene neparvovec, there were no pharmacological treatments for inherited retinal diseases. Standard of care included supportive services such as low-vision training and use of visual aid or adaptive mobility devices. The FDA has also approved a device for patients with severe retinitis pigmentosa which induces visual perception in blind patients via electrical stimulation of the retina.[2] Voretigene neparvovec is formulated as an adeno-associated virus vector-based therapy which has been genetically modified to express a normal RPE65 gene.[3] With use of the viral vector, the normal RPE65 gene is introduced into retinal epithelial cells and has the potential to increase normal RPE65 protein activity in retinal cells and restore the visual cycle.[3] It is

administered as a one-time subretinal injection during intraocular surgery. Injections are given in each eye at least 6 days apart with oral corticosteroids started 3 days before the surgery and tapered after the surgery.

Clinically relevant outcomes of interest include improvements in visual acuity, functional vision, and night vision. Increased mobility or independence, greater quality of life, and decreased disease progression are also important outcomes for patients with significant visual impairment.[4] Voretigene neparvovec was approved primarily based on a single phase 3 trial which assessed improvements in mobility evaluated with use of a newly developed tool called the multi-luminance mobility test (MLMT). The MLMT was developed during the course of phase 1 trials and provides a method to quantify changes in mobility performance at various light levels for patients who are visually impaired.[7] Patients were evaluated for the speed and accuracy with which they are able to navigate an obstacle course with both eyes and for each individual eye. The course had 12 different configurations (each standardized for the number of obstacles and turns) which were assigned in a randomized manner in an effort to avoid re-learning upon repetition of the test.[8] The course could be completed at 7 different light levels described in **Table 1,** and was administered from lower to higher light levels.[8] The lowest light level (corresponding to worst visual impairment and the highest MLMT score) at which the patient is able to pass the test was recorded.[1] Passing was defined as the ability to complete the course with fewer than 4 (out of 15 possible) errors and within 3 minutes.[7] Time penalties were also added if the patient went off the course, missed steps in the course, or required redirection.[7] The MLMT was validated with comparison to traditional visual acuity measures, visual function tests, and patient-reported quality of life. The MLMT was able to distinguish between patients with normal vision and those with visual acuity less than 20/63 vision on the Snellen chart.[2,7] Patients with visual acuity better than 20/63 had similar MLMT scores as patients without visual impairment.[7] Correlation of visual acuity in patients with and without visual impairment compared to MLMT scores was good (r^2 of 0.75 to 0.86), but there was weak correlation of MLMT with the degree of visual field (as assessed by the Goldmann test for visual field).[2,7] However, during development of this scale, 71% of tested patients had no change in MLMT score and it is unclear how changes in MLMT may correlate to changes in vision.[7] FDA reviewers considered a MLMT score change of at least 2 to be clinically significant, and a score change of 1 to likely correspond to learning of the course or background fluctuation between groups.[2] FDA reviewers acknowledged that this measure may vary as the difference in illuminance was not consistent between MLMT scores.[2] For example, a change in score from 4 to 6 corresponds to a difference of 9 lux whereas a change in score from 0 to 2 corresponds to a change of 275 lux. Because the MLMT is a relatively new test developed over the course of trials for voretigene neparvovec, it is unclear if an improvement in MLMT score of 2 corresponds to the actual ability of a patient to navigate in low light environments in the real world.

Table 1. Light levels and corresponding environmental description in the Multi-Luminance Mobility Test (MLMT). Light levels were measured at various points throughout the course, and were validated with less than 20% error.[2]

MLMT Score	Illuminance (lux)	Corresponding environment
0	400	Office environment or food court
1	250	Interior of elevator, library or office hallway
2	125	Interior of shopping mall, train or bus at night; 30 min before cloudless sunrise
3	50	Outdoor train station at night or inside of illuminated office building stairwell
4	10	60 minutes after sunset in a city or a bus stop at night
5	4	Cloudless summer night with half-moon or outdoor parking lot at night
6	1	Moonless summer night or indoor nightlight

Visual acuity, a secondary endpoint in this study, was standardized based on logarithm of the minimum angle of resolution (logMAR) scores. A logMAR score of 0.1 corresponds to a change of 5 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, and a change of 0.3 logMAR (15 letters) is commonly accepted as a clinically significant change.[2] Off-chart measurements including counting fingers, identifying hand movement, and light perception, were used if patients were unable to see the largest letters on the chart. Use of the ETDRS scale is often used to evaluate changes in vision; however, because visual impairment for RPE65 mediated retinal dystrophy typically begins with deceased peripheral and night vision, visual acuity may not accurately assess visual impairment in patients with less severe disease. In addition, changes in visual acuity from phase 1 trials were difficult to interpret, and it was not chosen as a primary endpoint for phase 3 trials.[2] In phase 1 trials, 46% of treated eyes had a statistically significant improvement (compared to 16% of untreated eyes), but 16% of treated eyes also had a statistically significant worsening in visual acuity compared to none of the untreated eyes.[2] Full-field light sensitivity threshold testing (FST), another method to assess visual function and night blindness, was also utilized as a secondary endpoint. With FST, light flashes at varying intensities are used to determine the luminance at which the patient is able to perceive light.[2] The minimum clinically important difference for FST has not been established, though values of 10 decibels or 1 log measurement have been suggested as being clinically significant.[1] Exploratory endpoints included quality of life and visual field measurements. Real world quality of life and activities of daily living were assessed using an un-validated, 25-item questionnaire with each question evaluated on a 0 to 10 scale with higher values indicating improved function (total range 0-250 points). The extent of a patient's visual field and peripheral vision was evaluated using the following metrics: Goldmann perimetry and Humphrey computerized testing. Goldmann perimetry is evaluated as the sum total of degrees perceived across 24 meridians with maximum degrees of 1200 to 1400 for non-visually impaired patients.[2] Humphrey testing is evaluated in decibels with higher values indicating improvements in vision. A change of 7 decibels is considered clinically significant.[2]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Voretigene neparvovec was approved primarily on the basis of a single, open-label, crossover, fair quality, phase 3 RCT (n=31) evaluating efficacy and safety in patients with retinal dystrophy associated with confirmed biallelic RPE65 mutations (**Table 3**). The majority of patients enrolled in this trial were white (68%) and female (58%) with an average age of 15 years (range 4-44 years).[1] Patients were required to have a visual acuity worse than 20/60 or visual field less than 20 degrees and sufficient viable retinal cells.[1] The amount of viable retinal cells were assessed using a variety of methods including optical coherence tomography (>100 microns), fundus photography, and clinical exam.[1] FDA reviewers noted that use of only optical coherence tomography to evaluate viable retinal cells may not accurately identify patients with viable retinal cells as 3 of the 20 subjects enrolled based on optical coherence tomography requirements failed to respond to treatment.[2] Therefore, labeling was updated to specify that the patient must have viable retinal cells as determined by the treating physician.[2] Patients were excluded if they had recent intraocular surgery or recent use of high dose vitamin A.[1] Patients were randomized 2:1 to voretigene neparvovec treatment or delayed treatment. Patients in the delayed treatment arm were crossed over to the treatment arm after one year. The primary endpoint was improvement in MLMT from baseline to one year. Secondary endpoints included assessments of visual acuity and assessments of visual function using FST. Other exploratory endpoints included changes in quality of life and other visual changes assessed by Goldmann perimetry or Humphrey computerized testing, contrast sensitivity testing, and pupillary light responses.

Patients in the control group were slightly older (mean age 15.9 years; median 14 years) than treatment group (mean age 14.7 years; median 11 years), and fewer patients randomized to treatment were able to pass the MLMT at 125 lux (with a score of 2) compared to placebo (57% vs. 40% in placebo arm) indicating that patients randomized to treatment had more severe visual impairment compared to control patients.[1] The impact of these differences is unclear, though not unexpected given the small population size. The study was designed as an open label trial due to ethical considerations of performing sham surgery in a mostly

pediatric population. However, this increases risk of performance bias and may bias results in favor of treatment, particularly for subjective outcomes such as quality of life. Risk for reporting bias was unclear. All specified outcomes were reported; however, funding for the study was provided by the manufacturer who was involved in trial design, data analysis, data interpretation, and publication.[1] In addition, the primary endpoint for the trial was changed after input from the FDA and other regulatory agencies. The initial primary endpoint was planned as the sum score of MLMT when evaluated using both eyes, the right eye, and left eye.[2] The primary endpoint was later changed to the MLMT score using both eyes, and scores for individual eyes were reported separately since there was concern that the average value would result in a score which was weighted toward the eye with better vision.

Improvement in MLMT was observed as early as 30 days and was maintained for up to 2 years following treatment. At one year, the mean change from baseline in MLMT score using both eyes was 1.8 (SD 1.1) compared to relatively little change for control patients (0.2; SD 1.0).[1] The mean difference was 1.6 (95% CI 0.72 to 2.41, p=0.0013).[1] Because voretigene neparvovec did not achieve a clinically important difference from the control arm, the FDA relied upon statistical analysis of both mean and median change in MLMT scores.[2,8] The median difference in MLMT score was 2 for patients randomized to voretigene neparvovc (vs. no change with control).[2] FDA reviewers also observed a ceiling effect with use of the MLMT scale which may lead to a systematic underestimation of the treatment effect.[8] For example, patients with a baseline score of 5 could only improve by one MLMT level. There were 4 patients randomized to the treatment arm who had a baseline score of 5 and achieved a maximum change in score of 1, compared to no patients in the control arm.[8] However, levels of 1 lux were chosen as the maximum light level on the MLMT scale because levels below 1 lux were not thought to be pertinent to activities of daily living, and it is unclear if improvement in ability to navigate the MLMT in light levels less than 1 lux has any clinical implications.[7] Similar MLMT scores were also observed with each individual eye.[2,8] Eleven patients (52%) had a change in MLMT score of greater than 2 using both eyes compared to 1 patient (10%) in the control group (MD 42%, NNT 3).[2,3,8] Five of these patients in the treatment arm had a change in MLMT score of 3 and one patient had a MLMT score change of 4.[2,3,8] Results for cross-over control patients were also comparable at 1 year following treatment.[2] Because difference in illuminance was not consistent between MLMT scores, a change in MLMT score of 2 may correspond to a wide range of illuminance levels from 9 lux to 275 lux, and it is unclear if a 2-point score improvement corresponds to the actual ability of a patient to navigate in low light environments in the real world.

Results from FST testing were generally consistent with MLMT evaluations. The mean difference in FST test was -2.11 (95% CI -3.19 to -1.04; p=0.0004) though the clinical significance of this difference is unclear.[1] Similarly, exploratory tests for visual fields demonstrated significant changes with Goldmann perimetry (MD 378.7 degrees; 95% CI 145.5 to 612.0; p=0.006) and Humphrey testing (MD 7.9 decibels, 95% CI 3.5 to 12.2; p<0.001).[2] Mean change in best corrected visual acuity at 1 year was not significantly different between treated patients and placebo (MD 0.16 logMAR corresponding to approximately 8 letters; 95% CI -0.14 to 0.08, p=0.17).[1,2] In a post-hoc analysis of visual acuity, 6 patients (30%) randomized to treatment had a clinically significant improvement in visual acuity (change of 15 or more letters) in the first eye, and 4 patients (20%) had a similar improvement for the second eye.[1] No patients in the control group had a clinically significant improvement in visual acuity.[1] Subgroup analyses based on age or sex demonstrated no differences in efficacy or safety.[2] Results for other subgroups included too few patients to make meaningful conclusions. However, 3 patients randomized to treatment had no improvement in MLMT score for at least one eye. All of these patients were unable to pass the baseline MLMT at the lowest score (400 lux) indicating that patients with advanced disease may not respond to treatment.[8] These patients also had worse visual acuity compared to other treated patients, with baseline visual acuity of 1.6, 1.87, and 2.06 logMAR corresponding to visual acuity less than 20/800.[1]

Despite changes in MLMT, FST and visual fields, there was little change in patient reported quality of life from 30 days to 1 year following treatment. This scale used to assess quality of life has not been validated, but assesses 25 items from 0 to 10 points (total range 0 to 250) with higher scores indicating less difficulty completing daily tasks. The mean improvement at 1 year with treatment was 2.6 to 3.9 points compared to an average change in the control group of -0.2 to 0.2 points (p=0.001). It is unlikely that this change, which corresponds to a difference of less than 2% on this scale, represents a clinically meaningful change in

quality of life. In addition, it is unclear if the effects of voretigene neparvovec will be maintained over time. Results from phase 1 trials of 2 similar formulations of adeno-associated viral vectors for treatment of RPE65 mediated retinal dystrophy indicate that effects of these products gradually decline over time beginning 1 to 3 years after treatment.[2,9] However, data from early phase 1 trials of voretigene neparvovec indicates that the effects of treatment are sustained for 2 to 3 years.[2] The reason for these differences in duration between products is unclear though it may be due to differences in formulation, vector design, or systemic use of perioperative steroids.[2] Long-term data for voretigene neparvovec are not available, and the impact on disease progression is unknown. Long-term follow-up for up to 15 years is planned for patients enrolled in the phase 3 trial.

Clinical Safety:

Safety analysis from the FDA included data from a phase 1 (n=12) and phase 3 trial (n=31).[2] In the phase 1 study, bilateral injections were given to patients in both eyes at intervals of 1.7 to 4.6 years.[2] In the phase 3 study, bilateral injections were only separated by 6 to 18 days. Overall, attrition was low; 2 patients in the phase 3 trial withdrew prior to treatment administration.[1] There were 8 serious adverse events reported in 7 patients; 2 of these events were considered related to treatment (endophthalmitis and permanent vision loss).[2] Ocular adverse events occurred in 66% of patients. Most common ocular events included conjunctival hyperemia or eye redness (22%), cataracts (20%), increased intraocular pressure (15%), retinal tear (10%), macular hole (7%), eye irritation, eye pain, and maculopathy (5%).[2] In addition, FDA labeling advises patients to avoid air travel, travel to high elevations, or scuba diving following administration of voretigene neparvovec.[3] Intraocular air bubbles may form following vitrectomy surgery and changes in altitude may result in expansion of air bubbles and irreversible vision loss. Labeling also recommends providers verify that air bubbles have dissipated by ophthalmic examination prior to engaging in any of these activities.[3] Air bubbles may remain for one week or more following surgery.[3] In general, these adverse reactions are consistent with the type and incidence of adverse events observed after vitrectomy surgery. However, the severity of some of these adverse effects is concerning, and the modest benefit associated with treatment should be weighed against the risks associated with subretinal surgery. Because of the small population enrolled in the clinical trials, the predicted frequency of these adverse effects with real world use is unclear. With administration of systemic steroids before and after surgery, there was no observed immune response to the drug. Post-marketing requirements include ongoing long-term follow-up of patients enrolled in clinical trials for up to 15 years, use of a registry study to evaluate safety in at least 40 patients for up to 5 years after administration, and requirements for pharmacy and surgical training for providers.

Table 2. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Genetic mutations in the human RPE65 protein lead to loss of visual function and retinal dystrophy. Voretigene neparvovec is an adeno-associated virus vector-based therapy which has been genetically modified to contain a normal RPE65 gene. With use of the viral vector, the normal RPE65 gene is introduced into retinal epithelial cells and has the potential to increase normal RPE65 protein activity in retinal cells and restore the visual cycle.
Bioavailability	Not applicable
Distribution and Protein Binding	Highest levels of viral vectors occurred in intraocular fluids. Low levels were detected in the optic nerve, optic chiasm, spleen, liver, and occasionally lymph nodes. Vector DNA was present in serum of 10% of patients for up to 3 days post-injection.
Elimination	In approximately 45% of patients, viral vector was present in tears from the injected eye and occasionally from the uninjected eye up to 3 days post-injection. Two patients (7%) had vector DNA in tear samples at 2 weeks after administration.
Half-Life	Not applicable
Metabolism	Not applicable

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Change in visual acuity
2) Change in functional or night vision
3) Quality of life and productivity
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Multi-luminance mobility test (MLMT)

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Russell, et al.[1] FDA Clinical Review.[2] Phase 3, open label, MC, crossover, RCT	1. Voretigene neparvovec $1.5x10^{11}$ vg (0.3 mL) subretinal injection in each eye 6-18 days apart 2. Delayed treatment; after 1 year, patients were crossed over to treatment arm Randomized 2:1 Prednisone 1 mg/kg/day PO x10 d (max 40 mg/d) beginning 3 days prior to each injection and tapered after surgery	Demographics: - Mean age: 15.1 years (SD 10.9) - Female: 58% - White: 68% - MLMT passing level <125 lux 1. 12 (57%) 2. 4 (40%) Key Inclusion Criteria: - Age ≥3 years - Biallelic RPE65 gene mutations - Visual acuity ≤20/60 or visual field <20 degrees - Sufficient viable retinal cells (retinal thickness by OCT >100 microns within the posterior pole, fundus photography and clinical exam) - Unable to pass MLMT at 1 lux (lowest tested level) but able to pass at higher lux Key Exclusion Criteria: - Use of high dose vitamin A (>3300 IU/ day) or other retinoid	ITT: 1. 21 2. 10 mITT (patients not given treatment excluded) 1. 20 2. 9 Attrition: 1. 1 (5%) 2. 1 (10%)	Primary Endpoint: Mean change from baseline in lux score for the lowest passing level of the MLMT at 1 year 1. 1.8 (SD 1.1) 2. 0.2 (SD 1.0) MD 1.6 (95% CI 0.72 to 2.41); p=0.0013 Secondary Endpoints: Mean white light FST testing with both eyes (mITT; log10 $cd.s/m^2$) 1. -2.08 (SD 0.29) 2. 0.04 (SD 0.44) MD -2.11 (95% CI -3.19 to -1.04); p=0.0004 Mean change from baseline in BCVA 1. 0.16 logMAR (8.1 letters)	NA NA	Serious ocular events: 1. 2 (9.5%) 2. 0 (0%) p-values NR	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization scheme generated by independent party but concealment of allocation unknown. Randomization stratified by age (<10 or ≥10 years) and baseline MLMT passing level (pass at ≥125 lux or <125 lux). Patients in control group were slightly older (mean age 15.9, median 14 years) than treatment group (mean age 14.7, median 11 years) and a larger percentage of patients with lower MLMT passing level were randomized to treatment (57%) vs. control (40%). Performance Bias: HIGH. Open-label study design. Detection Bias: LOW. Evaluators blinded to treatment group. MLMT evaluated by 2 independent, trained evaluators, with adjudication by a 3rd party if necessary. Data management and statistical analyses conducted by independent party. Attrition Bias: LOW. Attrition low; 1 patient from each group discontinued treatment; ITT analysis performed. One patient in treatment arm was determined to be ineligible after administration (passed MLMT at 1 lux). Reporting Bias: UNCLEAR. Primary outcome changed prior to data analysis in conjunction with FDA. Funding provided by Spark Therapeutics. Sponsors were involved in study design, data analysis, data interpretation, and publication. Two of the primary study investigators disclosed patent ownership for the product, though they have waived any financial interest in the patent. FDA subgroup analysis based on study site was not significantly different from the results of the primary analysis. **Applicability**: Patient: Population not applicable to patients with visual function better than 20/60 or visual field >20 degrees. Patients were required to have sufficient viable retinal cells as assessed by optical coherence tomography and clinical exam. Patients taking recent, vitamin A, tretinoin, isotretinoin, hydroxychloroquine, or other related retino-toxic compounds were excluded.

	Duration: 1 year	or retino-toxic compounds in the past 18 months - Recent intraocular surgery (within 6 months) - Other ocular or systemic conditions which would interfere study interpretation		2. 0.01 logMAR (1.6 letters) MD -0.16 logMAR (95% CI -0.41 to 0.08); p=0.17	NS			Intervention: Standard vitreoretinal techniques for subretinal surgery were used. Efficacy assessed at baseline, 30, 90, 180 and 365 days after 2nd injection (for treatment arm) or randomization (for delayed treatment). Comparator: Delayed treatment appropriate comparator. Use of sham or placebo control was inappropriate due to ethical considerations. Outcomes: MLMT developed over the course of the clinical trials. A change of 2 or more lux levels was considered a clinically meaningful difference. Secondary outcomes support primary analysis though there was no difference in BCVA. Setting: 2 sites in the United States

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BCVA = best corrected visual acuity; cd.s/m^2 = candela seconds per square meter; CI = confidence interval; FST = full-field light sensitivity threshold; ITT = intention to treat; IU = international units; logMAR = logarithm of the minimum angle of resolution; MC = multicenter; MD = mean difference; mITT = modified intention to treat; MLMT – multi-luminance mobility test; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; OCT = optical coherence tomography; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; vg = vector genomes

References:

1. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet.* 2017;390(10097):849-860.
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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LUXTURNA (voretigene neparvovec-rzyl) intraocular suspension for subretinal injection

Initial U.S. Approval: YYYY

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

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s). (1)

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

- The recommended dose of LUXTURNA for each eye is 1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL. (2.1)
- Perform subretinal administration of LUXTURNA to each eye on separate days within a close interval, but no fewer than 6 days apart. (2.1)
- Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of LUXTURNA to each eye), and followed by a tapering dose during the next 10 days. (2.1)

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

LUXTURNA is a suspension for subretinal injection, supplied in a 0.5 mL extractable volume in a single-dose 2 mL vial for a single administration in one eye. The supplied concentration (5×10^{12} vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2-mL vials. (3)

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

None.

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

- Endophthalmitis: Use proper aseptic injection technique and monitor for signs and symptoms of infection. (5.1)
- Permanent decline in visual acuity: Monitor for visual disturbances. (5.2)
- Retinal abnormalities: Monitor for macular abnormalities, retinal tears or breaks. Do not inject in the immediate vicinity of the fovea. (5.3)
- Increased intraocular pressure: Monitor and manage intraocular pressure elevations. (5.4)
- Expansion of intraocular air bubbles: Air travel and/or scuba diving is not recommended until any intraocular air bubbles have been absorbed. (5.5)
- Cataract: Subretinal injection of LUXTURNA may result in cataract formation or increase in the rate of cataract progression. (5.6)

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

The most common adverse reactions (incidence $\geq$ 5%) in the clinical trials were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Spark Therapeutics, Inc. at 1-855-SPARKTX, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Pediatric use: Use in infants under 12 months of age is not recommended because of potential dilution or loss of LUXTURNA after administration due to the active retinal cells proliferation occurring in this age group. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Voretigene neparvovec

Goal(s):

- Restrict use of voretigene neparvovec to patients with retinal dystrophy associated with biallelic RPE65 mutations

Length of Authorization:

Up to 6 months

Requires PA:

- Voretigene neparvovec (applies to both physician administered and pharmacy claims)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the patient greater than 1 year of age?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously enrolled in clinical trials of gene therapy for retinal dystrophy RPE65 mutations or been previously been treated with gene therapy for retinal dystrophy in the eye(s) receiving treatment?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5

Approval Criteria		
5. Does the patient have other pre-existing eye conditions or complicating systemic diseases that would eventually lead to irreversible vision loss and prevent the patient from receiving full benefit from treatment (eg. severe diabetic retinopathy)?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Does the patient have retinal dystrophy with confirmed biallelic RPE65 mutations?	**Yes:** Go to #7 Document genetic testing	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have a visual acuity of at least 20/800 OR have remaining light perception in the eye(s) receiving treatment?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have visual acuity of less than 20/60 OR a visual field of less than 20 degrees?	**Yes:** Go to #9 Document baseline visual function	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the provider document presence of neural retina and a retinal thickness >100 microns within the posterior pole as assessed by optical coherence tomography with AND have sufficient viable retinal cells as assessed by the treating physician?	**Yes:** Approve up to 2 doses for up to 6 months. Document retinal thickness and physician attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 3/18 (SS)
Implementation: TBD

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

PNW EPC Drug Effectiveness Review Project Summary Report – Atopic Dermatitis
New Drug Evaluation: Dupilumab

Date of Review: March 2018
Generic Name: Dupilumab
PDL Class: Dermatologicals

Literature Search: December, 2017
Brand Name (Manufacturer): Dupixent® (Regeneron)
AMCP Dossier Received: Yes

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

Research Questions:
1. For adults and children with atopic dermatitis (AD), do dupilumab, crisaborole, pimecrolimus, and tacrolimus differ in effectiveness versus each other or to topical corticosteroids?
2. For adults and children with AD, do dupilumab, crisaborole, pimecrolimus, or tacrolimus differ in harms versus each other or to topical corticosteroids?
3. Are there subgroups of patients based on demographics and comorbidities for which dupilumab, crisaborole, pimecrolimus, or tacrolimus are more effective or have fewer adverse events?

Conclusions:
Drug Effectiveness Review Project Report
- The Drug Effectiveness Review Project (DERP) report evaluated 4 fair quality head-to-head trials of topical calcineurin inhibitors in management of moderate-to-severe AD and concluded short-term treatment response (6 to 12 weeks) was not consistently different between tacrolimus and pimecrolimus. Short-term improvement in symptoms was modestly better with tacrolimus compared to pimecrolimus, using a symptom scale, reduction in the percentage of body surface area affected, and ratings of pruritus.[1] In a meta-analysis of these trials completed by DERP authors, a lower chance of response with pimecrolimus than with tacrolimus was observed [pooled relative risk (RR) 0.73; p=0.02; low statistical heterogeneity (I2) = 33.1%].[1] However, the DERP authors noted the absolute difference in risk was very small and not statistically significant (-0.09%, p=0.18), with moderate statistical heterogeneity (I2 = 68%).[1]
- One good quality systematic review completed in patients with moderate-to-severe AD symptoms concluded response to treatment and symptom improvement was similar between topical calcineurin inhibitors (TCI) and topical corticosteroids (TCS).[2]
- There is inadequate evidence to assess the relative efficacy and safety of crisaborole compared with TCI and TCS treatments.
- There is insufficient evidence regarding the long term safety of crisaborole.
- The DERP meta-analysis of the comparative calcineurin inhibitor trials did not show a difference between pimecrolimus and tacrolimus in withdrawal of therapy due to adverse events (pooled RR 1.16; 95% CI 0.43 to 3.14; I2 = 0%).[1]

- Moderate quality evidence shows that patients using calcineurin inhibitors experienced more adverse events compared to TCS. Specifically, skin burning (30% vs. 9%; RR 3.27; 95% CI 2.48-4.31; p< 0.00001) and pruritus (12% vs. 8%; RR 1.49; 95% CI 1.24-1.79; p<0.00001) occurred more frequently with TCI compared to TCS.[2]
- Patients with atopic dermatitis may have slightly increased risk of lymphoma, but evidence does not find that TCIs increase this risk.[1]
- Information on potential differences in effects of tacrolimus and pimecrolimus in population subgroups based on baseline disease severity, percentage of affected body surface area and ethnicity were identified. Because these observations were noted in small sample sizes or as part of a subgroup analysis, they have limited value to insufficient evidence.

New Drug Evaluation: Dupilumab

- Two good quality, short-term (16 week) randomized controlled trials (RCTs) demonstrated efficacy of dupilumab compared to placebo in managing symptoms of moderate-to-severe AD refractory to other topical therapies.[3] The primary outcome in the SOLO 1 and SOLO 2 trials was the proportion of patients who had both an Investigator Global Assessment (IGA) score of 0/1 and a reduction of 2 points or more in the 5-point IGA score from baseline at week 16. In SOLO 1, the primary outcome occurred in 85 patients (38%; Absolute Risk Reduction (ARR) 28%; Number Needed to Treat (NNT) = 4) who received dupilumab every other week and in 83 patients (37%; ARR 27%; NNT = 4) who received dupilumab weekly, as compared with 23 patients (10%) who received placebo (P<0.001 for both comparisons with placebo).[3] The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 patients (36%) who received dupilumab weekly, as compared with 20 patients (8%) who received placebo (P<0.001; ARR 28%; NNT = 4 for both comparisons with placebo).[3]
- A third phase 3 trial assessed the efficacy and safety of the 2 dose regimens of dupilumab with concomitant therapy of TCS with or without TCI, in comparison to placebo and TCS with or without TCI, over 16 weeks.[4] The co-primary endpoints were the proportion of subjects with IGA 0/1 (on a 5-point scale) and a reduction in IGA from baseline of 2 points or more at week 16. More patients who received dupilumab plus topical TCS (39%) achieved the co-primary endpoints compared to patients who received placebo plus TCS (12%; ARR = 27%; NNT = 4; p<0.0001) at week 16.[4]
- The overall incidence of adverse events was similar in the dupilumab groups and the placebo groups in the two SOLO trials. Serious adverse events and adverse events leading to treatment discontinuation were uncommon.
- There is insufficient evidence to compare dupilumab with TCI monotherapy, systemic cyclosporine or phototherapy. There is insufficient evidence on the expected duration of response to dupilumab, both once a course of therapy has been administered, and with repeated or ongoing therapy.[5]

Recommendations:

- Revise PA criteria for topical antipsoriatic drugs to include agents used to manage atopic dermatitis. Categorize these 2 classes of drugs as “Atopic Dermatitis Drugs” and “Antipsoriatics, Topical” on the OHP Preferred Drug List (PDL).
- Designate dupilumab as a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP). Apply clinical prior authorization (PA) criteria to dupilumab. Limit use to:
    - Moderate-to-Severe atopic dermatitis
    - Age of 18 years or greater
    - Prescribed by a dermatologist or allergist
    - History of inadequate response to at least 2 first line agents (moderate to high potency topical corticosteroids, narrowband UVB phototherapy, oral cyclosporine, methotrexate or azathioprine, or topical calcineurin inhibitors).
- Review costs and evaluate PDL assignments for crisaborole, pimecrolimus, and tacrolimus in the executive session.

Background:

Atopic dermatitis (AD) is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation.[6] Other clinical features may include xerosis, erythema, erosions, oozing, and lichenification of the skin. The most commonly affected areas include the face, elbows, knees, hands, and feet. The cause is unknown, but may be due to genetics or immunologic dysfunction.[7] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries and approximately 11% of U.S children.[8,9] Estimated prevalence of AD in U.S. adults is 3%.[8] Onset of AD is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years.[10] AD can persist into adulthood in about one third of affected individuals.[8] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life.[11] Sleep disturbance is a common association of AD and is thought to be largely attributable to pruritus.[10] Sleep disruption can lead to daytime drowsiness and irritability, resulting in impaired performance at school or work. The prevalence of depression, anxiety, conduct disorder is higher than the general population, particularly in severely affected children with AD.[7] Adults with AD are more likely to have depression than healthy individuals.[7] The skin of patients with AD is prone to secondary infections.[7] Progression to infection is often associated with a worsening of the disease. One report found that that the density of *Staphylococcus aureus* was associated with severity of AD.[12] Eczema herpeticum is a widespread skin infection with herpes simplex virus that occurs in up to 3% of patients, particularly in severely affected patients.[7]

The mainstays of therapy for AD are skin care with frequent application of an emollient to maintain the skin's epidermal barrier, avoidance of triggers, and anti-inflammatory therapy with TCS or a calcineurin inhibitor (e.g., pimecrolimus or tacrolimus) as needed.[7] Calcineurin inhibitors exert their anti-inflammatory properties by inhibiting calcineurin-dependent T-cell activation, thereby impeding production of proinflammatory cytokines and mediators.[13] The use of TCS and TCI therapies in AD is supported by The American College of Dermatology's 2014 guideline[14] and 2004 guidance from the National Institute for Health and Care Excellence.[5] Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of TCS can result in telangiectasia, increased hair, skin tears, easy bruising, poor wound healing, acne and rosacea, and thinning/atrophic skin changes, which can be permanent.[15] TCIs are considered a second-line option in both adults and children with AD who have not responded to TCS or when those treatments are not advisable.[16,17] Tacrolimus 0.03% ointment and pimecrolimus cream are indicated for use in individuals age 2 years and older, whereas tacrolimus 0.1% ointment is only approved in those older than 15 years.[16,17] The main rationale for TCI use is that they do not cause skin atrophy and are therefore of particular value in delicate skin areas such as the face, neck, and skin folds.[13] All topical preparations can sting, but there is evidence that this is even more of a problem with TCI preparations.[18] Furthermore, the Food and Drug Administration (FDA) labeling for tacrolimus and pimecrolimus include boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with TCI administration.[16,17] Patients with AD that cannot be controlled with TCS or TCI therapy can be treated with short-term phototherapy with narrow band ultraviolet B (UVB) light or systemic immunomodulators such as cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, or oral corticosteroids.[19] The use of systemic immunomodulators in AD is considered off label and only oral prednisone is FDA approved to treat AD. Treatment with cyclosporine carries important risks of acute and chronic nephrotoxicity, can have hemodynamic effects that result in hypertension,[20] and can increase the risk of infections and cancer.[21] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[20] As a result, treatment with cyclosporine for AD is typically limited to one year. 2004 National Institute for Health and Care Excellence (NICE) Guidance recommends systemic corticosteroids, phototherapy, and systemic immunosuppressants as "treatments of last resort" in AD patients.[5] The 2014 American Academy of Dermatology guidelines reinforce the NICE recommendations for systemic immunomodulators as treatments for patients with refractory AD who fail all other therapies.[22]

Two additional agents with novel mechanisms of action have recently been added to AD treatment algorithms. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor approved for mild-to-moderate AD in adults and children. PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity

is increased in AD.[23] Crisaborole is available as an ointment that is applied twice daily. Dupilumab is an injectable monoclonal antibody that has been evaluated as a systemic therapy for moderate-to-severe AD refractory to topical treatments in adults. More information about dupilumab is presented later in this report. Clinical trials are currently underway with other biologics including ustekinumab, secukinumab, and apremilast to assess their efficacy in treating patients with AD.[6]

Clinical studies have utilized several scales for defining the severity of AD, including the Severity Scoring of Atopic Dermatitis (SCORAD) index, the Eczema Area and Severity Index (EASI) and IGA. The SCORAD tool incorporates clinician estimates of disease extent and severity and subjective patient assessment of itching and sleep loss.[24] The extent of AD is graded by the clinician for specific areas of the body (head/neck, upper limbs, lower limbs, trunk and back) and is given a percentage score. AD severity includes a clinician assessment of the intensity of redness, swelling, oozing, dryness, scratch marks, and lichenification, which are graded on a 4-point scale rated as 0 (none), 1 (mild), 2 (moderate) or 3 (severe). Subjective symptoms such as itching and sleeplessness are scored by the patient using a visual analog scale (VAS) from 0 (no symptoms) to 10 (worst imaginable) for a total score of 20. When all 3 areas are added together, the total SCORAD score can range from 1 to 100. A SCORAD score greater than or equal to 50 indicates severe AD while a score less than 25 corresponds to mild AD.[24] The EASI assesses the severity of, and body surface area affected by, AD symptoms including erythema, induration/papulation/edema, excoriations, and lichenification.[25] Each symptom is graded systematically for specific anatomical regions and summarized in a composite score. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD.[25] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90. IGA is a clinician-reported outcome measure that has been used to evaluate severity of AD at a given point in time.[26] This measure was used to evaluate clinical response to treatment in studies evaluating new AD therapies.[4,27] In these trials, a 5-point scale ranging from 0 (clear) to 4 (severe) was used to assess changes in the severity of skin lesions. In most trials, scores less than or equal to 1 were generally classified as "treatment success," whereas scores greater than 1 were considered "treatment failure."[1] The IGA does not assess disease extent as body regions are not included in the IGA scoring. One systematic review concluded that although the IGA is easy to perform, the lack of standardization precludes any meaningful comparisons between studies which impedes data synthesis to inform clinical decision making.[26] The Investigator's Static Global Assessment (ISGA) does not assess changes in severity of skin lesions with treatment and may use a 6-point scale ranging from 0 (clear) to 5 (very severe). **Table 1** summarizes the 3 different measures used in clinical trials evaluating the efficacy of AD treatments. These scales are primarily used in clinical trials and rarely in clinical practice, as they were generally not designed for this purpose.[10]

Table 1. Assessment of Atopic Dermatitis in Clinical Trials[24,25,28]

	SCORAD	**EASI**	**IGA/ISGA**
Scoring	Range: 0 to 100 Score ≤ 25: Mild AD Score ≥ 50 : Severe AD	Range: 0 to 72 Mild AD: 7.1 – 21.0 Moderate AD: 21.1 – 50 Severe AD: 50.1 - 72	Range: 0 to 4 *or* 0 to 5 Score of 0 or 1 indicates disease clearing
Scale	4 point scale assessing intensity of erythema, edema/papulation, oozing/crusts, excoriations, and lichenification: 0 - absent 1 - mild 2 - moderate 3 - severe	4 point scale assessing erythema, induration, infiltration/papulation, edema, excoriation, and lichenification: 0 - none 1 - mild 2 - moderate 3 - severe	5 or 6 point scale based on assessment of erythema and infiltration/papulation: 0 - clear 1 - almost clear 2 - mild disease 3 - moderate disease 4 - severe disease 5- very severe disease

Body Regions	Distribution rated on a 0 to 4 scale for each body region (Head/Neck, Trunk Upper limbs, and Lower limbs): 0= no affected site 1 = 1 affected site 2 = 2 affected sites 3 = 3 affected sites 4= more than 4 affected sites	Proportionate values assigned to 4 separate body regions: Upper limbs (20%) Lower limbs (40%) Trunk (30%) Head/Neck (10%)	Not Used
Additional Assessments	Patient assessment of itching and sleep loss on a 0 to 10 VAS	None	None

Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ISGA = Investigator's Static Global Assessment; SCORAD = Severity Scoring of Atopic Dermatitis; VAS = Visual Analog Scale

The Health Evidence Review Commission (HERC) recently modified conditions funded on line 424 (moderate/severe inflammatory skin disease) to include psoriasis, AD, lichen planus, Darier disease, pityriasis rubra pilaris and discoid lupus.[29] Guideline Note 21 defines severe inflammatory skin disease as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: 1) at least 10% of body surface area involved; and/or 2) hand, foot or mucous membrane involvement. In addition, the HERC guidance stipulates first-line agents for treatment of severe AD/eczema include TCS, narrowband UVB, cyclosporine, methotrexate, and azathioprine. Second-line agents include topical pimecrolimus and topical tacrolimus and should be limited to those who fail or have contraindications to first-line agents.[29] When crisaborole was presented to the P and T committee at the May 2017 meeting, AD was an unfunded condition. Due to these recent changes to the prioritized list, moderate to severe AD will now be funded by HERC effective January 1, 2018. Mild AD is classified on line 544 and will therefore remain unfunded.

Methods:

The final December 2017 drug class report on AD by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1]

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

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

Summary Findings:

The objective of the DERP report focused on drugs to treat to AD is to review evidence for the comparative effectiveness and comparative harms of dupilumab, crisaborole, pimecrolimus, and tacrolimus when compared to each other and when compared to TCS or placebo.[1] In addition, the report reviewed evidence to determine if there are any subgroups of patients for which dupilumab, crisaborole, pimecrolimus, or tacrolimus are more effective or associated with fewer adverse events.[1] The DERP reviewers completed a systematic review based on a literature search from November 2007 through September 2017. Evidence from 46 publications are included in the DERP report: 37 articles reporting on 43 original trials, 2 companion publications to the included trials, 5 observational studies

and 2 systematic reviews.[1] Pairwise meta-analyses were conducted by the DERP authors for dupilumab and crisaborole versus placebo studies, and for studies comparing TCI products. DERP authors also conducted a network meta-analyses of data from trials of topical calcineurin inhibitors and topical crisaborole compared with topical steroids or placebo. Since the network meta-analysis is comprised of indirect comparisons, this summary of the DERP report will focus on direct comparisons of the AD agents with an emphasis on treatment of moderate to severe AD, which is funded by HERC. The results are organized according to the severity of patient symptoms (e.g., mild-to-moderate, moderate-to-severe, or resistant to topical treatment) as described in the corresponding trials. **Table 2** summarizes the mechanism, dosage form and FDA approved populations for the 4 drugs included in the AD DERP report.

Table 2. Drug Information for the AD Drugs summarized in the DERP report[1]

Generic Name	Trade Name	Mechanism	Dosage Form	FDA Approved Population
Dupilumab	Dupixent®	Monoclonal antibody	Subcutaneous Injection	Moderate to severe AD
Crisaborole	Eucrisa™	PDE4 inhibitor	Ointment	Mild to moderate AD
Pimecrolimus	Elidel®	Calcineurin inhibitor	1% Cream	Mild to moderate AD
Tacrolimus	Protopic®	Calcineurin inhibitor	0.03% and 0.1% Ointment	Moderate to severe AD
Abbreviations: AD = Atopic Dermatitis; DERP = Drug Effectiveness Review Project; FDA = Food and Drug Administration; PDE4 = Phosphodiesterase 4				

Efficacy and Safety

Head-to-Head Trials of Topical Calcineurin Inhibitors in Moderate to Severe AD

The DERP reviewers identified 4 fair quality head-to-head trials of tacrolimus ointment (0.03% or 0.1%) versus pimecrolimus 1% cream in patients with moderate to severe AD.[30-33] Two of the studies enrolled only children,[30,31] 1 study enrolled only adults,[32] and 1 study enrolled children and adults.[33] All but 1 study were 6 weeks in duration and the other study was 12 weeks in duration. The smallest trial (n=20) was open-label,[33] while the other 3 were investigator-blinded. All 4 trials reported response to treatment, with 3 trials using an IGA score of 0 or 1 to indicate disease clearing, while the open label trial did not describe the method of determining treatment success. The differences in improvement as measured by the EASI scale were statistically significantly greater with tacrolimus by 11% to 16% compared to pimecrolimus in 2 of 3 investigator-blinded trials.[1] Improvements in the percent of body surface area affected by AD varied widely across the studies, from a 64.6% reduction with tacrolimus in 1 study down to a 7% improvement with tacrolimus in another study.[1] Pruritus was improved more with tacrolimus than pimecrolimus in 1 of 3 studies reporting this outcome.[1] When the DERP authors pooled the results of these 4 studies, a lower chance of response with pimecrolimus than with tacrolimus was observed [pooled RR 0.73; p=0.02; I2 = 33.1%].[1] However, the DERP authors noted the absolute difference in risk was very small and not statistically significant (-0.09%, p=0.18), with moderate statistical heterogeneity (I2 = 68%).[1] This difference in response rate results indicates less certainty in the benefit of tacrolimus over pimecrolimus.[1]

Three of the TCI comparative trials evaluated adverse effects.[30-32] Application site reactions were evaluated in 3 trials, with 1 trial reporting adverse effects as the primary outcome.[31] The types of reactions reported were burning or stinging, itching, and erythema or irritation. One trial in children with moderate AD reported similar proportions of patients with any application site reaction at 4 days (28% vs. 24%), and also reported that the incidence decreased over time.[31] Across the 3 trials, significant differences were not consistently found in specific application site reactions, or other adverse events, such as skin infections.[30-32] The DERP meta-analysis of these 3 trials did not show a difference between pimecrolimus and tacrolimus in withdrawal of therapy due to adverse events (pooled RR 1.16, 95% CI 0.43 to 3.14, I2 = 0%).[1]

Head-to-Head Trials of Topical Calcineurin Inhibitors in Mild to Moderate AD

There are 2 fair quality trials of patients with mild to very moderate AD disease that compared tacrolimus ointment (0.03% or 0.1%) with pimecrolimus 1% cream which were summarized in one publication.[30] The pediatric study included only children with mild AD (n=426), while the adult study (n=413) included patients with mild (32%), moderate (45%), and severe disease (23%). The previously summarized DERP meta-analysis of TCI included a sub-group analysis from the 1 study that included adults with moderate AD disease. The studies were 6 weeks in duration and the investigators were blinded to treatment when conducting assessments. At the end of treatment, the percentage of improvement from baseline, by reduction in EASI score, was greater for tacrolimus ointment than for pimecrolimus cream in adults with any level of disease (54.1% vs. 34.9%, respectively; p<0.0001).[30] In the pediatric patients with mild AD, there was a statistically significant difference favoring tacrolimus over pimecrolimus at week 1 (39.2% vs. 31.2%, respectively; p = 0.04) and a trend for a continued advantage of tacrolimus compared with pimecrolimus at the end of treatment (52.1% vs. 42.7%, respectively; p = 0.07).[30] In both studies, regardless of treatment, the most common adverse events were local application site reactions, including stinging or burning. In the pediatric study, there were no significant differences noted between tacrolimus-treated and pimecrolimus-treated patients in the incidence rate of adverse events, although there was numerically greater incidence of burning with pimecrolimus (9.2%) than with tacrolimus (5.3%).[30] However, in the adult study, although there were no differences in withdrawals due to adverse events, application site burning occurred more frequently in the tacrolimus-treated patients than the pimecrolimus-treated patients (p=0.02).[30]

Topical Calcineurin Inhibitors Compared to Topical Corticosteroids in Moderate to Severe AD

When TCI were compared to TCS in patients with moderate to severe AD, the DERP investigators identified 1 good-quality systematic review[2] and 1 fair-quality trial.[34] The systematic review included 12 RCTs of moderate quality comparing calcineurin inhibitors (n=3492) to corticosteroids (n=3462) in children and adults.[2] Eleven of the 12 trials were conducted among patients with moderate-severe AD. The systematic review did not specify the potency of the corticosteroids used in the studies. The methods or scores used to determine treatment success across studies were not disclosed. The included trials were published between 2001 and 2015. Mean follow-up was 101 weeks (range 2-260 weeks). All participants applied calcineurin inhibitors or corticosteroids twice daily and all but 1 trial was funded by a pharmaceutical company. Treatment success was similar in the systematic review for calcineurin inhibitors and corticosteroids (72% vs. 68%; RR 1.15; 95% CI 1.00-1.31; p=0.04).[2] In addition, calcineurin inhibitors and corticosteroids had a similar percentage of patients with improvement of dermatitis (81% vs. 71%; RR 1.18; 95% CI 1.04-1.34; p=0.02).[2] There was high heterogeneity across studies (I2=93%).[1]

The systematic review noted there were no differences in adverse events requiring discontinuation between the corticosteroid and calcineurin treatment groups (1.8% vs. 1.9%; RR 0.95; 95% CI 0.66-1.38; p=0.79), severe adverse events (8.2% vs. 7.2%; RR 1.15; 95% CI 0.98-1.34; p=0.08), atrophy (0.8% vs. 0%; RR 5.66; 95% CI 1.00-31.91; p=0.05), or skin infection (12% vs. 11%; RR 1.08; 95% CI 0.94-1.24; p=0.29).[2] However, the number of adverse events (74% vs. 64%; RR 1.28; 95% CI 1.05-1.58; p=0.02) and adverse events related to treatment (11% vs. 8%; RR 1.45; 95% CI 1.15-1.83; p=0.002) were higher in the calcineurin inhibitor group compared with the corticosteroid group, with a higher rate of skin burning (30% vs. 9%; RR 3.27; 95% CI 2.48-4.31; P< 0.00001) and pruritus (12% vs. 8%; RR 1.49; 95% CI 1.24-1.79; p<0.00001).[2]

Crisaborole in Mild to Moderate AD

No studies were found comparing crisaborole with a TCI, dupilumab, or TCS formulations. To date, there are only 3 trials of crisaborole, all compared to placebo in patients with mild to moderate AD.[35,36] A good quality systematic review compiled by the Institute for Clinical and Economic Review (ICER) that evaluated these studies was also identified by the DERP reviewers.[23] Two 4-week studies similar in design enrolled children (n = 1522) with mild to moderate AD (39% mild), with 18% body surface area affected.[35] The other trial enrolled adults (n = 25) for 6 weeks to compare crisaborole to placebo.[36] Modest improvement was seen by investigators in more pediatric patients using crisaborole than placebo in erythema (59% vs. 40%; p<0.001), exudation (40% vs. 30%; p<0.001),

excoriation (60% vs. 48%; p<0.001), induration/papulation (55% vs. 48%; p=0.008) and lichenification (52% vs. 41%; p<0.001).[35] Patient assessment of pruritus improvement at day 29 was also greater with crisaborole (63% vs. 53%; p=0.002).[1] In these trials there were no serious adverse events reported, and very few patients withdrew due to adverse events. Application site pain was the most common adverse event reported (4.6% vs. 1.7%).[1] The other adverse events reported in the trials were not different between groups.

The DERP meta-analysis of these 3 trials found crisaborole resulted in more patients achieving response when compared to placebo (44% vs. 21%; pooled RR 1.67; 95% CI 1.15 to 2.47) using the Investigator's Static Global Assessment (ISGA) tool in children or the AD Severity Index (ADSI) score in adults, with total or partial clearance of disease constituting response.[1] There was moderate statistical heterogeneity in this analysis, (I2 = 68%), likely due to the larger treatment effect seen in the very small study of adults.[1] The DERP reviewers noted that a meta-analysis of the 2 pediatric trials was conducted by the authors of the ICER report and success rate was moderately higher in the pooled crisaborole arms than in the placebo arms (32.1% vs. 21.7%; p<0.0001).[23]

The main evidence on crisaborole comes from trials that randomized a total of 1016 patients to crisaborole therapy for 28 days compared to placebo.[23] There is inadequate evidence to assess the relative efficacy of crisaborole compared with topical calcineurin inhibitors and TCS.[23] Although crisaborole was well tolerated over this period of time, it is difficult to assess its safety compared with the other topical agents.[23] In the absence of longer trials or head-to-head trials, relative efficacy and safety of crisaborole is uncertain.[23]

Dupilumab in Moderate to Severe AD

Six RCTs compared dupilumab to placebo in adult patients with moderate to severe AD inadequately controlled with topical treatments. Three trials are of fair-quality due to lack of clarity related to randomization, allocation concealment and blinding.[37] The other 3 trials are of good quality.[27,38] The dupilumab trials were from 4 to 16 weeks in duration. There were no important differences in baseline characteristics between treatment and control groups in any of the 6 trials.[23] Trials were conducted at various sites across Europe, Asia and North America. All 6 trials comparing dupilumab to placebo reported response to treatment, using an IGA score of 0 or 1 to indicate disease clearing. All trials showed statistically significantly greater IGA responses in the dupilumab arms compared to placebo. The response rates were 11.8% to 40% for the dupilumab arms, with little difference between weekly and every other week dosing, and were 1.6% to 10.3% in the placebo arms.[1] The DERP meta-analysis of dupilumab included all 6 trials and found an increased chance of achieving an IGA response with dupilumab compared to placebo (pooled RR 4.10, 95% CI 3.10 – 5.42, p<0.0001, I2 = 0%).[1] Severe or serious adverse events with dupilumab were rare during treatment up to 16 weeks. The most common adverse events observed at 16 weeks were injection site reactions, nasopharyngitis, and headache, all having higher rates than placebo. The rates of any adverse event, serious adverse events, and discontinuation due to adverse event were slightly lower with dupilumab than placebo. In the DERP meta-analysis of the 6 trials comparing dupilumab to placebo, no statistically significant difference in withdrawals to adverse events between the two groups was found (pooled RR 0.98; 95% CI 0.50 – 1.92, p=0.96, I2 = 0%).[1]

Additional outcomes assessing symptom improvement, including percent change in EASI score and percent change in pruritus numerical rating scale (NRS) were reported in these trials. Dupilumab substantially increased the likelihood of achieving improvement on the EASI compared to placebo.[27] Results were similar with weekly or every other week dosing and in patients treated or not treated with topical TCS.[4] Dupilumab also improved pruritus. Four trials assessed the reduction of pruritus symptoms using percent change from baseline peak NRS score. Across the 4 trials, the reduction in peak NRS ranged from 40% to 56% in the dupilumab arms versus 5% to 29% in the placebo arms.[4,27,38] Dupilumab improved patient quality of life as measured by the Dermatology Life Quality Index (DLQI). Four trials measured the change in mean DLQI from baseline at 16 weeks and found greater improvement with dupilumab than placebo.[4,27,38] Anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) in 3 trials, and improvement was noted in patients taking dupilumab in all 3 studies.[4,27]

There is 1 fair-quality[37] and 1 good-quality trial[4] comparing dupilumab plus TCA to placebo plus TCA in adult patients with moderate-severe AD inadequately controlled with topical treatments. The 2 trials comparing dupilumab plus TCA to placebo plus TCA reported a response to treatment, with both studies using an IGA score of 0 or 1 to indicate disease clearing.[4,37] Pooling these 2 studies results in increased chance of response with dupilumab and corticosteroid than with corticosteroid alone (pooled RR 3.94, 95% CI 2.93 – 5.31, p<0.0001, I2=0%).[1] In 2 trials comparing dupilumab plus corticosteroid to corticosteroid alone, withdrawal due to adverse events was less likely for patients receiving dupilumab plus corticosteroids compared to corticosteroids alone (pooled RR 0.43, 95% CI 0.15 - 1.4, p = 0.12, I2 = 0%).[1] The DERP reviewers noted a recent systematic review conducted by ICER evaluated the effectiveness and value of dupilumab in AD.[23] The ICER review includes similar trials to those in the DERP report, and draws the same conclusions as the DERP reviewers.[1,23]

Risk of Cancer

The risk of cancers in patients with AD has been studied in 9 cohort and 19 case-control studies.[1] Many of these reports were included in a good-quality systematic review that specifically examined the risk of lymphoma with the use of TCI.[39] The systematic review found that there is a small increased risk of lymphoma among patients with AD compared to the general population, based on 4 cohort studies (odds ratio (OR) 1.43, 95% CI 1.12 to 1.81).[39] However, among patients with AD, the risk of lymphoma was not significantly increased with either tacrolimus (2 studies, OR 3.13, 95% CI 0.67 to 14.57) or pimecrolimus use (2 studies, OR 1.58, 95% CI 0.83 to 3.00).[39] Case control studies found no increased risk of lymphoma among patients with AD versus patients without AD, or with the topical calcineurin inhibitors.[1] In a fair-quality study of children conducted in the U.S. using the Pediatric Eczema Elective Registry (n=7,457), there was not an increased risk of lymphoma with pimecrolimus compared with the general population (OR 2.9, 95% CI 0.7 to 11.7).[40] The study was developed with input from the FDA and had 26,792 person-years of follow-up.[40] Tacrolimus was not studied in this evaluation. A poor-quality case-control study of 2,821 children found no increased risk of skin cancer with previous use of TCI (OR 0.50, 95% CI 0.25 to 0.98).[41] This study relied on survey data, with the potential for recall bias. Three cohort studies reported on the risk of any cancer with use of TCI in patients with AD.[40,42,43] In pediatric patients, there was no increased risk of cancer compared with the general population (OR 1.2, 95% CI 0.5 to 2.8).[40] The other 2 studies found the difference in risk for having used tacrolimus or pimecrolimus versus non-use to not be statistically significant.[42,43] Both studies had relatively short follow-up for studies of cancer development. Based on FDA analysis, reported cancers have occurred 90 to 159 days after treatment initiation.[1]

Effectiveness and Harms in Subgroups of Patients

Information on potential differences in effects of tacrolimus and pimecrolimus in subgroups of the population based on baseline disease severity, percentage of affected body surface area and ethnicity were identified. Because these observations were noted in small sample sizes or as part of a subgroup analysis, they have limited value due to insufficient evidence in these subgroups of AD populations.

New Drug Evaluation: Dupilumab

See **Appendix 2** for Highlights of Prescribing Information from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Dupilumab is an injectable interleukin (IL)-4 receptor antagonist approved for use in adults with moderate to severe AD not controlled with topical therapy. Binding of interleukin-4 receptor by dupilumab results in inhibition of IL-4 and IL-13 signaling which alters type 2 helper T (Th2) cell mediated immune responses and improves epidermal barrier abnormalities in AD.[37] Dupilumab therapy is initiated with a 600 mg subcutaneous (SC) injection loading dose followed by 300 mg SC every other week. Safety and efficacy of dupilumab in pediatric patients has not been established, although trials are currently being conducted in this population. In addition, several trials are currently investigating the efficacy of dupilumab in managing asthma refractory to other therapies.

Clinical Efficacy:

The Food and Drug Administration (FDA) approval of dupilumab is based upon 3 randomized, placebo-controlled, phase 3 trials. Two trials evaluated dupilumab as monotherapy and a third study evaluated dupilumab in combination with TCS. The 2 dupilumab monotherapy trials (SOLO 1 and SOLO 2) were of identical design and enrolled adults with moderate-to-severe atopic dermatitis (IGA score ≥ 3) whose disease was inadequately controlled by topical treatment.[27] The baseline demographics of the enrolled subjects was similar with respect to age (range of means: 35-39 years), duration of AD (range of means: 24-31 years), and baseline AD severity (47%-49% baseline IGA of 4). Many patients had received prior systemic treatments, including systemic corticosteroids (32-33%) and systemic immunosuppressants (25-31%).[27] The majority of patients treated with immunosuppressants received cyclosporine (20 - 23% of all patients).[27] Patients were randomly assigned in a 1:1:1 ratio to receive once weekly SC dupilumab (600 mg at week 0 followed by 300 mg), placebo SC once weekly, or dupilumab (600 mg at week 0 followed by 300 mg and placebo alternating every other week) for 16 weeks. The primary outcome was the proportion of patients who had both an IGA score of 0 or 1 (clear or almost clear) and a reduction of 2 points or more in the 5-point IGA score from baseline at week 16. SOLO 1 recruited 671 patients and SOLO 2 enrolled 708 patients in North America, Europe and Asia. In SOLO 1, the primary outcome occurred in 85 patients (38%; ARR 28%; NNT=4) who received dupilumab every other week and in 83 patients (37%; ARR 27%; NNT = 4) who received dupilumab weekly, as compared with 23 patients (10%) who received placebo (P<0.001 for both comparisons with placebo).[27] The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 patients (36%) who received dupilumab weekly, as compared with 20 patients (8%) who received placebo (P<0.001; ARR 28%; NNT=4 for both comparisons with placebo).[27]

A secondary outcome for SOLO 1 and SOLO 2 was the proportion of patients who had achieved EASI 75 from baseline to week 16. In both trials, EASI 75 response was reported in more patients who received each regimen of dupilumab (44% to 52%) than in patients who received placebo (12-15%; p<0.001; ARR 32% to 37%; NNT = 3 for all comparisons with placebo).[27] Dupilumab was also associated with reduction in pruritus. The baseline pruritus NRS score was based on the average of daily NRS scores for maximum itch intensity (daily score: 0 to 10) during the 7 days immediately preceding randomization for the dupilumab trials.[44] During the 2 trials, patients reported the intensity of their pruritus using the pruritus NRS via an interactive voice response system. At week 16, an improvement of at least 4 points in the peak score on the pruritus NRS occurred in more patients receiving dupilumab (35% to 40%) than in those receiving placebo (10% to 12%; ARR = 25% to 28%; NNT = 4; p<0.001 for all comparisons).[27]

Rescue treatment for AD could be provided at the discretion of the investigator. Subjects who received rescue treatment during the study treatment period were considered treatment failures, but were to continue study treatment if rescue consisted of topical medications. If a subject received rescue treatment with systemic corticosteroids or systemic immunosuppressive drugs, study treatment was immediately discontinued. In the two trials, more patients in the placebo group than in either dupilumab group received rescue treatment. In SOLO 1, the rates of rescue treatment were 21% among those receiving dupilumab every

other week and 23% among those receiving dupilumab every week, as compared with 51% among those receiving placebo; in SOLO 2, the rates were 15%, 21%, and 52%, respectively.[27]

Limitations of the SOLO trials include: 1) insufficient power to test differences between the two doses of dupilumab, 2) duration of the trials was not long enough to assess long-term safety, and 3) the trials only enrolled adults, although AD is more prevalent in children. It is notable that patients studied in the SOLO 1 and SOLO 2 trials had a substantial burden of disease. Although the entry criteria for the SOLO trials required an EASI score of at least 16 and an affected body surface area of at least 10%, the median EASI score at baseline was around 30 and the median affected body surface area was around 50%. Thus, the majority of patients had more severe disease than was required by the entry criteria for the trial. Although the indication for dupilumab in the FDA label is for moderate-to-severe disease that is inadequately controlled with topical treatment or for whom topical treatment is medically inadvisable, it is uncertain whether the patients for whom dupilumab is recommended by their clinicians will have similarly severe disease to those subjects in the randomized trials.[23]

A third trial phase 3 trial (LIBERTY AD CHRONOS) assessed efficacy and safety of the two dose regimens of dupilumab with concomitant therapy of TCS with or without TCI, in comparison to placebo and TCS with or without TCI at week 16 and week 52.[4] Adults with moderate-to-severe AD who had a previously documented inadequate response to topical medication or systemic treatment were enrolled in this trial.[4] The study was a randomized, double blind, multi-center, parallel group study in 740 adult subjects. Subjects were randomized in a 3:1:3 ratio to receive once weekly or every other week SC injections of 300 mg dupilumab, following a loading dose of 600 mg on Day 1, or matching placebo, respectively. All patients received concomitant TCS preparations and TCI formulations could be used in body locations considered inadvisable for TCS. Starting on day 1, all patients used once-daily medium-potency TCS, or low-potency TCS for sensitive skin areas (e.g., face). After AD was controlled (clear or almost clear), patients using medium-potency TCS switched to low-potency TCS for 7 days, then stopped; for sensitive skin locations, low-potency TCS or TCI could be tapered and stopped. Rescue treatment, consisting of any locally approved treatments for AD, including topical or systemic medications or phototherapy, could be used after week 2. Patients receiving high-potency TCS as rescue could continue with study drug. If rescue consisted of systemic medications or phototherapy, study drug was temporarily discontinued.

The co-primary endpoints were the proportion of subjects with IGA 0 or 1 (on a 5-point scale) and a reduction in IGA from baseline of 2 points or more at week 16. Three hundred nineteen subjects were randomly assigned to dupilumab once weekly, 106 subjects to dupilumab every other week, and 315 to placebo. At week 16, more patients who received dupilumab once weekly or every other week achieved the co-primary endpoints of IGA 0/1 (39% for both arms), compared to patients who received placebo (12%; ARR = 27%; NNT = 4; $p<0.0001$ for both groups compared to placebo).[4]

Secondary outcomes included the proportion of patients achieving 75% improvement in EASI from baseline to week 16 and proportion of patient achieving IGA 0/1 and 2-point or higher reduction from baseline at week 52. EASI 75 response at week 16 was reported in more patients who received each regimen of dupilumab (once weekly 64%; every other week 69%) than in patients who received placebo (22% $p<0.0001$ for both dupilumab regimens).[4] At week 52 more patients in the dupilumab groups achieved IGA scores of 0/1 and a reduction of greater than 2 points from baseline (once weekly 40%; every other week 36%) compared to placebo (13%; $p<0.0001$ vs. placebo for both dupilumab regimens).[4]

This study has limitations. Over half of the patients had moderate AD (indicated by an IGA score of 3) which is not the true target population for systemic, biologic therapy. Systemic therapy is generally reserved for severe AD, which comprised 48% of the patients (IGA score of 4) enrolled in this study. For some efficacy outcomes, such as the proportion of patients achieving IGA 0/1 and 2 point or higher improvement in IGA from baseline, EASI-75, and peak pruritus NRS improvement of 4 or higher and 3 or higher, the dupilumab every other week group showed greater variability over time compared with the dupilumab once weekly, which might reflect the smaller sample size (33%) of the dupilumab every other week group.[4] Additionally, quantification of the use of concomitant

topical medication was difficult, because there are logistical and technical barriers to accurately and consistently measure leftover content in tubes of TCS across more than 150 study sites.[4] What is needed are studies that compare dupilumab against existing systemic treatments such as methotrexate in people with severe AD or for those who have failed on phototherapy and one other systemic therapy.[45]

Clinical Safety:
The overall incidence of adverse events was similar in the dupilumab and placebo groups in the two SOLO trials. Serious adverse events and adverse events leading to treatment discontinuation were uncommon. The only serious adverse event that was reported in more than 2 patients in any treatment group was a serious exacerbation of AD, which was reported in 2 patients receiving dupilumab every other week and 3 patients receiving placebo in SOLO 1 and in 1 patient receiving weekly dupilumab and 5 patients receiving placebo in SOLO 2.[27] Adverse events categorized as infections or infestations developed in 35% of the patients receiving dupilumab every other week and in 34% of those receiving dupilumab every week, as compared with 28% of those receiving placebo in SOLO 1 and in 28%, 29%, and 32%, respectively, in SOLO 2.[27] The most common adverse events in the two trials were exacerbations of AD, injection-site reactions, and nasopharyngitis. Dupilumab-treated patients had a higher incidence of injection-site reactions, most of which were of mild or moderate severity. Of note, conjunctivitis occurred more frequently in the dupilumab groups than in the placebo groups. The pooled incidence of adverse effects observed at 16 weeks in the SOLO trials are presented in **Table 3**.

Table 3. Adverse Events with Dupilumab Monotherapy compared to Placebo through Week 16[46]

Common Adverse Events	Dupilumab N = 529	Placebo N = 517
Injection-site reactions	51 (10%)	28 (5%)
Conjunctivitis	51 (10%)	12 (2%)
Oral herpes	20 (4%)	8 (2%)
Other herpes simplex infections	10 (2%)	6 (1%)

The LIBERTY AD CHRONOS trial evaluated safety of dupilumab at 52 weeks of therapy. Overall rates of adverse events were similar across the treatment groups during the 52-week treatment period.[4] However, the dupilumab every other week group had higher rates of injection-site reactions than the placebo group (15% vs. 8%, respectively) and the incidence of conjunctivitis was higher in the dupilumab every other week group than in the placebo group (14% vs. 8%, respectively).[4] The incidence of adverse events observed in this 52 week trial are summarized in **Table 4**.

Table 4. Adverse Events with Dupilumab Every Other Week compared to Placebo through Week 52[4]

Adverse Events	Dupilumab N = 110 (%)	Placebo N = 315 (%)
≥ 1 adverse event	97 (88%)	266 (84%)
≥ 1 Serious Adverse Event	4 (4%)	16 (5%)
Nasopharyngitis	25 (23%)	61 (19%)
Injection-site reactions	16 (15%)	24 (8%)
Conjunctivitis	15 (14%)	25 (8%)
Any herpes infections	8 (7%)	25 (8%)

Look-alike / Sound-alike Error Risk Potential: None reported

Table 4. Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	Interleukin-4 Receptor Antagonist
Absorption	Bioavailability: 64%
Distribution and Protein Binding	Volume of Distribution: 4.6 liters
Half-Life	Not Available
Elimination	Monoclonal antibodies are primarily degraded into small peptides and amino acids by catabolism

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Symptom improvement
2) Quality of life
3) Serious adverse events
4) Study withdrawal due to adverse event

Primary Study Endpoint:

1) Percentage of patients with IGA score 0/1 and reduction of ≥ 2 points from baseline at week 16

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
Simpson EL, et al. [27] SOLO 1 Phase 3, DB, PG, MC, RCT N=671	1. Dupilumab 600 mg x 1 followed by 300 mg/week, SC 2. Dupilumab 600 mg x1 followed by 300 mg SC every other week alternating with placebo 3. Placebo SC weekly Duration: 16 weeks	Demographics: -Mean age: 39 y -Male: 58% -White: 67% - Mean AD duration: 28 y - Mean EASI: 31 -IGA score 4: 48% -Previous topical corticosteroids: 32% -Previous immunosuppressant: 26% -Median-affected BSA: 57% Key Inclusion Criteria: -Age 18 y or older -Moderate-to-severe AD (IGA 3 or 4), inadequately controlled by topical treatment -EASI score ≥ 16 -Chronic AD ≥ 3 years -AD involvement ≥ 10% BSA involvement -Pruritus NRS ≥ 3 Key Exclusion Criteria: -Treatment with an investigational drug -Treatment with immunomodulating drugs (corticosteroids, cyclosporine, azathioprine, etc.) or phototherapy 4 weeks before study enrollment.	ITT: 1.223 2.224 3.224 PP: 1.197 2.208 3.184 Attrition at week 52: 1.26 (12%) 2.16 (7%) 3.40 (18%)	Primary Endpoint: IGA score of 0/1 and reduction of ≥ 2 points from baseline at week 16 1.83 (37%) 2.85 (38%) 3.23 (10%) RR and CI NR P < 0.001 for 1 and 2 compared to placebo Secondary Endpoint: Secondary outcomes at week 16: EASI 75 1. 117 (52%) 2. 115 (51%) 3. 33 (15%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo EASI 90 1.74 (33%) 2.80 (36%) 3.17 (8%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Improvement in pruritus NRS ≥ 4 from baseline to week 16 1. 81 (40%) 2. 86 (40%) 3. 24 (12%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo	 27%/4 28%/4 37%/3 36%/3 25%/4 28%/4 28%/4 28%/4	Outcome: AEs ≥ 1 1. 150 (69%) 2. 167 (73%) 3. 145 (65%) SAEs ≥ 1 1. 2 (1%) 2. 7 (3%) 3. 11 (5%) Discontinuation due to AEs 1. 4(2%) 2. 4 (2%) 3. 2 (1%) Exacerbation of AD: 1. 21 (10%) 2. 30 (13%) 3. 67 (30%) Infections and Infestations: 1. 74 (34%) 2. 80 (35%) 3. 63 (28%) Nasopharyngitis: 1. 25 (11%) 2. 22 (10%) 3. 17 (8%) Conjunctivitis 1. 7 (3%) 2. 11 (5%) 3. 2 (1%) Injection Site Reactions 1. 41 (19%)	 NA NA NA NA NA NA	**Overall Trial Rating: Good Quality** **Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized 1:1:1 via centralized IVRS and stratified according to IGA score 3 or 4 and region. Baseline characteristics balanced Performance Bias: LOW. Blinded, coded kits containing dupilumab or placebo were used to mask the assigned treatment. All patients received injections every week by investigators to maintain blinding. Detection Bias: HIGH. All investigators were blinded to treatment. However, unblinding may have occurred due to large differences in efficacy between treatment groups or percentage of injection site reactions. Attrition Bias: LOW. Higher attrition rate in placebo group compared to dupilumab groups. LOCF after rescue treatment, subject considered a non-responder. Reporting Bias: LOW. Protocol available in supplementary appendix. All outcomes reported as stated a priori. CI were NR for outcomes giving uncertain estimate of precision. Funded by Sanofi and Regeneron Pharmaceuticals. **Applicability**: Patient: Children not evaluated although AD is more prevalent in pediatrics. Adults had median EASI score of 30 with median affected BSA of 57%, indicating severe disease. Intervention: 2 doses of dupilumab were appropriate based on results from Phase 2 trials Comparator: Placebo administered at same frequency as dupilumab to maintain blinding. Placebo suitable to assess efficacy. Outcomes: IGA score and EASI validated and used to evaluate AD in other trials. Setting: 160 global study sites. Proportion from the US was NR.

		-Treatment with biologic agents -Treatment with a live vaccine 12 weeks prior to study - 2 visits per week to a tanning booth within 4 weeks of study enrollment				2. 19 (8%) 3. 13 (6%)	NA	
Simpson EL, et al[27] SOLO 2 Phase 3, DB, MC, RCT N=708	1. Dupilumab 600mg x 1 followed by 300 mg/week, SC 2. Dupilumab 600mg x1 followed by 300 mg SC every other week alternating with placebo 3. Placebo Duration: 16 weeks	<u>Demographics</u>: -Mean age: 35 y -Male: 57% -White: 70% - Mean AD duration: 25 y -Mean EASI: 29 -IGA score 4: 48% -Previous corticosteroids: 33% -Previous immunosuppressant: 31% -Median-affected BSA: 53% <u>Key Inclusion Criteria</u>: -See SOLO 1 <u>Key Exclusion Criteria</u>: -See SOLO 1	<u>ITT</u>: 1.239 2.233 3.236 <u>PP</u>: 1.221 2.220 3.190 <u>Attrition</u>: 1.18 (8%) 2.13 (6%) 3.46 (19%)	<u>Primary Endpoint</u>: IGA score of 0/1 and reduction of ≥ 2 points from baseline 1.87 (36%) 2.84 (36%) 3.20 (8%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Secondary Endpoint: Secondary outcomes at week 16: EASI 75 1. 115 (48%) 2. 103 (44%) 3. 28 (12%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo EASI 90 1.73 (31%) 2.70 (30%) 3.17 (7%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Improvement in pruritus NRS ≥ 4 from baseline to week 16 1. 87 (38%) 2. 79 (35%) 3. 21 (10%)	28%/4 28%/4 36%/3 32%/3 24%/5 23%/5 28%/4	Outcome: <u>AEs ≥ 1</u> 1. 157 (66%) 2. 154 (65%) 3. 168 (72%) <u>SAEs ≥ 1</u> 1. 8 (3%) 2. 4 (2%) 3. 13 (6%) <u>Discontinuation due to AEs</u> 1. 3 (1%) 2. 2 (1%) 3. 5 (2%) <u>Exacerbation of AD</u> 1. 38 (16%) 2. 32 (14%) 3. 81 (35%) <u>Infections and Infestations</u> 1. 68 (29%) 2. 65 (28%) 3. 76 (32%) <u>Nasopharyngitis</u> 1. 20 (8%) 2. 20 (8%) 3. 22 (9%) <u>Conjunctivitis</u> 1. 9 (4%) 2. 9 (4%)	NA NA NA NA NA NA	**Overall Trial Rating: Good Quality** **Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: see SOLO 1 <u>Performance Bias</u>: see SOLO 1 <u>Detection Bias</u>: see SOLO 1 <u>Attrition Bias</u>: see SOLO 1 <u>Reporting Bias</u>: see SOLO 1 **Applicability**: <u>Patient</u>: see SOLO 1 <u>Intervention</u>: see SOLO 1 <u>Comparator</u>: see SOLO 1 <u>Outcomes</u>: see SOLO 1 <u>Setting</u>: see SOLO 1

				RR and CI NR P < 0.0001 for 1 and 2 compared to placebo	25%/4	3. 1 (<1%) <u>Injection Site Reactions</u> 1. 31 (13%) 2. 32 (14%) 3. 15 (6%)	NA	
Blauvelt A et al[4] LIBERTY AD CHRONOS Phase 3, DB, PC, PG, MC N=740	1. Dupilumab 600mg x 1 followed by 300 mg/week, SC +TCS 2. Dupilumab 600mg x1 followed by 300 mg SC every other week alternating with placebo +TCS 3. Placebo + TCS Duration: 52 weeks - Primary outcome assessment at 16 weeks	<u>Demographics</u>: -Mean age: 36 y -Male: 60% -White: 66% -AD duration: 27 y -Mean EASI score: 30 -IGA score 4: 48% -Average BSA %: 55 <u>Key Inclusion Criteria</u>: -Aged 18 y or older -AD ≥ 3 y -Inadequate response to TCS (with or w/o TCI) or systemic treatment 6 mos prior to screening -IGA score ≥ 3 -EASI score ≥ 16 <u>Key Exclusion Criteria</u>: -≥ 30% of total lesional surface located on areas of body unable to be treated with medium or high potency TCS -immunosuppressive or immunomodulating drugs or phototherapy for AD within 4 weeks before baseline - biologics, within 6 months prior to screening	<u>ITT</u>: 1.319 2.106 3.315 <u>PP</u>: 1.270 2.89 3.264 <u>Attrition</u>: 1.49 (15%) 2.17 (16%) 3.51 (16%)	<u>Primary Endpoints</u>: IGA score of 0/1 and reduction of ≥ 2 points from baseline to week 16 IGA Score 0/1 1.125 (39%) 2.41 (39%) 3.39 (12%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo <u>Secondary Endpoints:</u> EASI 75 at week 16: 1. 204 (64%) 2. 73 (69%) 3. 73 (23%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Improvement in pruritus NRS ≥ 4 from baseline to week 16: 1. 150 (51%) 2. 60 (59%) 3. 59 (20%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo EASI 75 at week 52: 1.73 (64%) 2.70 (65%) 3.17 (22%) RR and CI NR	 27%/4 27%/4 41%/3 46%/3 31%/4 39%/3 42%/3 43%/3	Outcome: <u>≥ 1 AE</u> 1.261 (83%) 2. 97(88%) 3. 266(84%) <u>≥ 1 SAE</u> 1. 9 (3%) 2. 4 (4%) 3. 5 (16%) <u>D/C due to AEs</u> 1. 9(3%) 2. 2 (2%) 3. 24 (8%) <u>Infections and Infestations</u> 1. 166(63%) 2. 63 (57%) 3. 182 (58%) <u>Nasopharyngitis</u> 1. 60 (19%) 2. 25 (23%) 3. 61 (19%) <u>Conjunctivitis</u> 1. 61 (19%) 2. 15 (14%) 3. 25 (8%) <u>Injection Site Reactions</u> 1. 60 (19%) 2. 16 (15%) 3. 24 (8%)	 NA NA NA NA NA	**Overall Trial Rating: Good** **Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: LOW. Patients assigned 3:1:3 via IVRS. Stratified by baseline AD severity (IGA 3 or 4) and geographic region (Asia Pacific, eastern Europe, North America, and western Europe). Similar baseline demographics. <u>Performance Bias</u>: LOW. Patients given dupilumab every other week received matching placebo in the weeks when dupilumab was not given. Blinded study drug kits with a medication numbering system were used. Placebo was provided in identical syringes. <u>Detection Bias</u>: LOW. The study remained blinded to all individuals (including patients, investigators, and study personnel) until the time of prespecified unblinding, except for the statistician who provided the randomization sequence, and independent data monitoring committee members. <u>Attrition Bias</u>: LOW. Attrition rate over 52 weeks was similar across all treatment groups. <u>Reporting Bias</u>: UNCLEAR. Study was funded by Sanofi and Regeneron Pharmaceuticals Inc. The funders participated in the conception and design of the study, analysis and interpretation of the data, and drafting and critical revision of the report. Conflicts of interest were declared for all 31 authors, 16 of whom had a financial conflict with the commercial sponsors. **Applicability**: <u>Patient</u>: Children not evaluated although AD is more prevalent in pediatrics. Subjects had

		-live vaccine 12 weeks before enrollment - regular use (more than 2 visits per week) of a tanning booth within 4 weeks before baseline		P < 0.0001 for 1 and 2 compared to placebo IGA score of 0/1 and reduction of ≥ 2 points from baseline to week 52: 1. 108 (40%) 2. 32 (36%) 3. 33 (13%) RR and CI NR P < 0.001 for 1 and 2 compared to placebo	 27%/4 23%/5			median EASI score of 30 with median affected BSA of 55%, indicating severe disease. However, 52% of patients had an IGA score of 3, indicating moderate AD. Intervention: 2 doses of dupilumab were appropriate based on results from Phase 2 trials over 52 weeks provided longer assessment time to assess safety and efficacy. Comparator: Dupilumab studied in combination with TCS/TCI therapies, standard of care for AD. Outcomes: IGA score and EASI validated and used to evaluate AD in other trials. Setting: 161 sites in 14 countries including Australia, Canada, Czech Republic, Hungary, Italy, Japan, the Netherlands, New Zealand, Poland, Romania, South Korea, Spain, the UK, and the US.
Abbreviations: AD = atopic dermatitis; AE = adverse effect; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; D/C = discontinuation; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ITT = intention to treat; IVRS = interactive voice response system; LOCF = last observation carried forward; MC= multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NRS = numerical rating scale; PC = placebo-controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous; SAE = serious adverse effect; TCS = topical corticosteroid; TCI = topical calcineurin inhibitors; y = years								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
CRISABOROLE	EUCRISA	TP	OINT. (G)	N
DUPILUMAB	DUPIXENT	SQ	SYRINGE	
PIMECROLIMUS	ELIDEL	TP	CREAM (G)	
TACROLIMUS	PROTOPIC	TP	OINT. (G)	
TACROLIMUS	TACROLIMUS	TP	OINT. (G)	

Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DUPIXENT® (dupilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1)

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection. (2.1)
- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield (3)

CONTRAINDICATIONS

Known hypersensitivity to DUPIXENT or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- *Hypersensitivity*: If a systemic hypersensitivity reaction occurs, discontinue DUPIXENT immediately and initiate appropriate therapy. (5.1)
- *Conjunctivitis and Keratitis*: Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
- *Comorbid Asthma*: Advise patients with comorbid asthma not to adjust or stop their asthma treatment without consultation with their physicians. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live Vaccines: Avoid use of live vaccines with DUPIXENT. (7.1)

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

Revised: 03/2017

Atopic Dermatitis and Topical Antipsoriatics

Goal(s):

Restrict dermatological drugs only for funded OHP diagnoses. Moderate/severe psoriasis and moderate/severe atopic dermatitis treatments are funded on the OHP. Treatments for mild psoriasis, seborrheic dermatitis, keroderma ~~(L110, L83, L850-852, L870-872, L900-902, L906, L940, L943)~~ and other hypertrophic and atrophic conditions of skin ~~(L119, L572, L574, L664, L908-909, L918-919, L922, L985)~~ are not funded.

Length of Authorization:

- From 6 to 12 months

Requires PA:

Non-preferred ~~drugs~~antipsoriatics
All atopic dermatitis drugs
STC = 92 and HIC = L1A, L5F, L9D, T0A
This PA does not apply to biologics for psoriasis, which is subject to separate clinical PA criteria.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for seborrheic dermatitis, keroderma or other hypertrophic and atrophic conditions of skin?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the diagnosis psoriasis?	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Is the Psoriasis Moderate/Severe? Moderate/Severe psoriasis is defined as: • Having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one of the following: 1. At least 10% body surface area involved or with functional impairment and/or: 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #5	**No:** Pass to RPh; deny, not funded by the OHP.
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Approve for length of treatment; maximum 1 year.
~~5.~~7. Is the diagnosis atopic dermatitis?	**Yes:** Go to #8	**No:** Go to #17

Approval Criteria		
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)? • Having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one of the following: 1)At least 10% body surface area involved or with functional impairment and/or: 2)Hand, foot or mucous membrane involvement	**Yes:** Go to #9	**No:** Pass to RPh. Deny; not funded by the OHP.
9. Is the drug topical tacrolimus, pimecrolimus or crisaborole?	**Yes:** Go to #10	**No:** Go to #13
10. What is the age of the patient?	**Age less than 2 years**: Pass to RPh. Deny; medical appropriateness.	**Ages 2 years and older:** Go to #11
11. Does the patient meet the age requirements per the FDA label? -Tacrolimus 0.1% ointment is only FDA approved for patients 16 years of age and older. -Tacrolimus 0.03% ointment, pimecrolimus 1% cream, and crisaborole ointment are only FDA approved for patients 2 years of age and older.	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 first line agents indicated for the treatment of moderate to severe AD (topical corticosteroids)?* *Note pimecrolimus and crisaborole are only FDA approved to manage moderate AD, while tacrolimus is FDA approved to manage severe AD.	**Yes:** Document drug and dates trialed, and intolerances (if applicable): 1. _____ (dates) 2. _____ (dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the drug dupilumab?	**Yes:** Go to #14	**No:** Go to #17
14. What is the age of the patient? -Dupilumab injection is only FDA approved for patients 18 years of age and older	**Age 17 years or younger**: Pass to RPh. Deny; medical appropriateness.	**Ages 18 years and older:** Go to #15
15. Is the medication being prescribed by or in consultation with a dermatologist or allergist?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
16. Does the patient have a documented contraindication, intolerance, or failed trials of at least 2 first line agents indicated for the treatment of Moderate to Severe AD (moderate to high potency topical corticosteroid (such as clobetasol, betamethasone, halobetasol or fluocinonide), narrowband UVB phototherapy, topical tacrolimus, topical pimecrolimus, oral cyclosporine, oral methotrexate, or oral azathioprine)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1. _____ (dates) 2. _____ (dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
17. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.*	**If funded, or clinic provides supporting literature:** Approve for length of treatment.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *3/18 (DM); 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*

**The Health Evidence Review Commission has stipulated via Guideline Note 21 that mild, uncomplicated inflammatory skin conditions including psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis rubra pilaris, and discoid lupus are not funded. Uncomplicated is defined as no functional impairment; and/or involving less than 10% of body surface area and no involvement of the hand, foot, or mucous membranes.*

References:
1. Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed December 27, 2017.

Exclusion List

- Deny payment for drug claims for drugs that are only FDA-approved for indications that are not covered by the Oregon Health Plan (OHP).
- Other exclusionary criteria are in rules at: www.oregon.gov/OHA/healthplan/pages/pharmacy-policy.aspx

Excerpt from OAR 410-121-0147 Exclusions and Limitations (DMAP Pharmaceutical Services Program)
1) The following items are not covered for payment by the Division of Medical Assistance Programs (DMAP) Pharmaceutical Services Program: (a) Drug products for diagnoses below the funded line on the Health Services Commission Prioritized List or an excluded service under Oregon Health Plan (OHP) coverage; (b) Home pregnancy kits; (c) Fluoride for individuals over 18 years of age; (d) Expired drug products; (e) Drug products from non-rebatable manufacturers, with the exception of selected oral nutritionals, vitamins, and vaccines; (f) Active Pharmaceutical Ingredients (APIs) and Excipients as described by Centers for Medicare and Medicaid (CMS); (g) Drug products that are not assigned a National Drug Code (NDC) number; (h) Drug products that are not approved by the Food and Drug Administration (FDA); (i) Drug products dispensed for Citizen/Alien-Waived Emergency Medical client benefit type; (j) Drug Efficacy Study Implementation (DESI) drugs (see OAR 410-121-0420); (k) Medicare Part D covered drugs or classes of drugs for fully dual eligible clients (see OAR 410-121-0149, 410-120-1200, & 410-120-1210).

NOTE: Returns as "70 – NDC NOT COVERED"

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. For what reason is it being rejected?		

Approval Criteria		
3. "70" NDC Not Covered (Transaction line states "Bill Medicare"	**Yes:** Go to the Medicare B initiative in these criteria.	**No:** Go to #2B
4. "70" NDC Not Covered (Transaction line states "Bill Medicare or Bill Medicare D"	**Yes:** Informational Pa to bill specific agency	**No:** Go to #2C
5. "70" NDC Not Covered (due to expired or invalid NDC number)	**Yes:** Informational PA with message "The drug requested does not have a valid National Drug Code number and is not covered by Medicaid. Please bill with correct NDC number."	**No:** Go to #2D
6. "70" NDC Not Covered (due to DME items, excluding diabetic supplies) (Error code M5 –requires manual claim)	**Yes:** Informational PA (Need to billed via DME billing rules) 1-800-336-6016	**No:** Go to #2E
7. "70" NDC Not Covered (Transaction line states "Non-Rebatable Drugs")	**Yes:** Pass to RPh. Deny (Non-Rebatable Drug) with message "The drug requested is made by company that does not participate in Medicaid Drug Rebate Program and is therefore not covered"	**No:** Go to #2F
8. "70" NDC Not Covered (Transaction line states "DESI Drug")	**Yes:** Pass to RPh. Deny (DESI Drug) with message, "The drug requested is listed as a "Less-Than-Effective Drug" by the FDA and not covered by Medicaid."	**No:** Pass to RPh. Go to #3

Approval Criteria		
9. RPh only: "70" NDC Not Covered (Drugs on the Exclusion List) All indications need to be evaluated to see if they are above the line or below the line.	**Above:** Deny with yesterday's date (Medically Appropriateness) and use clinical judgment to APPROVE for 1 month starting today to allow time for appeal. Message: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	**Below:** Deny. Not funded by the OHP. Message: "The treatment for your condition is not a covered service on the Oregon Health Plan."

If the MAP desk notes a drug is often requested for a covered indication, notify Lead Pharmacist so that policy changes can be considered for valid covered diagnoses.

Exclusion List		
Drug Code	**Description**	**DMAP Policy**
DCC = 1	Drugs To Treat Impotency/ Erectile Dysfunction	Impotency Not Covered on OHP List
DCC = B	Fertility Agents	Fertility Treatment Not Covered on OHP List
DCC = D	Diagnostics	DME Billing Required
DCC= F, except HSN = 018751 002111 002112 002070 002113 016924	Weight Loss Drugs	Weight Loss Not Covered on OHP List except In cases of co-morbidity. Exceptions are Prior Authorized
DCC= Y	Ostomy Supplies	DME Billing Required
HIC3= B0P	Inert Gases	DME Billing Required

HIC3= L1C	Hypertrichotic Agents, Systemic/Including Combinations	Cosmetic Indications Not Covered on OHP List
HIC3= Q6F	Contact Lens Preparations	Cosmetic Indications Not Covered on OHP List
HIC3=X1C	IUDs	DME Billing Required
HIC3=D6C	Alosetron Hcl	IBS Not Covered on OHP List
HIC3=D6E	Tegaserod	IBS Not Covered on OHP List
HIC3=L1D	Hyperpigmentation Agents	
Drug Code	**Description**	**DMAP Policy**
HIC3=L3P	Astringents	
HIC3=L4A	Topical Antipruritic Agents	
HIC3=L5A; Except HSN= 002466, 002557 006081 (Podophyllin Resin)	Keratolytics	Acne, Warts, Corns/Calluses; Seborrhea Are Not Covered on OHP List
HIC3=L5B	Sunscreens	Cosmetic Indications, Acne, ~~Atopic Dermatitis,~~ Warts, Corns/Callouses; Diaper Rash, Seborrhea Are Not Covered on OHP List
HIC3=L5C	Abrasives	Cosmetic Indications, Acne, ~~Atopic Dermatitis,~~ Warts, Corns/Callouses; Diaper Rash, Seborrhea Are Not Covered on OHP List
HIC3=L5E	Anti Seborrheic Agents	Seborrhea Not Covered on OHP List
HIC3=L5G	Acne Agents	Acne Not Covered on OHP List
HIC3=L5H	Acne Agents, Topical	Acne Not Covered on OHP List
HIC3=L6A; Except HSN = 002577 002576 002574 002572 (Capsaicin)	Irritants	Acne, ~~Atopic Dermatitis,~~ Seborrhea, Sprains Not Covered on OHP List

HIC3=L7A	Shampoos	Cosmetic Indications, Seborrhea, Not Covered on OHP List
HIC3=L8A	Deodorants	Cosmetic Indications Not Covered on OHP List
HIC3=L8B	Antiperspirants	Cosmetic Indications Not Covered on OHP List
HIC3=L9A	Topical Agents, Misc	Cosmetic Indications, Acne, ~~Atopic Dermatitis,~~ Warts, Corns/Callouses; Diaper Rash, Seborrhea, are Not Covered on OHP List
HIC3=L9B	Vit A Used for Skin	Acne Not Covered on OHP List
HIC3=L9C	Antimelanin Agents	Pigmentation Disorders Not Covered on OHP List
HIC3=L9D	Topical Hyperpigmentation Agent	Pigmentation Disorders Not Covered on OHP List
HIC3=L9F	Topical Skin Coloring Dye Agent	Cosmetic Indications Not Covered on OHP List
HIC3=L9I	Topical Cosmetic Agent; Vit A	Cosmetic Indications Not Covered on OHP List
HIC3=L9J	Hair Growth Reduction Agents	Cosmetic Indications Not Covered on OHP List
Drug Code	**Description**	**DMAP Policy**
HIC3=Q5C	Topical Hypertrichotic Agents	Cosmetic Indications Not Covered on OHP List
~~HIC3=Q5K~~	~~Topical Immunosuppressants~~	~~Atopic Dermatitis Not Covered on OHP List~~
HIC3=Q6R, Q6U, Q6D	Antihistamine-Decongestant, Vasoconstrictor and Mast Cell Eye Drops	Allergic Conjunctivitis Not Covered on OHP List
HIC3= U5A, U5B, U5F & S2H plus HSN= 014173	Herbal Supplements " Natural Anti-Inflammatory Supplements" - Not Including Nutritional Supplements such as: Ensure, Boost, Etc.	

HSN = 004045 + ROA = TOPICAL	Clindamycin Topical	Acne Not Covered on OHP List
HSN=003344	Sulfacetamide Sodium/Sulfur Topical	Acne Not Covered on OHP List
HSN=008712, 004022 + ROA=TOPICAL	Erythromycin Topical	Acne Not Covered on OHP List
HSN=025510	Rosacea	Acne Not Covered on OHP List
TC=93; Except HSN = 002363 (dextranomer) 002361 (zno)	Emollients/Protectants	Cosmetic Indications, Acne, ~~Atopic Dermatitis,~~ Warts, Corns/Callouses; Diaper Rash, Seborrhea, Psoriasis Are Not Covered on OHP List

P&T Review: *3/18; 2/23/06*
Implementation: *TBD; 5/1/16; 9/1/06; 1/1/12*

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

Drug Evaluation: dichlorphenamide (Keveyis®) tablets

Date of Review: March 2018
Generic Name: dichlorphenamide

End Date of Literature Search: 01/03/18
Brand Name (Manufacturer): Keveyis (Taro Pharmaceuticals)
Dossier Received: No, dossier pending at time of request

Research Questions:

1. Does dichlorphenamide have superior efficacy compared to placebo or is it more effective than currently available medications (e.g. acetazolamide) for the treatment of hyperkalemic and hypokalemic periodic paralyses (HyperPP and HypoPP, respectively)?
2. Is dichlorphenamide safe for the treatment of HyperPP and HypoPP and what is the relative safety compared to current treatments?
3. Are there subpopulations (i.e. age, gender, ethnicity, disease duration or severity) for which dichlorphenamide is more effective or associated with more harms?

Conclusions:

- Evidence for dichlorphenamide includes 2 poor quality randomized control trials (RCTs) with high risk for performance, detection, attrition and reporting bias.[1,2] In addition, data were limited by small overall sample sizes for HypoPP (n=44 and 42, respectively) and HyperPP (n=21 and 31, respectively).[1,2] These flaws in study design substantially limit interpretation of study results and may bias results in favor of treatment.[1,2] It's difficult to draw any meaningful conclusions regarding efficacy and safety of dichlorphenamide based on these flawed studies.
- For patients with HyperPP, there is insufficient evidence that dichlorphenamide is more effective than placebo in reducing weekly paralytic attack rates or severity weighted attack rates over 9 weeks. [1,2] Statistical significance for weekly paralytic attack rate and severity weighted attack rate was inconsistent between studies.[1,2] In addition, there was no significant difference in the 36-Item Short Form Survey (SF-36) mental or physical components of quality of life for patients with HyperPP, and in some cases, placebo was non-significantly better than dichlorphenamide.[1]
- For patients with HypoPP, there is insufficient evidence that dichlorphenamide is more effective than placebo in reducing weekly paralytic attack rates (MD 0.9 ± 1.4; p= 0.02 and median difference [MD] -2.2, 95% confidence interval [CI], -6.8 to -0.4; p=0.02), preventing acute disease worsening (MD 26.5%; number needed to treat [NNT] 5), or reducing the severity weighted attack rate (MD 1.1 ± 1.5 and median difference -5.2; 95% CI, -25.2 to -1.2; p= 0.02) over a 9-week treatment period.[1,2] Though results achieved statistical significance, data are limited by high risk for performance bias, high attrition rates, use of per-protocol analyses, poorly reported data, and broad exclusion criteria limiting applicability to the Oregon Health Plan (OHP) population.
- There is insufficient evidence that dichlorphenamide improves quality of life compared to placebo in patients with HypoPP over 9 weeks. Mean difference in the SF-36 physical component scores was 7.29 points (95% CI 2.26-12.32) with dichlorphenamide compared to placebo over a 9-week period (scale range 0-100).[1] There was no significant difference between groups for the mental component score, and both groups showed a numerical decline in quality of life. The clinical significance of this change is unclear, and results are significantly limited by high risk of bias in studies which affect interpretation of these results. The overall change in quality of life score (including physical, mental, and emotional components) was not reported.[1]

- There is insufficient evidence to evaluate safety of dichlorphenamide. Numerous side effects were substantially more common in the dichlorphenamide group compared to the placebo group including paresthesia (number needed to harm [NNH] 3), and dichlorphenamide had numerically higher rates of discontinuation due to adverse events (statistical difference not reported).[1,2] Dichlorphenamide labeling includes warnings for increased risk of falls, hypersensitivity, concomitant use of aspirin, hypokalemia and metabolic acidosis.[3] In addition, the following serious adverse events were reported post approval: cardiac failure, amnesia, convulsion, fetal death, hallucination, pancytopenia, psychotic disorder, nephrolithiasis, rental tubular necrosis, stupor, tremor, and syncope.[4] Though cause and effect have not clearly been established, the severity of these adverse effects is concerning.
- There is insufficient evidence to ascertain whether dichlorphenamide would provide more benefits or risks to selected subpopulations including children or patients with mild and severe periodic paralysis.[1,2] There is insufficient evidence to compare dichlorphenamide to other medications used for periodic paralysis or acetazolamide at this time. Acetazolamide labeling includes similar adverse effects, but there have been no trials directly comparing the safety or efficacy of acetazolamide to dichlorphenamide.[5,6,7]

Recommendations:

- Recommend implementation of prior authorization (PA) criteria for dichlorphenamide **(Appendix 2)**.

Background:

Primary periodic paralyses are genetic neuromuscular disorders characterized by flaccid limb paralysis due to channel abnormalities in skeletal muscle tissue.[8-13] Genetic mutations in the SCN4A and CACNA1S genes affect sodium and calcium channels respectively.[7] These channel defects allow for the dysregulation of potassium fluctuations in skeletal muscles.[7] HypoPP is more common, with a prevalence of 1 in 100,000 compared to 1 in 200,000 for HyperPP.[10-13] Based on the Oregon Medicaid population, there may be 10 people with HypoPP and 5 people with HyperPP. HyperPP affects both genders equally whereas HypoPP is 3 to 4 times more clinically prevalent in men.[8-13] Age of onset is typically younger than 10 years old for both conditions, but may start later in HypoPP.[7,10,12] Episodes generally occur more often at younger ages and decrease in frequency as age increases.[7,10,12]

Episodes of HyperPP may last minutes to hours and episodes of HypoPP may last several hours. Some patients experience episodes which may last for a day or more.[8-13] The episodes of paralysis are related to the serum level of potassium, with either hyperkalemia or hypokalemia acting as the precipitating factor.[8-13] Other activities or actions that affect potassium levels such as a high carbohydrate diet, rest after exercise, fasting, and stress can also precipitate paralytic attacks.[8-13] Medications which affect potassium levels such as steroids, insulin, and diuretics may also trigger attacks.[8-13] Some people may experience few attacks in their lifetime or require no treatment, but some may experience frequent attacks, causing a sharp decrease in quality of life.[8-13] Long-term consequences include myopathies, possibility of arrhythmias due to potassium fluctuations, and permanent muscle weakness.[7-9,11,13] Data from several small studies indicate patients with either form of periodic paralysis are likely to experience myopathies and weakness during middle age, when the attacks start to become less frequent. [7-9,11,13] As many as 80% of patients with HyperPP over the age of 40 may develop permanent muscle weakness and 33% may develop progressive myopathies.[7] There does not appear to be a correlation between attack frequency and development of myopathies. [7-9,11,13] Myopathies from HypoPP and Hyper PP tend to affect the muscles of the pelvic girdle and the extremities. [7-9,11,13]

Symptoms of HyperPP and HypoPP are typically not life-threatening and differ from Andersen-Tawil Syndrome (ATS), a more severe form of the disease which is associated with complications in other tissues besides skeletal muscle.[7,8-13] ATS is caused by a defect in the KCNJ2 gene which is responsible for creating the KIR 2.1 potassium channel and affects cardiac, skeletal, and facial muscles.[7] It causes a triad of features: cardiac arrhythmias, flaccid muscle weakness, and skeletal malformations (including a short stature, low set ears, clinodactyly, hypo or micrognathia, and hypo or hypertelorism).[7] Paramytonia congenita is another similar condition which differs from HypoPP and HyperPP in that it can cause periodic paralysis with muscle tension instead of muscle weakness.[14]

Diagnosis of HypoPP and HyperPP is first based on genetic testing to determine the presence of mutations in the SCNA4 and CACNA1S genes.[7] However, not all patients have an identifiable mutation, in which case diagnosis is based on clinical tests and characteristics.[7] A positive family history of either condition, confirmed hypo- or hyperkalemia during an attack, typical episode triggers, and a positive long-exercise test are indicative of these conditions.[7] The long exercise test determines muscle action potential over numerous time points after performing isometric exercises in specific muscles to induce a paralytic episode.[7] A drop of >40% in the compound muscle action potential (CMAP) after the long exercise test indicates the presence of these conditions.[7]

Currently, there is no guideline-based standard of care for these conditions.[7-9] There are also no guidelines for when to start treatment, if any treatment should be used in a preventative capacity, or for treatment of any permanent muscle weakness that may occur.[7-9] Lifestyle and diet modifications to avoid potassium shifts are recommended, but may not prevent attacks from occurring altogether.[7] Dichlorphenamide is the first FDA-approved medication for HypoPP and HyperPP.[7] Medications which have historically been used to treat HypoPP include oral potassium and spironolactone.[7-9] Medications occasionally used for HyperPP include inhaled beta agonists and thiazide diuretics.[7-9] These treatment suggestions are based on case reports.[7-13] Acetazolamide is a carbonic anhydrase inhibitor that has been used to treat both paralysis types, introducing the idea that another carbonic anhydrase inhibitor, dichlorphenamide, may also work.[7-9] Evidence regarding acetazolamide's efficacy is poor, as it is based primarily on case reports and single blind studies in two patients.[7-13] One small RCT (n=8) found that acetazolamide provided a statistically significant improvement in muscle strength, but did not evaluate attack frequency or quality of life.[15] Another uncontrolled retrospective analysis of 14 HypoPP patients in the United Kingdom taking acetazolamide, demonstrated only 57% of the patients experienced treatment benefit (i.e. decrease in attack rate or severity).[16] The exact rate or frequency of attacks was not reported.[16] Case reports of acetazolamide indicate that patients with specific mutations (such as CACNA1S mutations) are more likely to respond to acetazolamide.[16] However, additional controlled trials need to be conducted to establish efficacy. The exact mechanism of action of these medications for the treatment of periodic paralysis is unknown, but several theories have recently emerged.[7-9] Carbonic anhydrase inhibitors cause kaliuresis, increase bicarbonate excretion, and a non-anion gap acidosis.[7] This action may lead to increased opening of the calcium dependent potassium channels in skeletal muscle and reduce susceptibility to paralytic attacks.[7]

The main goals of therapy are to reduce attack frequency and severity and increased quality of life. The minimal clinically important differences (MCID) has not been described for periodic paralysis and these outcomes.[7-9] Quality of life was assessed in one of the studies using the SF-36 version 2 assessment, a validated tool to measure patient perceptions regarding their physical, mental, and emotional standing.[1,2,17] The SF-36 version 2 is used for a variety of chronic conditions, and the estimated score used to establish a MCID varies depending on the condition. In patients with rheumatoid arthritis, changes of 4.4 points in the physical component score and 3.1 points in the mental component score have been suggested as a MCID.[18] For patients with chronic obstructive pulmonary disorder, asthma, or heart disease, a score change of 6-8.5 points has been considered as a clinically meaningful improvement.[19] The MCID for the SF-36 has not been established in patients with HyperPP and HypoPP. Each of the 36 questions are scored from 0-100 based on the chosen response.[17] The scores are averaged by group (physical, mental, or emotional).[17] The final outcome for each group falls on the scale between 0 and 100, with 100 being the best patient satisfaction.[17] In clinical trials, means and medians were used to document attack rates from weeks 2-9 during treatment phases.[1,2] The patient-reported attack severity was also assessed using numerical scales with ranges from 1-4 or 1-10 with 4 or 10 being most severe.[1,2] Scores were reported as the average over the last 8 weeks of treatment.[1,2] Intolerable increases in attack frequency or severity requiring withdrawal were also examined in the HypoPP groups to assess worsening of the condition.[1,2]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The FDA approved dichlorphenamide under the orphan drug designation for the treatment of HyperPP and HypoPP.[3,4] This approval was based on two poor quality studies (HYP-HOP and Study 2), each consisting of two sub-studies of patients with HyperPP and HypoPP.[3] Both studies were phase 3, multicenter, placebo-controlled, RCT.[1,2] One of the studies had a crossover design with 4 phases (run-in period, 2 treatment phases, and an active washout period).[2] The other trial had one treatment phase.[1] Overall bias was high due to potential unblinding and high attrition rates in both studies (**Table 2**).[1,2] The studies have limited applicability to the entire population with these conditions because patients with severe (>3 attacks/day) or very mild (<1 attack/week) affliction, as well as chronic kidney, liver, heart, thyroid, and lung diseases were excluded.[1,2] Only one study included participants younger than 18 years of age.[2] Additionally, dichlorphenamide was not studied in patients with other neuromuscular diseases, certain glaucoma variations, or in patients taking concomitant beta blockers, calcium channel blockers, or diuretics.[1,2] The primary outcome in most instances was median attack rate per week or improvement of mean attack rate per week.[1,2] The HypoPP arm in Study 2 used a primary endpoint of acute worsening necessitating withdrawal from the study as the primary outcome. This outcome was chosen because a high percentage of patients (approximately 65%) were receiving treatment with dichlorphenamide or acetazolamide prior to the studies, which could lead to worsening symptoms if randomized to placebo.[2] This was expected given the availability of these medications as off-label treatment, but it limits applicability to treatment naïve patients and increases risk of selection bias. Important secondary outcomes were the severity weighted attack rate and SF-36 mental and physical component score changes from baseline.[1,2] Currently, there are no established minimal clinically important difference thresholds for these outcomes in HyperPP and HypoPP.[7-9] Patients who were treatment naïve received 50mg of dichlorphenamide twice daily, but doses for treatment-experienced patients varied based on their current dose of acetazolamide (ACZ) or dichlorphenamide.[1,2] Treatment phases were 9 weeks in duration.[1,2]

The HYP-HOP study compared dichlorphenamide to placebo for patients with HyperPP (n=44) and HypoPP (n=21).[1] Patients were included if they had genetically definite, clinically definite, or clinically probable HypoPP or HyperPP.[1] Genetically definite was defined as a documented genetic mutation associated with HypoPP or HyperPP with either two attacks of tetraparesis or one attack with a positive family history. Clinically definite included patients who fit the aforementioned attack parameters and typical clinical features of either condition in addition to documented hypo- or hyperkalemia during an episode or a positive family history for either condition. Clinically probable was defined as meeting the previously mentioned attack rate parameters and typical clinical features.[1] The mean dose of dichlorphenamide in the HyperPP arm was 77.1 ± 31.0 mg/day and 93.75 mg/day in the HypoPP arm.[1] The primary outcome of median weekly attack rate was significantly lower with dichlorphenamide compared to placebo in the HypoPP arm (dichlorphenamide 0.3, placebo 2.4; treatment effect [TE] -2.2;- 95% CI -6.8 to -0.4; p=0.02).[1] The difference was not significant in the HyperPP arm.[1] The overall changes in median attack rates per week from baseline were low, with the largest difference in the HyperPP group which decreased from a median of 2 attacks per week to 0.9 attacks per week.[1] However, attack rate was non-significant for HyperPP.[1] The median severity-weighted attack rate was significantly lower with dichlorphenamide compared to placebo for the HypoPP (0.6 vs 5.7 for placebo, TE -5.2 [95% CI -25.2 to-1.2], p=0.02) but not HyperPP arm (1.0 vs 5.7 for placebo, TE -4.9 [95% CI NA to 1.2], p=0.03) due to the CI in the HyperPP group crossing the null.[1] Changes in quality of life, as assessed by SF-36 scores, were not consistent between sub-studies, were generally below thresholds set for other conditions, and in some cases placebo had improvement while dichlorphenamide showed worsening.[1,18,19] Acute worsening evaluated in the HypoPP arm was defined as an intolerable increase in attack frequency or severity requiring withdrawal from the study.[1] Five participants (21%) in the placebo group and none in the dichlorphenamide arm reached this endpoint (NNT 5).[1]

Study 2 used a crossover study design to compare dichlorphenamide to placebo and included both a Potassium Sensitive Periodic Paralysis (PSPP) group and a HypoPP group.[2] The PSPP group included both patients with HyperPP and Paramytonia congenita, and it is unclear if there were differences in response rates between these populations as no data was provided regarding the number of HyperPP patients in the PSPP group.[2] Participants aged 10-75 years were eligible for enrollment (mean age 37-38 years).[2] Diagnostic criteria used for the HypoPP arm include a typical clinical profile, normal serum thyroxine level, and documented hypokalemia during an attack in the patient or one of their family members. Diagnostic criteria for the PSPP arm include presence of a mutation in

the α subunit of the sodium channel and a positive potassium challenge in the patient or a family member (without the presence of a sodium channel mutation on skeletal muscle).[2] The primary outcomes were mean improvement in attack rates per week for the PSPP group and intolerable increase in frequency or severity of attacks necessitating withdrawal from the study for the HypoPP group.[2] The primary analysis for HypoPP patients included only participants who completed both treatment phases.[2] Eleven participants (32.4%) reached the endpoint in the placebo phase and only 2 participants (5.8%) reached the endpoint in the dichlorphenamide phase (p=0.02; NNT of 4 over 9 weeks).[2] The mean attack rate per week in the PSPP sub-study showed a statistically significant reduction with dichlorphenamide compared to placebo (MD 2.3 ± 2.9; p=0.006).[2] The mean improvement in attack rate per week in the HypoPP arm also showed a statistically significant reduction compared to placebo (MD 0.9 ± 1.4; p=0.02).[2] While the results for reduction of attacks per week between dichlorphenamide and placebo were significant, the improvement from baseline was different between the sub-studies, indicating there may be more benefit in the PSPP group.[2] The secondary endpoint for both sub-studies was mean improvement in the severity weighted attack rate.[2] The HypoPP (MD 1.1 ± 1.5) and PSPP (MD 4.6 ± 5.7) sub-studies showed a significant decrease in the dichlorphenamide group compared to placebo (p=0.01 and p=0.003, respectively).[2] Overall, dichlorphenamide demonstrated some effect on attack frequency and severity compared to placebo for patients with HypoPP and HyperPP.[1,2] However, the sample size was small due to the rarity of disease, and analysis based on an even smaller per protocol population in study 2 severely limits interpretation of these results.[1,2] Attrition was high in both studies. Risk of performance and detection bias was high due to broken blinding in all sub-studies.[1,2] This is particularly concerning given the subjective nature of patient-reported outcomes including attack severity and quality of life. Additionally, the observed reduction in attack rate and severity does not appear to correlate with a consistently increased quality of life as assessed by the SF-36 scale.[1,2,7-9] Reporting bias was high in study 2 due to inconsistencies in reported data and lack of data for individual groups.[2] Since it was approved under the orphan drug designation, it is not required to assess efficacy in the pediatric population.[4] Further studies would need to be conducted in this population before using it in children at time of diagnosis. Additional studies comparing dichlorphenamide to acetazolamide or other therapies would also be warranted to determine if other options are effective. Due to poor quality of the studies and substantial bias, the lack of internal validity may have skewed the outcomes in favor of the treatment groups. Therefore, conclusions regarding efficacy based on these trials may be unreliable.

Clinical Safety:

The FDA safety analysis included 21 patients with HyperPP and 44 patients with HypoPP from the HYP-HOP study.[3] The most common side effects seen in greater than 5% of patients and more common in the dichlorphenamide group compared to placebo include paresthesia, cognitive disorder, dysgeusia, and confusional state (**Table 1**).[3] The NNH for paresthesia in the dichlorphenamide group compared to placebo over a 9-week period was 3 in the HypoPP arm of the HYP-HOP trial.[1] Compared to placebo, both the HypoPP (TE -13.1 mmHg) and HyperPP (TE -9.4 mmHg) arms showed a significant decrease of mean systolic blood pressures in the dichlorphenamide groups.[1] Only the HypoPP arm showed a significant decrease in diastolic blood pressures for dichlorphenamide compared to placebo (TE -7.4 mmHg).[1] Withdrawal due to adverse events occurred for one patient (4.2%) with HypoPP and 2 patients (16.7%) with HyperPP compared to placebo.[1]

Data regarding serious adverse events in patients with HyperPP and HypoPP was limited. Serious adverse events reported in trials included rash requiring hospitalization and a fractured humor, each of which only occurred in one patient.[1] The 52-week safety data included 53 patients, 8 of whom developed new renal calculi and 2 patients had an increase in the number or size of pre-existing calculi.[1] Statistical differences between groups were not reported.[1] Additionally, labeling for dichlorphenamide includes warnings for hypersensitivity/anaphylaxis, hypokalemia, metabolic acidosis, concomitant use of aspirin, and risk of falls.[3] Baseline and periodic monitoring of serum potassium and bicarbonate is recommended.[3] The exact rate of these adverse events is unclear, though risk of falls may be higher in the elderly population and with higher doses.[3] Additional adverse events reported in the post-approval period include the following: cardiac failure, amnesia, convulsion, fetal death, hallucination, pancytopenia, psychotic disorder, nephrolithiasis, rental tubular necrosis, stupor, tremor, and syncope.[4] Though cause and effect have not clearly been established, the severity of these adverse effects is concerning.

Table 1. Adverse Reactions occurring in more than 5% of patients and greater in the dichlorphenamide group than the placebo group.[3]

Adverse Reaction	Dichlorphenamide (%) n=36	Placebo (%) n=29
Paresthesia	44	14
Cognitive disorder	14	7
Dysgeusia	14	0
Confusional state	11	0
Headache	8	7
Hypoesthesia	8	0
Lethargy	8	0
Fatigue	8	0
Muscle spasms	8	0
Rash	8	0
Dizziness	6	0
Diarrhea	6	3
Nausea	6	0
Malaise	6	0
Weight decrease	6	0
Arthralgia	6	3
Muscle twitching	6	0
Dyspnea	6	0
Pharyngolaryngeal pain	6	0
Pruritis	6	0

In comparison to dichlorphenamide, acetazolamide has similar side effects including metabolic acidosis, potentially increased risk of falls in the elderly, malaise, paresthesia, and cognitive disturbances.[5,6] However, no trials provide direct comparative evidence regarding safety or rates of side effects.[6] Hematologic side effects such as agranulocytosis and thrombocytopenia may occur with both medications.[5,6,20,21]

The FDA is requiring the manufacturer to conduct a post-marketing trial to assess the pharmacokinetic profile of dichlorphenamide and identify additional cytochrome P450 drug-drug interactions.[4] Though FDA documents indicate these studies may have been completed in 2016, results are not yet published.[4] Overall, there is little evidence of poor quality to adequately support and assess the safety profile of dichlorphenamide. Trials included few patients and were limited to 9 weeks. It is unclear if the benefits of long-term treatment with dichlorphenamide outweigh the potential risks associated with therapy.

Pharmacology and Pharmacokinetic Properties: Currently unknown.[3,20,21]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Attack frequency
2) Severity of attacks
3) Increased attack rate or severity
4) Quality of life
5) Treatment related side effects
6) Serious adverse events
7) Study withdrawal due to an adverse event

Primary Endpoints:
1) Median weekly attack frequency, mean improvement of
2) Intolerable increase in attack rate or severity necessitating withdrawal

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Sansone et al.[1] HYP-HOP NCT00494507 Phase 3 DB, PC, RCT, MC, PG Evaluated two separate populations, one studying participants with HyperPP (presented here) and the other studying HypoPP (see below)	1. DCP 50mg BID, 20% of current ACZ home dose as DCP, or current home dose of DCP 2. placebo BID Randomization ratio not used 9 weeks 52 week uncontrolled study period followed the DB, PC controlled 9 week study	Demographics: • Mean age: 42 years • Male gender: 43% • Treatment naïve: 52% • Median attack rate per week: DCP 2.0 placebo 4.0 • Mental SF-36 mean scores (0-100): DCP 47.2 placebo 45.9 • Physical SF-36 mean scores (0-100): DCP 41.0 placebo 37.3 Key Inclusion Criteria: • Genetically confirmed, clinically confirmed, or clinically probable HyperPP • Age >18 • At least 1 episode of weakness per week, but less than 3 episodes daily	ITT: 1. 12 2. 9 Attrition: 1. 25% 2. 0%	Primary Endpoint: Assessed during weeks 2-9 **Median attack rate per week** 1. 0.9 2. 4.8 TE: -4.1 (95% CI, *NA to 0.9) p= 0.1 Secondary Endpoint: Assessed during weeks 2-9 **Median severity-weighted attack rate (scale of 1-10)** 1. 1.0 2. 5.7 TE: -4.9 (95% CI, *NA to 1.2) p= 0.03 **Mean Improvement in SF-36 scores from baseline** 1. Mental -0.90; Physical 1.12 2. Mental 2.81; Physical -1.15 MD Mental: -3.71 (95% CI -13 to 5.58); p=0.41; MD Physical: 2.27 (95% CI -3.08 to 7.71); p=0.38	NA NA NA; NA	Outcome: **Paresthesia** 1. 8 (67%) 2. 3 (33%) p-value 0.2 **Cognitive disorder** 1. 2 (17%) 2. 0 (0%) P-value NR **Serious adverse event** 1. 1 (8.3%) 2. 0 (0%) P-value NR **Study withdrawal due to adverse event** 1. 2 (16.7%) 2. 0 (0%) P-value NR 95% CI NR	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Used computer generated randomization plan. Utilized web-based allocation concealment. Performance Bias: HIGH. Placebo and DCP matched by appearance and taste. Substantial differences in adverse events and subjective symptom improvement may have resulted in unblinding. At week 9, providers correctly identified 90-91% of patients randomized to DCP and 82-87% of patients on placebo. Detection Bias: HIGH. Adequate blinding methods used, but substantial differences in adverse events and lack of improvement for patients randomized to placebo led to unblinding. Attrition Bias: HIGH. ITT used. Missing diary entries prior to week 9 counted as no attacks. There was a 27% difference in diary entry median compliance between treatment groups. Data for patients who withdrew from the study were calculated based on available data. 25% dropout difference in HyperPP. Reporting Bias: UNCLEAR. 95% CI and p-values provided for efficacy endpoints. Reported all main outcomes of interest. Primary outcome planned as the mean number of attacks per week, but reported as a median. Measures of variance not reported. Overall change in SF-36 score was not reported. Funding provided by grants from the National Institutes of Health, Muscular Dystrophy Association, and Medical Research Council (UK).

		Key Exclusion Criteria: • Evidence of ATS, respiratory muscle weakness, or cardiac arrhythmias during attacks • Renal, hepatic, thyroid, lung, or heart disease • Chronic, non-congestive acute-angle glaucoma • Any other neuromuscular disease • History of worsening symptoms with ACZ • Concurrent use of other medications altering potassium levels		*NA: 2/9 placebo participants experienced acute worsening, assigned arbitrarily large attack rate for analysis Treatment effect for median outcomes calculated as the median of the bootstrap distribution of the treatment group differences in median response (DCP - placebo); mean differences used for mean outcomes				**Applicability**: Patient: Broad exclusion criteria. Studied in adults likely not newly diagnosed. Not studied in severe or very mild disease, or other chronic conditions. Gender percentages appropriate (HyperPP generally equally prevalent in both genders). Small sample size studied. Intervention: 50mg BID is accepted starting dose for treatment naive patients or at a dose comparable to current therapy with titration based on symptoms. Mean dose of DCP was 77.1 ± 31.0 mg/day Comparator: Placebo appropriate to determine efficacy. Lifestyle changes (e.g. diet, exercise) not monitored. Lack of comparison to acetazolamide limits conclusions regarding place in therapy. Outcomes: Clinically relevant outcomes evaluated. Power not met, but statistically significant differences found in some outcomes. Significant differences between DCP and placebo for reduction in severity-weighted attack rates. Only randomized over 9-week period. Large differences between side effect rates. Setting: Hospitals in the United States, United Kingdom, and Italy. 62% of participants were from the United States. Patients were admitted to the hospital for 3 days at treatment initiation which may not happen in practice.
1. Sansone et al.[1] Phase 3 DB, PC, RCT, MC, PG Evaluated two separate populations, one studying participants with HyperPP (see above) and the other studying HypoPP (presented here)	1. DCP 50mg BID, 20% of current ACZ home dose as DCP, or current home dose of DCP 2. Placebo BID Randomization ratio not used 9 weeks 52 week uncontrolled study period followed the DB, PC controlled 9 week study	Demographics: • Mean age: 44 years • Male gender: 73% • Treatment naïve: 28% • Median attack rate per week: DCP 1.1 placebo 1.8 • Mental SF-36 mean scores (0-100): DCP 52.1 placebo 48.5 • Physical SF-36 mean scores (0-100): DCP 39.2 placebo 42.1 Key Inclusion Criteria: • Genetically confirmed, clinically confirmed, or clinically probable HypoPP • See HYP-HOP	ITT: 1. 24 2. 20 Attrition: 1. 8.3% 2. 5%	Primary Endpoint: Assessed during weeks 2-9 **Median attack rate per week** 1. 0.3 2. 2.4 TE: -2.2, (95% CI, -6.8 to -0.4); p=0.02 Secondary Endpoint: Assessed during weeks 2-9 **Median severity-weighted attack rate (scale of 1-10)** 1. 0.6 2. 5.7 TE: -5.2 (95% CI, -25.2 to -1.2) P= 0.02	NA NA	Outcome: **Paresthesia** 1. 9 (38%) 2. 1 (5%) P= 0.01 **Cognitive disorder** 1. 5 (21%) 2. 2 (10%) P-value NR **Serious adverse event** 1. 1 (4.2%) 2. 0 (0%) P-value NR	33%/ 3 NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. See HYP-HOP. Performance Bias: HIGH. See HYP-HOP. Baseline attack rates lower in the HypoPP arm compared to HyperPP. Detection Bias: HIGH. See HYP-HOP. Attrition Bias: HIGH. See HYP-HOP. There was a 7% difference in diary entry median compliance between treatment groups. Reporting Bias: UNCLEAR. See HYP-HOP. **Applicability**: Patient: See HYP-HOP. Gender differences appropriate (HypoPP 3-4 times more common in men). Intervention: See HYP-HOP. Mean dose of DCP was 93.75 mg/day. Potassium supplementation commonly used during HypoPP attacks. Comparator: See HYP-HOP. Outcomes: See HYP-HOP. P-values indicate statistical differences between DCP and placebo for median attack rates and severity weighted attack rates. Setting: See HYP-HOP. 55% of participants from the United States.

	Patients allowed to take potassium supplements during acute attacks of HypoPP	Key Exclusion Criteria: • See HYP-HOP • Known mutation in the α subunit of the mutated sodium channel (more commonly associated with HyperPP)		**Mean Improvement in SF-36 scores from baseline** 1. Mental -0.96; Physical 4.68 2. Mental -6.52; Physical -2.61 MD Mental: 5.56 (95% CI -0.69 to 11.81); p=0.08 MD Physical: 7.29 (95% CI 2.26 to 12.32); p=0.006 **Intolerable increase in attack rate or severity necessitating withdrawal from phase** 1. 0 (0%) 2. 5 (21%) p-value 0.01 Treatment effect: see above	NA; NA 21%/ 5	**Study withdrawal due to adverse event** 1. 1 (4.2%) 2. 0 (0%) P-value NR 95% CI NR	NA	
2. Tawil et al.[2] NCT00004802 Phase 3 DB, PC, MC, crossover, RCT Analysis consists of two separate populations: participants with HypoPP (presented here) and the other studying PSPP (HyperPP and Paramytonia Congenita with periodic paralysis; see below)	1. DCP 50 mg BID, 20% of ACZ home dose as DCP, or current home dose of DCP 2. Placebo BID Randomization ratio not used 4 phase trial • *Phase I*: run-in period to assess journaling ability • *Phase II*: 9 week trial, all pre-study medications for PP stopped • *Phase III*: 9-week active washout	Demographics: • Mean age: 38 years • Male gender: 76% • Treatment naïve: 43% • Mean attack rate/week: 2.5 Key Inclusion Criteria: • 10-75 years old • >1 distinct episode/week but <3 episodes daily • Positive clinical profile meeting diagnostic criteria of HypoPP Key Exclusion Criteria: • Pregnancy or no contraceptive use • History of thyroid, heart, respiratory, hepatic, or heart disease • History of worsening symptoms with ACZ	ITT: 42 PerP: Primary Analysis 34 Secondary Analysis 17 Attrition: Dropout during placebo phases versus DCP phases 1. 5 2. 1 Dropout during any time 8 (19%)	Primary Endpoint: Assessed weeks 2-8 during Phase II and IV **Intolerable increase in attack rate or severity necessitating withdrawal from phase*** 1. 2 (5.9%) 2. 11 (32.4%) P= 0.02 Secondary Endpoints: Assessed weeks 2-8 during Phases II and IV **Mean improvement in attack rate per week** 1. NR 2. NR MD 0.9 ± 1.4 P= 0.02 **Mean improvement in severity weighted attack rate (scale of 1-4)** 1. NR 2. NR MD 1.1 ± 1.5 P= 0.01	26.5% /4 NA NA	Outcome: **Paresthesia** 1. 16 (42%) 2. 0 Outcome: **Cognitive disorder** 1. 8 (21%) 2. 0 Outcome: **Study withdrawal due to adverse event** 1. 2 (4.8%) 2. NR P-value and 95% CI NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Used computer generated randomization plan with blocking and stratification. Sealed opaque envelopes used. Baseline characteristics not reported between groups though all patients received placebo and DCP. Performance Bias: HIGH. Adequate blinding procedures. Medications identical in appearance. Blinding likely broken due to adverse events and subjective symptom improvement. Detection Bias: HIGH. Blinding almost entirely broken due to presumed efficacy and side effects of DCP. Unclear if power met, but differences between groups were statistically significant. Attrition Bias: HIGH. Not all data clearly described or available. Only 55% of patients completed all 4 phases of the HypoPP study. Did not use ITT; primary analysis only included data from 34 patients (81%) with HypoPP who had complete data from all phases. Attack rates only reported for 17 participants (23%) with HypoPP who had complete data. Reporting Bias: HIGH. No protocol or supplementary material available, outcomes specified a priori. Attack rates only reported as a mean difference between treatment and placebo. There were inconsistencies in reported data, and attack rate was not reported for individual groups. Unclear how severity weighted attack rate was calculated.

	• *Phase IV*: 9-week crossover trial, all pre-study medications for PP stopped Patients allowed to take potassium supplements during acute attacks of HypoPP	• History of life-threatening respiratory muscle weakness or cardiac arrhythmias • Concurrent use of other medications altering potassium levels or affecting the heart						**Applicability**: Patient: Pediatric patients allowed to participate. Not studied in severe or very mild disease, or other chronic conditions. Gender percentages appropriate (HypoPP 3-4 times more common in men). Few patients studied. Intervention: 50mg BID is accepted starting dose, titration can occur. Consistent dose not used. Potassium supplementation commonly used during HypoPP attacks. Comparator: Placebo used, diet and exercise not recorded but mimicked home routine during hospitalization Outcomes: Clinically relevant outcomes evaluated. Only used 9-week randomized treatment periods. Large differences between side effect rates. Setting: MC in United States and Canada from 1992 to 1995. Patients were admitted to the hospital for 3 days at treatment initiation to monitor for acute worsening with weekly follow-up which may not happen in practice.
2. Tawil et al.[2] NCT00004802 Phase 3 DB, PC, MC, crossover, RCT Analysis consists of two separate populations: participants with HypoPP (see above) and the other studying PSPP (HyperPP and Paramytonia Congenita with periodic paralysis; presented here)	1. DCP 50 mg BID, 20% of ACZ home dose as DCP, or current home dose of DCP 2. Placebo BID Randomization ratio not used 4 phase trial • *Phase I*: run-in period to assess journaling ability • *Phase II*: 9 week trial, all pre-study medications for PP stopped • *Phase III*: 9-week active washout	Demographics: • Mean age: 37 years • Male gender: 58% • Treatment naïve: 35% • Mean attack rate/week: 3.8 Key Inclusion Criteria: • 10-75 years old • >1 distinct episode/week but <3 episodes daily • Positive clinical profile meeting diagnostic criteria of PSPP Key Exclusion Criteria: • Pregnancy or no contraceptive use • History of thyroid, heart, respiratory, hepatic, or heart disease • History of worsening symptoms with ACZ	ITT: 31 PerP: 16 Attrition: Dropout during placebo phases versus DCP phases 1. 3 2. 2 Dropout during any time 16 (51.6%)	Primary Endpoint: Assessed weeks 2-8 during Phase II and IV **Mean improvement in attack rate per week** 1. NR 2**.** NR MD 2.3 ± 2.9 P= 0.006 Secondary Endpoints: Assessed weeks 2-8 during Phases II and IV **Mean improvement in severity weighted attack rate (scale of 1-4)** 1. NR 2. NR MD 4.6 ± 5.7 P= 0.003	NA NA	Outcome: **Paresthesia** 1. 11 (35%) 2. 2 (8%) Outcome: **Cognitive disorder** 1. 7 (24%) 2. 1 (3%) Outcome: **Study withdrawal due to adverse event** 1. 1 (3.2%) 2. NR P-values and 95% CI NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. See Tawil, et al. Performance Bias: HIGH. See Tawil, et al. Detection Bias: HIGH. See Tawil, et al. Attrition Bias: HIGH. Not all data clearly described or available. >50% attrition in PSPP sub-study. Did not use ITT; subjects used for analysis were those with complete attack rate data for both treatment phases. Reporting Bias: HIGH. See Tawil, et al. **Applicability**: Patient: Paramytonia congenita and HyperPP combined, impossible to distinguish efficacy for each condition. Pediatric patients allowed to participate. Not studied in severe or very mild disease, or other chronic conditions. Gender percentages appropriate (HyperPP generally equally prevalent in both genders). Few patients studied. Intervention: 50 mg BID is accepted starting dose, titration can occur. Consistent dose not used. Comparator: Placebo used, diet and exercise not recorded but mimicked home routine during hospitalization. Outcomes: Clinically relevant outcomes evaluated. Only used 9-week randomized treatment periods. Large differences between side effect rates. Setting: MC in United States and Canada from 1992 to 1995. Patients were admitted to the hospital for 3 days at treatment initiation to monitor for acute worsening with weekly follow-up which may not happen in practice.

	• *Phase IV*: 9-week crossover trial, all pre-study medications for PP stopped	• History of life-threatening respiratory muscle weakness or cardiac arrhythmias • Concurrent use of other medications altering potassium levels or affecting the heart						

Abbreviations [alphabetical order]: ACZ = acetazolamide; ARR = absolute risk reduction; ATS = Andersen-Tawil Syndrome; BID = twice daily; CI = confidence interval; DB = double blind; DCP = dichlorphenamide; HyperPP = hyperkalemic periodic paralysis; HypoPP = hyperkalemic periodic paralysis; ITT = intention to treat; MC = multicenter; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PG = parallel group; PP = periodic paralysis; PerP = per protocol; PSPP = potassium sensitive periodic paralysis; RCT = randomized controlled trial; SF-36 = short form-36; TE = treatment effect.

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Appendix 1: Prescribing Information Highlights[3]

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KEVEYIS™ (dichlorphenamide) tablets, for oral use
Initial U.S. Approval: 1958

RECENT MAJOR CHANGES

Indications and Usage: treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants (1)	8/2015
Dosage and Administration (2)	8/2015
Warnings and Precautions (5.1, 5.4, 5.5)	8/2015

INDICATIONS AND USAGE

KEVEYIS™ is an oral carbonic anhydrase inhibitor indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants (1)

DOSAGE AND ADMINISTRATION

- Initial dose: 50 mg twice daily (2)
- Titrate dose based on individual response (2)
- The maximum recommended dose is 200 mg daily (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg (3)

CONTRAINDICATIONS

- Hepatic insufficiency (4)
- Severe pulmonary obstruction (4)
- Hypersensitivity to dichlorphenamide or other sulfonamides (4)
- Concomitant use with high dose aspirin (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity / Anaphylaxis / Idiosyncratic reactions: discontinue KEVEYIS™ at the first appearance of skin rash or any sign of immune-mediated or idiosyncratic adverse reaction (5.1)
- Hypokalemia: baseline and periodic measurement of serum potassium are recommended; if hypokalemia develops or persists, consider reducing the dose or discontinuing KEVEYIS™ (5.3)
- Metabolic acidosis: baseline and periodic measurement of serum bicarbonate are recommended; if metabolic acidosis develops or persists, consider reducing the dose or discontinuing KEVEYIS™ (5.4)
- Falls: consider reducing the dose or discontinuing KEVEYIS™ in patients who experience falls (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 10% and greater than placebo) include paresthesias, cognitive disorder, dysgeusia, and confusional state (6)

To report SUSPECTED ADVERSE REACTIONS, contact Taro at 1-866-923-4914, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Aspirin: Anorexia, tachypnea, lethargy, and coma have been reported with concomitant use of dichlorphenamide and high-dose aspirin. The concomitant use of KEVEYIS™ and high dose aspirin is contraindicated. KEVEYIS™ should be used with caution in patients receiving low dose aspirin (4, 5.2, 7.1).

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2015

Dichlorphenamide

Goal(s):

- Encourage appropriate use of dichlorphenamide for Hyperkalemic and Hypokalemic Periodic Paralysis.

Length of Authorization:

- Up to 3 months for the first authorization and first renewal. Up to 6 months for renewals thereafter.

Requires PA:

Dichlorphenamide

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP funded condition AND is the requested treatment funded by the OHP for that condition? Note: Treatments referenced on an unfunded line of the prioritized list (http://www.oregon.gov/oha/HPA/CSIHERC/Pages/Prioritized-List.aspx) are not funded by the OHP.	**Yes**: Go to #3	**No**: Pass to RPh. Deny; not funded by the OHP.
3. Is the request for continuation of dichlorphenamide treatment previously approved by Fee-For-Service?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the requested treatment for Andersen-Tawil Syndrome or Paramytonia congenita?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5

Approval Criteria		
5. Is the request for treatment of Hyperkalemic or Hypokalemic Periodic Paralysis based on genetic testing or clinical presentation?	**Yes:** Go to #6	**No**: Pass to RPh. Deny; medical appropriateness. Note: Dichlorphenamide is not indicated for other forms of periodic paralysis.
6. Does the patient have an average baseline attack rate of ≥1 attack per week?	**Yes:** Go to #7 Document baseline attack rate.	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient previously experienced disease worsening upon treatment with acetazolamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Dichlorphenamide was not studied in this population due to potential for similar disease worsening effects.	**No:** Go to #8
8. Have potential precipitating factors (including lifestyle and recent medication changes) been considered or ruled out with no documented change in attack rate or severity upon modification to therapy or lifestyle? Note: Medications which affect potassium levels include, but are not limited to, oral potassium, steroids, insulin, and diuretics.	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Note: Lifestyle and medication changes are generally regarded as first line therapy.

Approval Criteria		
9. Is the patient currently taking ≥1000mg of aspirin daily?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Concurrent use of ≥1000mg aspirin daily with dichlorphenamide is contraindicated.	**No:** Go to #10
10. Is the patient ≥18 years old?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness. Note: There is insufficient evidence of safety and efficacy in the pediatric population.
11. Have baseline serum potassium and bicarbonate been documented as >3.5 mmol/L and >22 mmol/L respectively?	**Yes:** Approve for up to 3 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the weekly average attack rate decreased from baseline?	**Yes:** Go to #2 Document attack rate.	**No:** Pass to RPh. Deny; medical appropriateness.
2. Have the serum potassium and bicarbonate been measured and documented as >3.5 mmol/L and >22 mmol/L respectively since the last approval?	**Yes:** Approve for 3 months at first renewal and up to 6 months for renewals thereafter.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 3/18 (EH)
Implementation: TBD

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Anti-Parkinson's Agents

Date of Review: March 2018
Generic Name: safinamide

End Date of Literature Search: 01/03/2018
Brand Name (Manufacturer): Xadago® (US WorldMeds)
Dossier Received: Yes

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

Purpose for Class Update:
To evaluate for new comparative evidence between anti-Parkinson's agents and review the evidence and place in therapy of safinamide, which was recently approved by the United States (U.S.) Food and Drug Administration (FDA) as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

Research Questions:
1. Is there new comparative evidence that anti-Parkinson's agents differ in efficacy or effectiveness for alleviating symptoms and stabilizing disease in adults with PD?
2. Is there new comparative evidence that anti-Parkinson's agents differ in serious adverse events or tolerability when used to manage adults with PD?
3. Are there specific subpopulations (based on age, gender, race, disease severity, disease subtype, or concomitant therapies) for which one anti-Parkinson's agent is better tolerated or more effective than other available agents for PD?

Conclusions:
- One new guideline from the National Institute for Health and Care Excellence (NICE) was identified since the time of last review which supports the current preferred drug list (PDL) and prior authorization (PA) criteria.[1] One new FDA-approved formulation of extended-release amantadine (Gocovri™) which is indicated for treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy was identified since the time of last review.[2] No new safety alerts or comparative evidence of anti-Parkinson's agents were identified.
- There is low quality of evidence that amantadine ER improves dyskinesia as rated by the Unified Dyskinesia Rating Scale (UDysRS) with treatment differences compared to placebo of -7.9 points and -14.4 points (studies=2). UDysRS total scores range from 0 to 104 with higher scores indicating greater severity of dyskinesia.[3]
- There is low quality of evidence that adjunct safinamide 100 mg in addition to levodopa therapy improves total daily "on" time with no or non-troublesome dyskinesia compared to placebo at 24 weeks (Study-016: mean difference vs. placebo 0.55 hours per day (h/d); 95% CI 0.07-0.94; p=0.0223; SETTLE study:

mean difference vs. placebo 0.96 h/d; 95% CI 0.56 to 1.37; p<0.001) in patients with mid-late PD with moderate severity disease (mean Hoehn and Yahr score of 2.8 and 2.5 in the two trials, respectively).[4,5]

- There is low quality of evidence that adjunct safinamide 100 mg in addition to levodopa therapy improves total daily "off" time compared to placebo at 24 weeks (Study-016: mean difference vs. placebo -0.6 h/d; 95% CI -1.0 to -0.2; p=0.0034; SETTLE study: mean difference vs. placebo -1.03 h/d; 95% CI -1.40 to -0.67; p<0.001).[4,5]
- There is low quality of evidence that adjunct safinamide 100 mg in addition to levodopa therapy improves Parkinson's-disease health related quality of life as rated by the Parkinson's Disease Questionnaire (PDQ-39) scale compared to placebo at 24 weeks (Study-016: -28.4 vs. -11.9 points, respectively, on total PDQ-39 scale; mean difference -16.5 points; 95% CI -31.9 to -1.1; p=0.0360; SETTLE study: -3.17 and -0.68 points, respectively, on the PDQ-39 summary index; mean difference -2.49; 95% CI -3.98 to -0.68; p=0.006).[4,5] The maximum total score on the total PDQ-39 scale which indicates worst health-related quality of life is 800, while the maximum score on the PDQ-39 summary index is 100.[6,7] A minimum clinically important difference on the PDQ-39 summary index is considered by NICE guidance to be around 1.6 points.[6,7]
- There is insufficient evidence supporting benefit of safinamide in Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor activity) scores in early stage PD as adjunct therapy to dopamine agonists based on three phase 3 trials.[8-11] This indication was denied approval by the FDA.[11]
- There is insufficient evidence to compare safinamide to any other anti-Parkinson's agents or evaluate differences in specific subpopulations.

Recommendations:

- Modify PA criteria (**Appendix 4**) to:
    - Add specific clinical criteria for safinamide which limits use to FDA-approved indication and
    - Add renewal criteria which requires physician attestation of condition improvement.
- Evaluate comparative costs in executive session.

Previous Conclusions:

- Since the previous Parkinson's disease drug class scan, there is limited new comparative evidence from one systematic review with meta-analysis and three randomized controlled trials. There are also two new levodopa and carbidopa formulations approved by the FDA for the treatment of Parkinson's disease and one new FDA safety alert.
- There is low quality evidence that levodopa monotherapy is more effective than levodopa-sparing therapy for improving activities of daily living and motor symptoms as measured by the UPDRS [Scale 0-176, 0 = no disability, 176 = worst disability; mean difference 0.95 (52 point scale), 95% CI, 0.51 to 1.39; p<0.0001 and 2.89 (108 point scale), 95% CI, 1.56 to 4.21; p<0.0001, respectively] but less effective than levodopa-sparing therapy for improvement of mental functioning [mean change from baseline -0.30 (16 point scale), 95% CI, -0.51 to -0.09; p=0.0005]. The clinical significance of these differences remain unclear.
- There is low quality evidence that levodopa monotherapy results in a worsening of motor complications compared to levodopa-sparing treatment (33.7% vs. 24.4%, respectively; p<0.0001), has increased risk of dyskinesia (RR 1.88, 95% CI, 1.37 to 2.59; p<0.0001), and higher incidence of wearing-off phenomenon (41.2% vs. 29.6%; p<0.00001). There is insufficient evidence of no difference in self-reported quality of life measurement scores between levodopa and levodopa-sparing therapy in the treatment of PD.

Previous Recommendations:

- No further review or research needed at this time. After the executive session, no changes in the PDL were made.

Background:

Parkinson's disease (PD) is a neurodegenerative disorder resulting in dopamine cell degeneration with a prevalence of up to 329 per 100,000 people.[12,13] The median age of onset is 60 years and men are 1.5 times more likely to develop PD than women.[14] PD is characterized by motor symptoms including akinesia, muscle rigidity, and tremor at rest.[13] PD may also be broken out into subtypes based on age of onset, motor phenotypes, cognitive impairments, or other non-motor symptoms.[15] While the onset of PD is gradual and early symptoms may be unnoticed or undiagnosed, it is a progressive disorder which results in significant disability.[14,16] The mean duration of disease from time of diagnosis to death is 15 years. [13]

Disease severity is commonly measured with the Hoehn and Yahr staging scale, which ranges from 1 to 5 with higher stages indicating greater disease severity.[17] Stage one indicates unilateral involvement typically with minimal or no functional disability, while stage 5 indicates confinement to bed or wheelchair unless aided.[17]

Nonpharmacologic therapies for the treatment of PD include exercise therapy and speech therapy.[18] Early pharmacologic treatment of PD includes levodopa/carbidopa and dopamine agonists such as ropinirole and pramipexole.[14,16] While dopaminergic therapies are initially effective, motor complications often develop over time.[19] One such motor complication is "off" time which is defined as periods of time when PD symptoms return as medication effect wears off.[19] This is in contrast to "on" time which is defined as time when PD motor symptoms are well controlled.[4] Commonly utilized medications for "off" time motor fluctuations are catechol-O-methyl transferase (COMT) inhibitors such as entacapone and tolcapone as well as monoamine oxidase B (MAO-B) inhibitors such as rasagiline, and selegiline.[19] Safinamide, which was approved in 2017, is also a MAO-B inhibitor.[20] In clinical trials, "on" and "off" time is commonly recorded through patient diaries.[4,5] It is unclear what is a clinically significant change in "on" or "off" time. In a Cochrane review on adjuvant treatment to levodopa in patients with PD with motor complications, COMT inhibitors and MAO-B inhibitors were found to reduce "off" time by 0.83 h/d and 0.93 h/d, respectively, compared to placebo.[21] Another motor complication is dyskinesia, or drug-induced involuntary movements, which can be treated by adjusting doses of existing therapies or adding amantadine.[1,19] While evidence is limited, amantadine may reduce dyskinesia by 24-45%.[19,22,23] Deep brain stimulation may also be considered for patients with symptoms inadequately controlled by medical therapy.[1]

The Unified Parkinson's Disease Rating Scale (UPDRS) assesses impairment and disability in PD and consists of four sections and 55 items.[3,24] Part I focuses on non-motor experiences of daily living which include mentation, behavior, and mood, Part II focuses on activities of daily living, Part III focuses on motor aspects, and Part IV focuses on complications of therapy.[3,24] Each item in each section is ranked on a 5-point scale and higher scores indicate more severe disease.[3] The minimum clinically important difference (MCID) in total UPDRS score is thought to be reduction of 4.1-4.5 points out of a total score of 199 points.[25,26] For UPDRS parts II and III specifically, the MCID is likely a reduction of around 2 points and 2.5-6 points, respectively, on scales that range from 0 to 52 and 0 to 108, respectively.[7,25,27,28] These two sections are most commonly seen as endpoints in recent clinical trials.[4,5] A validated modified UPDRS, the MDS-UPDRS, was established in 2008 by the Movement Disorder Society which retains the original scale's structure and provides clarity to ambiguities and also addresses additional factors of PD.[3,29]

There are a variety of different scales to classify severity of dyskinesias. The Unified Dyskinesia Rating Scale (UDysRS) is a 4-part scale which assesses dyskinesia.[30] Items on the scale are assessed from 0 to 4 with 0 indicating normal and 4 indicating severe.[30] Total scores can range from 0 to 104, with higher

scores indicating greater severity of dyskinesia.[30] Another dyskinesia scale, the Dyskinesia Rating Scale (DRS) also measures dyskinesia and scores can range from 0 to 48, with higher scores indicating greater severity of dyskinesia.[7,31] The MCID for the UDysRS and DRS is unclear.[7]

Quality of life in PD is often measured on the Parkinson's Disease Questionnaire (PDQ-39) which is a 39-item scale covering mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily comfort.[6] The maximum total score on the scale, which indicates worst health-related quality of life, is 800 with a maximum score of 100 in each of the 8 dimensions.[6,7] However, the total score can also be summarized into an index score (ranging from 0-100).[7] NICE guidance considers a change of 1.6 points in this index score to be a likely MCID indicating "a little worse".[6,7]

Fee-for-Service Utilization July 1, 2017 to September 30, 2017
In the third quarter of 2017, approximately 69% of pharmacy claims for anti-Parkinson's agents in the Oregon Medicaid Fee-For-Service (FFS) population were for the preferred agents which include benztropine, carbidopa/levodopa, carbidopa/levodopa/entacapone, entacapone, pramipexole, selegiline, and trihexyphenidyl.

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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

Systematic Reviews:
No new moderate-high quality systematic reviews were identified. After review, 4 systematic reviews were excluded due to poor quality.[32-35]

New Guidelines:
National Institute for Health and Care Excellence (NICE)
In July 2017, an update to the 2006 guideline for PD in adults was published by NICE.[1] The major changes in this update include new recommendations on treating PD symptoms, deep brain stimulation, monitoring and managing impulse control disorders, and palliative care.[1] Recommendations regarding pharmacological treatment of motor symptoms include:

Management principles:

- Before starting treatment, discuss the patient's clinical circumstances, lifestyle circumstances, preferences, needs and goals, and the potential benefits and harms of the different drug classes (**Table 1**).[1]
- Anti-Parkinson's agents should not be withdrawn abruptly.[1]
- "Drug holidays" should not be taken with anti-Parkinson's agents due to risk of neuroleptic malignant syndrome.[1]

Table 1. Potential benefits and harms of levodopa, dopamine agonists, and MAO-B inhibitors[1] (adapted from the NICE guidelines)

	Levodopa	Dopamine Agonists	MAO-B Inhibitors
Motor Symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of Daily Living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor Complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse Events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

Abbreviations: MAO-B = monoamine oxidase B

*Specified adverse events include: excessive sleepiness, hallucinations, and impulse control disorders

First-line treatment:

- Offer levodopa to people in the early stages of PD whose motor symptoms impact their quality of life.[1]
- Consider a choice of dopamine agonists, levodopa, or MAO-B inhibitors for people in the early stages of PD whose motor symptoms do not impact their quality of life.[1]
- Do not offer ergot-derived dopamine agonists (such as cabergoline and bromocriptine) as first-line treatment for PD .[1]

Adjuvant treatment of motor symptoms:

- Offer a choice of dopamine agonists, MAO-B inhibitors, or COMT inhibitors as an adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy after discussing clinical and lifestyle circumstances as well as potential benefits and harms of different drug classes.[1]
- Choose a non-ergot-derived dopamine agonist in most cases, because of the monitoring that is needed with ergot-derived dopamine agonists.[1]
- Only consider an ergot-derived dopamine agonist as an adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy and whose symptoms are not adequately controlled with a non-ergot-derived dopamine agonist.[1]
- If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine.[1]
- Do not offer anticholinergics to people with PD who have developed dyskinesia and/or motor fluctuations.[1]

New Formulations or Indications:

Gocovri™ (amantadine hydrochloride) (August 2017): A new extended-release (ER) capsule formulation of amantadine (Gocovri™) was approved for the treatment of dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications.[2] The recommended

dosing is 137 mg daily for one week followed by the maintenance daily dose of 274 mg.[2] The daily dose is recommended to be taken at night in order to provide high levels of drug in the morning and daytime based on the pharmacokinetics.[36] Gocovri™ is the first medication approved by the FDA specifically for levodopa induced dyskinesia.[36]

Approval was based on two randomized, double-blind, placebo-controlled trials.[2] Key inclusion criteria for these trials were at least a mild functional impact of dyskinesia (score of ≥2 on part IV of the MDS-UPDRS) and at least 2 half-hour time intervals between 9am to 4pm of documented "on" time (periods when PD medications provide good benefit for motor symptoms) with troublesome dyskinesia for 2 consecutive days prior to day 1 of the study.[37,38] The mean age of patients in the trials was 64.8 years.[37,38] The primary endpoint in both trials was the change from baseline in total score of the UDysRS at week 12.[37,38] The maximum score for the UDysRS is 104 points, indicating maximum severity.[30]

In the first study, 63 patients received amantadine ER and 60 patients received placebo.[38] At baseline, the mean "on" time with troublesome dyskinesia at baseline was 4.6 hours and the mean UDysRS total score was 39.7.[38] At week 12, the mean change in UDysRS was -15.9 in the amantadine ER group and -8.0 in the placebo group (treatment difference: -7.9 points; 95% CI -12.5 to -3.3; p<0.001).[38] There were no serious drug-related adverse events (AEs) reported in either group, but a greater proportion of amantadine ER-treated patients discontinued treatment due to drug-related AEs compared to placebo patients (19.0% vs. 6.7%, respectively).[38] The most common AEs for amantadine- and placebo-treated patients were visual hallucinations (23.8% vs. 1.7%, respectively), peripheral edema (23.8% vs. 0%, respectively), dizziness (22.2% vs. 0%, respectively), and dry mouth (17.5% vs. 0%, respectively).[38]

In the second study, 37 patients received amantadine ER and 38 patients received placebo.[37] At baseline, the mean "on" time with troublesome dyskinesia at baseline was 5.4 hours and the mean UDysRS total score was 40.7.[37] At week 12, the mean change in UDysRS was -20.7 for the amantadine ER group and -6.3 for the placebo group (treatment difference: -14.4; 95% CI -20.4 to -8.3; p<0.0001).[37] One patient in the amantadine ER group experienced a study drug-related serious AE (2.7%) compared to no patients in the placebo group.[37] Additionally, a greater proportion of amantadine ER-treated patients discontinued treatment due to study drug-related AEs compared to placebo-treated patients (16.2% vs. 5.3%, respectively). The most common AEs reported for amantadine and placebo were dry mouth (13.5% vs. 2.6%, respectively), nausea (13.5% vs. 2.6%, respectively), decreased appetite (10.8% vs. 0%, respectively), insomnia (10.8% vs. 0%, respectively), and orthostatic hypotension (10.8% vs. 0%, respectively).[37]

Both trials were manufacturer-funded and had high overall attrition (>10%) for a relatively short (12 week) trial duration.[37,38] There is currently no evidence comparing immediate release and extended release amantadine formulations for dyskinesia in PD.

New FDA Safety Alerts:
No new safety alerts identified.

Randomized Controlled Trials:
A total of 102 citations were manually reviewed from the initial literature search. After further review, all 102 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

NEW DRUG EVALUATION: Xadago® (safinamide)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Safinamide is a MAO-B inhibitor approved by the FDA as an adjunct treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes.[20] Two clinical trials, Study-016 and SETTLE, contribute to the efficacy data for this indication.[4,5] Study-016 also has an 18 month extension study (Study-018).[39] While not FDA-approved for a second indication, 3 additional phase 3 trials (Study-015, Study-017, and MOTION) were conducted to study safinamide in early PD as adjunct to dopamine agonist therapy.[8-11] This indication of adjunct treatment to dopamine agonist therapy in early PD was ultimately not approved by the FDA, and therefore these studies will not be included in the comparative evidence table below.[11,20]

*Studies Evaluating Safinamide in the Mid-Late PD Population as an Adjunct to Levodopa (**Table 4**)*
Study-016 was a multicentered, randomized, double-blinded, placebo-controlled, parallel-group phase 3 trial in which patients were randomized 1:1:1 to safinamide 100 mg/day (n=224), safinamide 50 mg/day (n=223), or placebo (n=222) for 24 weeks.[5] Included patients had a diagnosis of idiopathic PD for at least 3 years, Hoehn and Yahr stages 1-4 during "off" periods, and motor fluctuations including over 1.5 hours of "off" time per day.[5] All patients took concomitant levodopa and the mean daily total "on" time with no or non-troublesome dyskinesia was 9.4 hours, with a mean UPDRS part III score of 28.1.[5] At week 24, benefit in the primary endpoint of change in mean daily total "on" time with no or non-troublesome dyskinesia was found for both the safinamide 100 mg group (mean difference 0.55 h/d; 95% CI 0.07-0.94; p=0.0223) and safinamide 50 mg group (mean difference 0.51 h/d; 95% CI 0.12-0.99; p=0.0130) compared to placebo.[5] A benefit was observed in quality of life, with change in total PDQ-39 score from baseline to week 24 with safinamide 100 mg (-28.4 points; 95% CI -31.9 to -1.1; p=0.0360) but not with safinamide 50 mg (-16.4 points; 95% CI -20.0 to 10.9; p=0.5603) compared to placebo (-11.9 points).[5] This manufacturer-funded fair quality trial had high overall attrition (11.2%) but had adequate concealment of allocation and blinding.[5] All of the treatment centers were located in India, Romania, or Italy, which limits applicability to the Oregon Medicaid population as well as U.S. patients in general.[5]

The SETTLE study was a double-blinded, placebo-controlled, parallel-group phase 3 trial in which patients were randomized 1:1 to either placebo (n=275) or safinamide 50 mg/day on days 1-13, followed by 100 mg/day starting on day 14 (n=274) if there were no tolerability issues, for a total of 24 weeks.[4] At day 14, 90.9% of the safinamide group and 94.1% in the placebo group were prescribed the 100 mg/day target dose.[4] Inclusion criteria were similar to Study-016.[4] All patients took concomitant levodopa with a mean dose of 776.6 mg/day. Mean Hoehn and Yahr stage was 2.5 (indicating moderate severity disease) and mean UPDRS part III score was 22.9.[4] At week 24, benefit in the primary endpoint of change from baseline to week 24 in mean daily "on" time without troublesome dyskinesia was found with safinamide (1.42 h/d; mean difference vs. placebo 0.96 h/d; 95% CI 0.56 to 1.37; p<0.001) compared to placebo (0.57 h/d).[4] Benefit was also seen in quality of life, measured by the PDQ-39 summary index score, with safinamide compared to placebo (-3.17 vs. -0.68 points, respectively; mean difference -2.49; 95% CI -3.98 to -0.68; p=0.006).[4] This manufacturer-funded fair quality trial had high overall attrition of 11.5% with adequate randomization and blinding.[4] Only 18% of patients were from North America, which may limit applicability to the Oregon Medicaid population.[4]

Study-018 was an 18-month multicentered, randomized, double-blind, placebo-controlled, parallel-group extension study of Study-016.[39] Patients who had completed Study-016 and were treatment compliant, or who had discontinued Study-016 but had completed efficacy evaluations at weeks 12 and 24 were included.[39] Patients continued in the same treatment group that they had been randomized to in Study-016.[39] Changes in concomitant PD medications were

allowed and because many patients had other medications increased, conclusions about efficacy may be limited.[11] At week 78, no benefit was found in the primary endpoint of mean change from baseline (defined as the start of Study-016) in total score of the Dyskinesia Rating Scale during "on" time with safinamide 100 mg/day (mean difference -0.59 h/d; 95% CI -1.40 to 0.21; p=0.1469) or safinamide 50 mg/day (mean difference -0.51 h/d; 95% CI -1.32 to 0.29; p=0.2125) compared to placebo.[39] However, there was a statistically significant benefit seen in the secondary endpoint of mean change from baseline to week 78 in total daily "on" time without troublesome dyskinesia with both safinamide 100 mg/day (mean difference -0.83 h/d; 95% CI 0.39 to 1.27; p=0.0002) and safinamide 50 mg/day (mean difference -0.67 h/d; 95% CI 0.23 to 1.11; p=0.0031) compared to placebo.[39] This poor quality manufacturer-funded trial had high overall attrition of 19.1% and high risk of reporting bias, as only differences versus placebo were reported rather than actual values for many of the secondary endpoints.[39]

Study-016, SETTLE, and Study-018 provide data to support efficacy of safinamide for idiopathic PD when used as an adjunct to levodopa for improvement of "off" episodes.[4,4,20] Improvement was seen in motor complications through total daily "on" time with no or non-troublesome dyskinesia.[4,4,20] Quality of life as measured by PDQ-39 scores was also improved.[4,5]

In February 2017, an evidence summary on PD with motor fluctuations with a focus on safinamide was published by NICE.[7] No recommendations specific to safinamide were made but NICE guidance on PD in adults (detailed previously in this review) was referenced and it was noted that choice of treatment should depend on patient characteristics and preferences after a discussion of risks and benefits with the patient.[1,7]

Studies Evaluating Safinamide in Early PD Population as Adjunct to Dopamine Agonist

Three phase 3 studies (Study-015, Study-017, and MOTION) were completed studying safinamide in early PD as an add-on therapy to dopamine agonists, which is an indication ultimately not approved by the FDA due to insufficient efficacy evidence.[8-11] Patients in all three studies were required to be on single dopamine agonist therapy (which does not include levodopa) and Study-015 excluded patients on additional PD medications other than a single dopamine agonist.[8-10] The primary outcome in Study-015 was change in UPDRS part III (motor examination) total score from baseline to week 24.[9] There was no change in the primary outcome with safinamide 200 mg per day versus placebo (-3.9 vs. -3.6, respectively; 95% CI -2.3 to 1.4; p=0.65) but there was a benefit seen with safinamide 100 mg per day versus placebo (-6.0 vs. -3.6, respectively; 95% CI -3.7 to -0.1; p=0.0419).[9] However, the FDA notes that pre-specified hierarchical statistical comparison was documented in the statistical analysis plan requiring comparison of the 200 mg strength prior to the 100 mg strength.[9,11] Therefore, statistical testing could not be formally conducted for the 100 mg dose as the 200 mg dose did not show statistically significant results.[9,11]

Study-017 was a 12-month randomized, double-blind, placebo-controlled extension study of Study-015.[8] The primary endpoint was time from baseline (randomization in Study-015) to an "intervention" which was defined as an increase in the dose of dopamine agonist; addition of another dopamine agonist, levodopa, or other PD treatment; or discontinuation due to lack of efficacy.[8] No benefit was seen in the primary endpoint with the safinamide groups (pooled doses) versus placebo (559 days vs. 466 days, respectively; p=0.3342).[8] Change in UPDRS part III scores was a secondary endpoint and no benefit was seen with safinamide (pooled doses) versus placebo (-3.0 vs. -1.7, respectively; p=0.1893).[8] Similarly, in the MOTION trial, there was no significant benefit in change from baseline to week 24 of UPDRS part III with safinamide 50 mg/day versus placebo (least squares mean difference vs. placebo -0.65; p=0.259) or 100 mg/day versus placebo (least squares mean difference vs. placebo -1.04; p=0.073).[10,11]

Based on these 3 trials, the FDA determined that there was not sufficient evidence to support approval of safinamide in the early PD population as adjunct to dopamine agonist therapy.[11]

Clinical Safety:
The most common adverse events in Study-016 and SETTLE associated with safinamide 100 mg/day where the incidence for safinamide was at least 2% greater than for placebo include dyskinesia, fall, nausea, and insomnia (**Table 2**).[4,4,20]

Table 2. Selected Adverse Reactions with an Incidence of ≥2% with Safinamide 100 mg/day and Greater than Placebo

	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=498)	Placebo (n=497)
Dyskinesia	21%	17%	9%
Fall	4%	6%	4%
Nausea	3%	6%	4%
Insomnia	1%	4%	2%

Serious adverse events (SAE) occurred in 9.8% (n=22) and 8.1% (n=18) of patients treated with safinamide 100 mg/day and placebo, respectively in Study-016.[5] No specific pattern of SAEs was determined.[5] In SETTLE, 9.5% (n=26) and 6.6% (n=18) of safinamide- and placebo-treated patients experienced SAEs.[4] SAEs which occurred in more than one safinamide-treated patient included breast cancer (n=2) and visual hallucinations (n=2).[4]

Dyskinesia was the most commonly reported AE in both Study-016 and SETTLE.[4,5] The incidence was 21.1%, 18.3%, and 12.6% in the safinamide 50 mg/day, safinamide 100 mg/day, and placebo groups in Study-016.[5] However, severe dyskinesia was only reported in 0.9%, 1.8%, and 2.3% of those same groups.[5] In SETTLE, the incidence overall was 14.6% in the safinamide group compared to 5.5% in the placebo group, but only reported as severe in 1.8% and 0.4% in those same groups, respectively.[4]

In long-term extension trial data, the percent of patients experiencing newly treatment-emergent AEs (TEAEs) in Study-018 for safinamide 100 mg/day, safinamide 50 mg/day, and placebo groups were 78.3%, 76.7%, and 85.1%, respectively.[33] For those same groups, serious TEAEs occurred in 18.9%, 16.9%, and 16.0% of patients.[39] During the 2-year treatment period of Study-016 and Study-018 combined, worsening of PD and dyskinesia were the most frequent TEAEs.[33] Worsening of PD was reported in 23.9%, 22.2%, and 24.0% of patients treated with safinamide 100 mg/day, safinamide 50 mg/day, and placebo, respectively. Dyskinesia was reported in 27.8%, 31.2%, and 21.7% of those groups, respectively.[33] Discontinuation due to TEAEs occurred in 6.7%, 5.3%, and 5.7% of the safinamide 100 mg/day, safinamide 50 mg/day, and placebo groups. [33]

Per FDA labeling, safinamide is contraindicated in patients with concomitant use of other MAO inhibitors, opioids, and dextromethorphan and patients with a history of hypersensitivity to safinamide or in severe hepatic impairment (Child-Pugh C).[20]

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

Table 3. Pharmacology and Pharmacokinetic Properties.[20]

Parameter	
Mechanism of Action	Inhibition of monoamine oxidase B (MAO-B), which blocks the catabolism of dopamine
Oral Bioavailability	95%
Distribution and Protein Binding	165 L volume of distribution; not highly protein bound (unbound fraction of 11-12%)
Elimination	Metabolism through 3 main pathways; none of metabolites have pharmacological activity; ~5% eliminated unchanged, mainly in urine
Half-Life	20-26 hours
Metabolism	Hydrolytic oxidation, oxidative cleavage, and conjugation with glucuronic acid

Abbreviations: L = liter

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement ("on" time, "off" time, UPDRS, UDysRS, DRS)
2) Quality of life (PDQ-39)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Total daily "on" time

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. Borgohain R, et al[5] STUDY-016 Phase 3, randomized, MC, DB, PC, PG	1. Safinamide 100 mg/d 2. Safinamide 50 mg/d 3. Placebo 4 phases: • 10 d screening period • 4 wk L-dopa stabilizat-ion period	Demographics: -Age: 59.9 y -Male: 71.8% -Asian: 80.6% -White: 19.4% -Mean Hoehn & Yahr stage: 2.8 -Concomitant L-dopa: 100% -Concomitant dopamine agonist: 60.8% -Concomitant anticholinergic: 37.1% -Mean daily total "on" time with no or non-troublesome dyskinesia: 9.4 h	ITT: Total: 669 1. 224 2. 223 3. 222 Attrition: Total: 11.2% 1. 29 (12.9%) 2. 21 (9.4%) 3. 25 (11.3%)	Primary Endpoint: Change in mean daily total "on" time with no or non-troublesome dyskinesia at week 24: 1. 1.36 ±2.625 h 2. 1.37 ±2.745 h 3. 0.97 ±2.375 h *1 vs. 3:* LS mean change: 0.55 h (95% CI, 0.07-0.94); P=0.0223 *2 vs. 3:* LS mean change: 0.51 h (95% CI, 0.12-0.99); P=0.0130 Secondary Endpoints: (reported as change from baseline to week 24) Change in total daily "off" time: 1. -1.3 h 2. -1.3 h 3. -0.7 h	 NA NA	Study drug-related AE: 1. 67 (29.9%) 2. 69 (30.9%) 3. 51 (23.0%) P=0.1395 RR & 95% CI NR Serious AE: 1. 22 (9.8%) 2. 8 (3.6%) 3. 18 (8.1%) P=0.0286 RR & 95% CI NR DC due to AE:	 NA NA NA 4.5% /23	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomization by computer-generated randomization schedule, administered by central IVRS. Baseline characteristics balanced. Performance Bias: Low. Safinamide and placebo identical in appearance. Protocol approved in all countries studied. Detection Bias: Low. Investigators, patients, and caregivers blinded to treatment. Attrition Bias: High. Overall attrition >10%. MMRM analysis utilized for primary endpoint with

	• 24 wk treatment period • Optional 1 wk taper period Randomized 1:1:1	-Mean UPDRS-III: 28.1 Key Inclusion Criteria: -30-80 y of age -idiopathic PD ≥3 y -Hoehn & Yahr stage I-IV during "off" -motor fluctuations (>1.5 h "off" time/d) Key Exclusion Criteria: -late-stage PD with severe, disabling peak-dose or biphasic dyskinesia -late-stage PD with unpredictable or widely swinging symptom fluctuation -dementia, major psychiatric illnesses, severe and progressive medical illnesses		*1 vs. 3:* LS mean difference: -0.6 h (95% CI, -1.0 to -0.2); P=0.0034 *2 vs. 3:* LS mean difference: -0.6 h (95% CI, -0.9 to -0.2); P=0.0043 Change in UPDRS Part III (motor) scores during "on": 1. -6.9 2. -6.1 3. -4.3 *1 vs. 3:* LS mean change: -2.6 (95% CI, -4.1 to -1.1); P=0.0006 *2 vs. 3:* LS mean change: -1.8 (95% CI, -3.3 to -0.4); P=0.0138 Change in UPDRS Part II (activities of daily living) scores during "on": 1. -2.2 2. -1.7 3. -1.2 *1 vs. 3:* -1.0 h (95% CI, -1.7 to -0.3); P=0.0060 *2 vs. 3:* -0.5 h (95% CI, -1.2 to 0.2); P=0.1253 Change in "off" time following first morning L-dopa dose: 1. -1.2 h 2. -1.1 h 3. -0.6 h *1 vs. 3:* -0.6 h (95% CI, -1.0 to -0.2); P=0.0011 *2 vs. 3:* -0.5 h (95% CI, -0.9 to -0.2); P=0.0031 Change in PDQ-39 total score: 1. -28.4 2. -16.4 3. -11.9 *1 vs. 3:* -16.5 (95% CI, -31.9 to -1.1); P=0.0360 *2 vs. 3:* -4.5 (95% CI, -20.0 to 10.9); P=0.5603	NA NA NA NA NA NS NA NA NA NS	1. 14 (6.3%) 2. 11 (4.9%) 3. 12 (5.4%) P=0.8497 RR & 95% CI NR Dyskinesia: 1. 41 (18.3%) 2. 47 (21.1%) 3. 28 (12.6%) RR, 95% CI, & p-value NR Severe dyskinesia: 1. 1.8% 2. 0.9% 3. 2.3% RR, 95% CI, & p-value NR	NA NA NA NA NA NA	no imputations for missing data. ITT analysis used. Reporting Bias: Unclear. All primary and secondary efficacy endpoints reported, although study protocol not available. Funded by Newron and Merck Serono. **Applicability**: Patient: Broad exclusion criteria limits applicability to more severe disease or patients with significant comorbid conditions. Intervention: Safinamide dose appropriate and approved by the FDA. Comparator: A MAO-B inhibitor comparator would have been a more meaningful comparison than placebo. Outcomes: Outcomes appropriate for condition. Setting: 52 treatment centers in India (35), Romania (10), and Italy (7). May limit applicability to the U.S. population.
2. Schapira, et al[4] SETTLE DB, PG, PC, phase 3 trial	1. Safinamide 50 mg/d for days 1-13, then 100 mg/d starting on day 14 if no tolerability issues	Demographics: -Age: 61.9 y -Male: 60.9% -White: 67.6% -North America: 18.6% -Western Europe: 39.9%	ITT: Total: 549 1. 274 2. 275 Attrition: Total: 63 (11.5%)	Primary Endpoint: Change from baseline to week 24 in mean daily "on" time without troublesome dyskinesia: 1. +1.42 h/d 2. +0.57 h/d LS mean difference: 0.96 h/d (95% CI, 0.56 to 1.37); P<0.001	 NA	Study drug-related AE: 1. 78 (28.5%) 2. 76 (27.6%) Serious AE: 1. 18 (6.6%) 2. 26 (9.5%)	 NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomization and allocation via computerized central IVRS. Baseline characteristics balanced. Performance Bias: Low. Placebo was provided as matching tablets

	2. Placebo daily 24 weeks Randomized 1:1	-Mean Hoehn & Yahr stage: 2.5 -Mean levodopa dose: 776.6 mg/d -Mean Part II UPDRS Score: 10.2 -Mean Part III UPDRS Score: 22.9 Key Inclusion Criteria: -30-80 y of age -idiopathic PD ≥3 y -Hoehn & Yahr stage I-IV during "off" -motor fluctuations (>1.5 h "off" time/d) -L-dopa responsive and on stable regimen x4w Key Exclusion Criteria: -severe, disabling peak-dose or biphasic dyskinesia -wide or unpredictable symptom fluctuations -current diagnosis of a clinically significant medical condition other than PD	1. 29 (10.6%) 2. 34 (12.4%)	Secondary Endpoints: Change in "off" time from baseline to week 24: 1. -1.56 h/d 2. -0.54 h/d LS mean difference: -1.03 (95% CI, -1.40 to -0.67); P<0.001 Change in UPDRS Part III score from baseline to week 24: 1. -3.43 2. -1.83 LS mean difference: -1.82 (95% CI, -3.01 to -0.62); P=0.003 Change in UPDRS Part II score from baseline to week 24: 1. -1.07 2. -0.75 LS mean difference: -0.43 (95% CI, -1.02 to 0.16); P=0.15 Patients with improvement on CGI-C (scores of 1-3): 1. 57.7% 2. 41.8% LS mean difference: 1.92 (95% CI, 1.36 to 2.70); P<0.001 Change from baseline to week 24 in PDQ-39 summary index score: 1. -3.17 2. -0.68 LS mean difference: -2.33 (95% CI, -3.98 to -0.68); P=0.006	NA NA NS 15.9 %/7 NA	Study drug-related serious AE: 1. 3 (1.1%) 2. 6 (2.2%) DC due to AE: 1. 12 (4.4%) 2. 10 (3.6%) Deaths: 1. 1 (0.4%) 2. 2 (0.7%) Dyskinesia: 1. 40 (14.6%) 2. 15 (5.5%) RR, 95% CI, & p-value NR	NA NA NA NA	in matching blister packs. Protocol approved at each center. Detection Bias: Low. Study site personnel and patients blinded. Attrition Bias: High. Overall attrition >10%. LOCF approach to missing data utilized for a chronic, deteriorating condition. ITT analysis. Reporting Bias: Unclear. Protocol available. All primary and secondary outcomes reported on. Funded by Newron and Merck Serono. The funder was involved in collection, management, analysis, and interpretation of data as well as preparation and review of the manuscript. **Applicability**: Patient: Broad exclusion criteria limits applicability to more severe disease or patients with significant comorbid conditions. Intervention: Safinamide dose appropriate. Comparator: A MAO-B inhibitor comparator would have been a more meaningful comparison than placebo. Outcomes: Outcomes appropriate for condition. Setting: Only 18% of patients were from North America. The majority of patients were from western Europe or the Asia-Pacific region.

Abbreviations [alphabetical order]: AE = adverse event; ARR = absolute risk reduction; CGI-C = Clinical Global Impression-Change; CI = confidence interval; d = day; DB = double-blind; DC = discontinuation; DRS = Dyskinesia Rating Scale; h = hour; ITT = intention to treat; IVRS = interactive voice-response system; L-dopa = levodopa; LS = least squares; MC = multicenter; mg/d = milligrams per day; mITT = modified intention to treat; MMRM = mixed model repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR= not reported; NS = not significant; PC = placebo controlled; PD = Parkinson's disease; PDQ-39 = Parkinson's Disease Questionnaire; PG = parallel-group; PP = per protocol; TEAE = treatment-emergent adverse event; wk = week; Y = years

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Appendix 1: Current Preferred Drug List

PDL	Generic	Brand	Route	Form
Y	PRAMIPEXOLE DI-HCL	MIRAPEX	ORAL	TABLET
Y	PRAMIPEXOLE DI-HCL	PRAMIPEXOLE DIHYDROCHLORIDE	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	CARBIDOPA-LEVODOPA	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	SINEMET 10-100	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	SINEMET 25-100	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	SINEMET 25-250	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA	CARBIDOPA-LEVODOPA ER	ORAL	TABLET ER
Y	CARBIDOPA/LEVODOPA	SINEMET CR	ORAL	TABLET ER
Y	SELEGILINE HCL	SELEGILINE HCL	ORAL	CAPSULE
Y	ENTACAPONE	COMTAN	ORAL	TABLET
Y	ENTACAPONE	ENTACAPONE	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	CARBIDOPA-LEVODOPA-ENTACAPONE	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 150	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 100	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 50	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 200	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 75	ORAL	TABLET
Y	CARBIDOPA/LEVODOPA/ENTACAPONE	STALEVO 125	ORAL	TABLET
Y	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	ORAL	ELIXIR
Y	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	ORAL	TABLET
Y	BENZTROPINE MESYLATE	BENZTROPINE MESYLATE	ORAL	TABLET
N	CARBIDOPA	CARBIDOPA	ORAL	TABLET
N	CARBIDOPA	LODOSYN	ORAL	TABLET
N	AMANTADINE HCL	AMANTADINE	ORAL	CAPSULE
N	AMANTADINE HCL	AMANTADINE	ORAL	SOLUTION
N	AMANTADINE HCL	AMANTADINE	ORAL	TABLET
N	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	ORAL	CAPSULE
N	BROMOCRIPTINE MESYLATE	PARLODEL	ORAL	CAPSULE
N	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	ORAL	TABLET
N	BROMOCRIPTINE MESYLATE	PARLODEL	ORAL	TABLET
N	ROPINIROLE HCL	REQUIP	ORAL	TABLET
N	ROPINIROLE HCL	ROPINIROLE HCL	ORAL	TABLET
N	ROPINIROLE HCL	REQUIP XL	ORAL	TAB ER 24H
N	ROPINIROLE HCL	ROPINIROLE ER	ORAL	TAB ER 24H
N	PRAMIPEXOLE DI-HCL	MIRAPEX ER	ORAL	TAB ER 24H
N	PRAMIPEXOLE DI-HCL	PRAMIPEXOLE ER	ORAL	TAB ER 24H

N	CARBIDOPA/LEVODOPA	CARBIDOPA-LEVODOPA	ORAL	TAB RAPDIS
N	CARBIDOPA/LEVODOPA	RYTARY	ORAL	CAPSULE ER
N	TOLCAPONE	TASMAR	ORAL	TABLET
N	TOLCAPONE	TOLCAPONE	ORAL	TABLET
N	SELEGILINE HCL	SELEGILINE HCL	ORAL	TABLET
N	SELEGILINE HCL	ZELAPAR	ORAL	TAB RAPDIS
N	RASAGILINE MESYLATE	AZILECT	ORAL	TABLET
N	RASAGILINE MESYLATE	RASAGILINE MESYLATE	ORAL	TABLET
N	ROTIGOTINE	NEUPRO	TRANSDERM	PATCH TD24
N	SAFINAMIDE MESYLATE	XADAGO	ORAL	TABLET
N	AMANTADINE HCL	GOCOVRI	ORAL	CAP ER 24H

Appendix 2: Medline Search Strategy on 1/3/2018

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
1 pramipexole.mp. 1544
2 exp Carbidopa/ 2408
3 exp Levodopa/ 16907
4 exp Selegiline/ 2482
5 entacapone.mp 675
6 exp Trihexyphenidyl/ 956
7 exp Benztropine/ 735
8 exp Amantadine/ 5987
9 exp Bromocriptine/ 7598
10 ropinirole.mp. 954
11 tolcapone.mp. 479
12 rasagiline.mp. 680
13 rotigotine.mp. 573
14 safinamide.mp. 136
15 Parkinson Disease/ or Antiparkinson Agents/ or antiparkinson.mp. 68001
16 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 36314
17 15 and 16 12495
18 limit 17 to (English language and humans and yr="2016 –Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 102

Appendix 3: Prescribing Information Highlights for Safinamide[20]

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

XADAGO (safinamide) tablets, for oral use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
XADAGO is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes (1)

Limitations of Use: XADAGO has not been shown to be effective as monotherapy for the treatment of PD.

----------DOSAGE AND ADMINISTRATION----------
- Start with 50 mg administered orally once daily at the same time of day; after two weeks, the dose may be increased to 100 mg once daily, based on individual need and tolerability (2.1)
- Hepatic Impairment: Do not exceed 50 mg once daily in patients with moderate hepatic impairment; contraindicated in patients with severe hepatic impairment (2.2, 4)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 50 mg and 100 mg (3)

----------CONTRAINDICATIONS----------
XADAGO is contraindicated in patients with:
- Concomitant use of the following drugs:
  - Other monoamine oxidase inhibitors or other drugs that are potent inhibitors of monoamine oxidase (e.g., linezolid) (4, 7.1)
  - Opioid drugs (e.g., tramadol, meperidine and related derivatives); selective norepinephrine reuptake inhibitors; tri-or tetra-cyclic or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John's wort (4, 7.2, 7.3, 7.5)
  - Dextromethorphan (4, 7.4)
- A history of a hypersensitivity to safinamide (4)
- Severe hepatic impairment (Child-Pugh C: 10-15) (4)

----------WARNINGS AND PRECAUTIONS----------
- May cause or exacerbate hypertension (5.1)
- May cause serotonin syndrome when used with MAO inhibitors, antidepressants, or opioid drugs (5.2)
- May cause falling asleep during activities of daily living (5.3)
- May cause or exacerbate dyskinesia; consider levodopa dose reduction (5.4)
- May cause hallucinations and psychotic behavior (5.5)
- May cause problems with impulse control/compulsive behaviors (5.6)
- May cause withdrawal-emergent hyperpyrexia and confusion (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence on XADAGO 100 mg/day at least 2% greater than placebo) were dyskinesia, fall, nausea, and insomnia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds, LLC, Inc. at 1-888-492-3246 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Selective Serotonin Reuptake Inhibitors: Monitor patients for serotonin syndrome (7.3)
- Sympathomimetic Medications: Monitor patients for hypertension (7.5)
- Tyramine: Risk of severe hypertension (7.6)
- Substrates of Breast Cancer Resistance Protein (BCRP): Potential increase in plasma concentration of BCRP substrate (7.7)

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

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

Revised: 3/2017

Anti-Parkinson's Agents

Goals:

- Promote preferred drugs for Parkinson's disease.
- Restrict use for non-funded conditions ~~like~~ (e.g., restless leg syndrome).
- To limit utilization of safinamide to FDA-approved indications.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis Parkinson's disease or another chronic neurological condition?	**Yes:** Go to #5	**No:** Go to #3
3. Is the diagnosis Restless Leg Syndrome?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #4
4. RPh only: All other indications need to be evaluated to determine if treatment is for a funded condition.	**Funded:** Go to #5	**Not Funded:** Deny; not funded by the OHP.
5. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**.	**No:** Go to #6.

Approval Criteria		
6. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #7~~Approve for the shorter of 1 year or length of prescription.~~
7. Is the request for safinamide?	**Yes:** Go to #8	**No:** Approve for the shorter of 1 year or length of prescription.
8. Does the patient have a diagnosis of Parkinson's disease and experiences "off" episodes?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the patient currently taking levodopa/carbidopa?	**Yes:** Approve for the shorter of 1 year or length of prescription.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for the shorter of 1 year or length of prescription.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: *3/18 (JP); 7/16 ~~(DE)~~; 9/14; 9/13; 09/10*
Implementation: *TBD; 8/16, 1/1/14, 1/1/11*

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

New Drug Evaluation: Belimumab Injection, Intravenous and Subcutaneous

Date of Review: March 2018
Generic Name: Belimumab
PDL Class: Biologics for Autoimmune Conditions

End Date of Literature Search: 10/20/2017
Brand Name (Manufacturer): Benlysta® (GlaxoSmithKline)
Dossier Received: No

Research Questions:

1. What is the safety and effectiveness of belimumab in reducing symptoms and improving functional outcomes in patients with systemic lupus erythematosus (SLE)?
2. What are the comparative harms of belimumab in patients with SLE?
3. Are there certain sub-populations in which belimumab may be beneficial or cause more harm?

Conclusions:

- The composite SLE responder index (SRI) was developed by investigators after Phase 2 trials of belimumab failed to show a meaningful reduction in disease activity as assessed by the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score.[1] Consequently, the researchers developed the composite SRI in an effort to avoid relying on one single index to assess response to belimumab in Phase III trials. The composite SRI tool includes the SELENA-SLEDAI score to address global disease improvement, the British Isles Lupus Assessment Group (BILAG) score to assess organ specific disease worsening or improvement, and the Physician Global Assessment (PGA) tool for items that were not addressed by the other two indices.[1] The SRI was not validated prior to use in the belimumab Phase 3 trials, although it was used as the tool to assess primary efficacy of belimumab in these trials. The use of composite outcomes in the belimumab trials is problematic. The 3 assessments may have overstated the response to therapy, relied on subjective assessments and were inadequately reported. These issues may have led to an overstatement of how well belimumab alleviated symptoms of SLE in clinical trials.
- The efficacy of belimumab for intravenous (IV) administration was evaluated in 2 fair quality, Phase III, randomized controlled studies, BLISS-52 (n=865) and BLISS-76 (n=819), in adult patients with SLE.[2,3] The primary outcome measure was the composite SRI which only required 4 point improvement on a 100 point scale (SELENA-SLEDAI) and no worsening in the BILAG or PGA scores. Of note, the American College of Rheumatology (ACR) has defined minimum improvement on the SELENA-SLEDAI score as a 6 point increase and a 4 point change in this scale was used to assess response in the BLISS trials. In the BLISS-52 trial, the proportion of responders as assessed by the composite SRI, was significantly higher for intravenous belimumab groups than for placebo (44% responders) at 52 weeks (1 mg/kg; 51% responders; Odds Ratio (OR) 1.55; 95% CI 1.1 to 2.2; p = 0.013; ARR = 7%; NNT = 15) and (10 mg/kg; 58% responders, OR 1.8; 95% CI 1.3 to 2.6; p = 0.0006; ARR = 14%; NNT = 8).[2] In the BLISS-76 trial, there was a statistical difference in the percentage of participants achieving SLE response rate at 52 weeks in the belimumab 10 mg/kg group versus placebo (43.2% vs. 33.5%, OR 1.5; 95% CI

1.1 to 2.2; p=0.02; ARR = 9.7%; NNT = 11).[3] No significant difference between belimumab 1 mg/kg and placebo was observed at 52 weeks in the BLISS-76 trial. In the BLISS-76 trial, significance in SLE responder rates was not observed at 76 weeks for either belimumab group when compared to placebo. Six years after the publication the of the IV belimumab studies, the efficacy of subcutaneous (SC) belimumab was evaluated at doses of 200 mg once a week over 52 weeks compared to placebo in 816 subjects.[4] After 52 weeks, 61.4% of patients in the SC belimumab group had clinical improvement based on the SRI compared with 48.4% of participants in the placebo group (OR 1.68; 95% CI 1.25–2.25; p= 0.0006; ARR = 13%, NNT = 8).[4]

- The most common adverse reactions that occurred in greater than 5% of subjects who received belimumab intravenously during Phase II and III clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine and pharyngitis.[5] Discontinuation of belimumab therapy due to any adverse reaction was similar in the belimumab (6.2%) and placebo-treatment (7.1%) arms.[5] The most common reasons for discontinuation were infusion reactions, lupus nephritis and infections.[5] In the trials of belimumab SC, local injection site reactions were the most frequently reported adverse effects.[5]
- Patients with severe active lupus nephritis and central nervous system lupus were excluded from all belimumab trials. Belimumab in combination with other biologics or intravenous cyclophosphamide has not been studied in clinical trials. Therefore, the use of belimumab is not recommended in these situations.[5] There is insufficient evidence to assess the impact of belimumab therapy on reducing organ damage or mortality in SLE patients.

Recommendations:

- Designate belimumab as a non-preferred agent with prior authorization (PA) criteria on the on the Practitioner-Managed Prescription Drug Plan (PMPDP).

Background:

SLE is a complex autoimmune connective-tissue disorder that affects the skin, joints, kidneys, heart, lungs, nervous system, and blood vessels. The disease has a wide range of clinical symptoms characterized by unpredictable remissions and relapses. SLE predominately affects women aged 15 and 45 years with a female to male ratio of 9:1.[6] African Americans, Asian Americans, and Hispanics have about a 3 to 4 times higher frequency of lupus than white non-Hispanics and often have more severe disease.[7] Generalized symptoms include fever, fatigue, rash, oral ulceration, hair loss and arthralgia. The hallmarks of SLE include abnormal B lymphocyte function, chronic inflammation, and development of autoantibodies. The ACR developed classification criteria in 1982 to assist in diagnosis of SLE which was updated in 1997.[8] The Systemic Lupus International Collaborating Clinics (SLICC) group revised the ACR criteria in 2012 to improve clinical relevance and incorporate new knowledge regarding SLE.[9] Patients are classified as having SLE if: 1) they satisfy 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least one clinical criterion and one immunologic criterion or 2) if they have biopsy-proven nephritis compatible with SLE in the presence of ANA or anti-dsDNA antibodies.[9] Clinical and immunologic criteria from the SLICC classification are presented in **Table 1**.

Table 1. SLE classification criteria from the Systemic Lupus International Collaborating Clinics (SLICC) [9]

A. Clinical Criteria	B. Immunologic Criteria
Cutaneous Lupus (Acute or Chronic)	ANA level above laboratory reference range
Oral Ulcers	Anti-double stranded (ds)DNA antibody level above laboratory reference range
Alopecia	Anti-Sm antibody to Sm nuclear antigen
Synovitis involving 2 or more joints	Antiphospholipid antibody
Serositis (pleuritis or pericarditis)	Low complement (C3, C4, CH50)
Neurologic symptoms	Direct Coombs test in the absence of hemolytic anemia
Hemolytic anemia	
Leukopenia (<4,000/mm^3 at least once)	

Thrombocytopenia (<100,000/mm3at least once)	
Renal involvement with proteinuria or red blood cell casts	

In the U.S., about 35% of adults with SLE have clinical evidence of nephritis at the time of diagnosis, with an estimated total of 50–60% developing nephritis during the first 10 years of disease.[10] The prevalence of nephritis is significantly higher in African Americans and Hispanics than in whites, and is higher in men than in women.[10] Renal damage is more likely to develop in nonwhite groups. Overall survival in patients with SLE is approximately 95% at 5 years after diagnosis and 92% at 10 years after diagnosis.[11] The presence of lupus nephritis (LN) significantly reduces survival to approximately 88% at 10 years, with even lower survival in African Americans.[11] An ACR task force panel developed guidelines for screening, treatment and management of lupus nephritis in 2012.[12]

Clinical trials have used 3 validated scales to measure disease activity in SLE. The British Isles Lupus Assessment Group (BILAG) developed a disease activity index in 1984 which was updated in 2004.[13] There are 101 items within this index distributed over 9 organ systems (mucocutaneous, neurology, musculoskeletal, cardiorespiratory, vasculitis, renal, abdominal, ophthalmic, and hematology). Disease activity occurring over the past month is compared to the month before in each organ system. The BILAG index is evaluated on an ordinal scale ranging from 0 (symptoms not present), 1 (symptoms improving), 2 (same symptoms), 3 (worse symptoms) or 4 (new symptoms).[13] After recording the scores for each assessment into a computer program, the disease activity is categorized into 5 different levels from A through E which scores patients on the need for need for medication therapy. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of 20 mg daily or higher. Grade B represents moderate disease activity requiring a lower dose of systemic corticosteroids, topical corticosteroids, topical immunosuppressive drugs, antimalarials, or non-steroidal anti-inflammatory drugs (NSAIDs). Grade C indicates mild stable disease, while grade D implies no disease activity but the system had previously been affected and symptoms resolved. Grade E indicates no current or previous disease activity.[14] The maximum score on the BILAG index is 81. The Food and Drug Administration (FDA) has designated the BILAG index as its favored scale to measure SLE response in clinical trials.[15] A major clinical response is defined by the FDA guidance as a patient with BILAG C scores or better after 6 months of therapy with no BILAG A or B scores between 6 and 12 months.[15] Partial clinical response is defined as BILAG C score or better at 6 months with no new BILAG A or B scores and maintenance of response without flare for 4 months.[15]

The SLE Disease Activity Index (SLEDAI) was developed in 1985 through consensus of 15 lupus experts in Toronto and was updated in 2002.[16] It has 24 items for assessment of 9 systems: 16 items involve clinical assessment and 8 items are based on laboratory results such as blood complement levels, increased anti-DNA antibody levels, low platelets or low white blood cell count. Symptoms are recorded if they have been present over the past 10 days regardless of severity or whether the symptom has improved or deteriorated. Unlike the BILAG index, organ involvement is weighted by system: central nervous involvement is multiplied by 8 while joint pain and kidney disease are multiplied by 4. Scoring is based on whether manifestations are present or not present (in a range of 1 to 8) for each of the items. All the individual item scores are added to provide a global score, with a possible maximum score of 105.[16] According to ACR, a clinically meaningful difference in the SLEDAI has been reported to be improvement by 6 points or worsening by 8 points.[17] The SLEDAI was modified in The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial to the SELENA-SLEDAI system.[18] This modification added clarification to some of the definitions of disease activity, but did not change the basic scoring system.

The Physician Global Assessment (PGA) is a 10-centimeter visual analog scale (VAS) using a 4 point scale for assessment of disease activity over the previous 2 weeks.[19] No flare scores 0 points, mild flare scores 1.0 point, moderate flares score between 2.0 and 2.5 points and severe flares score a 3 on the 0–3 analog scale. An increase of at least 0.3 points (> 10% on the 3 point-VAS) from baseline is considered clinically significant worsening of disease.[19] **Table 2** compares the 3 different assessments used to confirm response to drug therapy in SLE clinical trials.

Table 2. Overview of Different SLE Disease Activity Indices[20]

	PGA	BILAG-2004	SELENA-SLEDAI
Number of Items	1	101	24
Number of Organ Systems	All	9	9
Total Score Range	0-3	0-81	0-105
Review Period	Current	30 days	10 days
Objective/Subjective	Subjective	Both	Objective
Weighted Variables	No	No	Yes
Organ Severity Assessment	No	Yes	Yes
Previous Versions	-	BILAG (1988)	SLEDAI (1992) and SLEDAI-2K (2000)
Advantages	Sensitive to patients overall condition	Organ specific severity score	Easy to apply in general practice
Disadvantages	Physician dependent; semi-quantitative	Time consuming; requires training	Only provides global severity score

Abbreviations: BILAG: British Isles Lupus Assessment Group; PGA: Physician Global Assessment; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index;

The composite Systemic Lupus Erythematosus Responder Index (SRI) was developed based on an exploratory analysis of belimumab in a dose-ranging, phase 2 trial.[21] In this trial, belimumab failed to show a meaningful reduction in disease activity as assessed by the SELENA-SLEDAI score or prevent flares relative to placebo at 24 weeks.[1] Consequently, the researchers developed the composite SRI in an effort to avoid relying on one single index to assess response to SLE therapy in Phase 3 trials. According to the investigators, the intent was to capture clinically meaningful change in response to therapy and insure there would not be significant worsening in overall disease activity.[21] Using the SRI, a responder is defined as having the following response to therapy : 1) at least a 4-point reduction in SELENA-SLEDAI score; 2) no worsening in the BILAG score; and 3) no deterioration from baseline in the PGA score by 0.3 or more points.[21] According to the investigators, in the composite SRI tool the SELENA-SLEDAI score addresses global disease improvement, the BILAG assessment covers organ specific disease worsening, and PGA is used as a safety net for items that were not addressed by the other two indices.[21] The SRI was not validated before it was used in the Phase 3 safety and efficacy belimumab trials. The use of composite outcomes in the belimumab trials is problematic. The 3 assessments overstate the response to therapy, consist of subjective assessments and were inadequately reported. These problems may have led to an overstatement of how well belimumab reduced SLE disease activity in clinical trials.

The goal of SLE treatment is to control the inflammatory reaction and organ damage while minimizing the adverse effects of the treatments. Treatments range from anti-malarial drugs (e.g., hydroxychloroquine), systemic corticosteroids and immunosuppressive agents (e.g., azathioprine, cyclophosphamide). Intravenous administration of belimumab, a monoclonal antibody with activity against B-lymphocytes, was approved by the FDA to manage adult SLE patients with active, autoantibody-positive disease in conjunction with standard of care in 2011. A subcutaneous formulation belimumab was FDA approved in adults for the same indication in 2017. Belimumab has not been studied as a solo agent in treating SLE, nor has it been studied in combination with other biologic agents such as rituximab or cyclophosphamide. Efficacy of belimumab has not been evaluated in patients with severe active lupus nephritis or severe active CNS lupus.

Fee for Service Utilization

As of January 2017 there were no fee for service (FFS) claims for belimumab SC at any Oregon pharmacies. There was one single CCO claim in October 2017. There were no medical claims in 2017 for the IV formulation of belimumab.

Clinical Guidelines: National Institute for Health and Care Excellence (NICE)

NICE published guidance regarding the use of belimumab as an IV infusion for treating active autoantibody-positive SLE in June 2016.[22] For assessment of symptom improvement, NICE adopted similar metrics that were used in the BLISS trials (SELENA-SLEDAI improvement by 4 points or more) instead of the ACR recommendations of improvement in SELENA-SLEDAI greater than 6 points or more. Belimumab is recommended as an option as add-on treatment for active autoantibody-positive SLE in adults only if all of the following apply:

- There is evidence for serological disease activity (defined as positive anti-double stranded DNA and low complement) and a SELENA-SLEDAI score of greater than or equal to 10 despite standard treatment.[22]
- Treatment with belimumab is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more.[22]

As a condition of these recommendations, the committee recommended re-evaluation in 3 years and that efficacy assessments include:

- clinical response measured by BILAG Index and SLEDAI scoring[22]
- organ damage accrual using the SLICC Damage Index and BILAG Index[22]
- use of corticosteroids[22]

NEW DRUG EVALUATION: Belimumab

See **Appendix 1** for **Highlights of Prescribing Information** of belimumab from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The first biologic agent FDA approved for management of SLE is belimumab, a human monoclonal antibody which binds to the soluble form of B-lymphocyte stimulator (BLyS) and inhibits its biologic activity. BLyS is overexpressed in patients with SLE and its concentrations correlate with disease activity and antibody titers.[23] The binding of BLyS with belimumab results in reduced numbers of circulating B-lymphocytes and a reduction in antibody titers in SLE patients.[23]

The safety and efficacy of belimumab for IV administration was evaluated in 2 Phase 3, randomized controlled studies, BLISS-52 (n=865) and BLISS-76 (n=819), in adult patients with SLE. All patients received standard of care treatment with corticosteroids, antimalarials, NSAIDs, and immunosuppressive agents (azathioprine, methotrexate, and mycophenolate) in combination with either belimumab or placebo. Both studies were multi-center, placebo-controlled, double-blinded trials. The studies excluded patients who had received prior B-cell targeted therapy or IV cyclophosphamide, as well as those with active lupus involving the kidneys or central nervous system. Both studies were conducted in a similar fashion, but on different geographic populations with some baseline demographic differences. BLISS-52 was conducted in Eastern Europe, Latin America and Asia-Pacific regions over 52 weeks. BLISS-76 was conducted in North America, Western Europe and Latin America over 76 weeks. The 2 studies randomly assigned a total of 1,684 patients with auto antibody-positive, active disease (defined as a SELENA-SLEDAI score ≥6) to receive IV belimumab 1 mg/kg or 10 mg/kg plus standard therapy or placebo plus standard therapy in a 1:1:1 ratio. The primary outcome was the proportion of patients who responded to therapy as assessed by the composite SRI at week 52. In both trials, at week 52 more patients treated with belimumab 10 mg/kg met the SRI criteria for improvement in disease activity when compared to placebo-treated patients. In BLISS-52 the response rates were 57.6% (belimumab 10 mg/kg) versus 43.6% (placebo) [OR 1.8; 95% CI 1.3 to 2.6; p=0.0006] and in BLISS-76 the response rates were 43.2% for belimumab 10mg/kg and 33.5% for placebo [OR 1.5; 95% CI 1.1 to 2.2; p=0.02].[24,25] There was no significant difference detected in disease response between belimumab 1 mg/kg and placebo in the BLISS-76 trial at week 52. However, a difference was detected in BLISS-52 between belimumab 1 mg/kg and placebo at week 52 (51.4% vs. 43.6% respectively; OR 1.6; 95% CI 1.1 to 2.2; p= 0.013).[2] At week 76 in the BLISS-76 trial, the differences between doses of belimumab 1mg/kg or 10mg/kg compared to the placebo arm were not statistically significant.[25] Reasons for this finding are unclear although compared to BLISS-52, the patients in BLISS-76 were older, had a longer duration of SLE, and a higher proportion of patients were white and using prednisone greater than 7.5mg per day at baseline. One suggestion is that patients with longer, more established disease, such as those found in the BLISS-76 trial, may be less responsive to belimumab over time.[25] Based on these trial results, the FDA approved belimumab dosing as 10mg/kg via IV infusion at 2 week intervals for the first 3 doses followed by every 4 weeks thereafter.[5]

The efficacy of SC belimumab was evaluated at doses of 200 mg once a week which yielded target plasma concentrations similar to administration of belimumab 10mg/kg IV every 4 weeks.[4] This clinical trial was conducted over 52 weeks at 177 sites in North, Central and South America, Europe, Australia and Asia. Seventy percent of the sites were based outside of the U.S. A total of 816 patients were randomized 2:1 to SC belimumab (n = 544) or placebo (n=272) in adults with active SLE continuing standard therapy. The inclusion criteria for this study required a SELENA–SLEDAI score of 8 or higher at screening, whereas the IV BLISS-52 and BLISS-76 studies required a SELENA–SLEDAI score of 6 or higher. This requirement for a higher SELENA–SLEDAI was driven by data from the IV studies that highlighted that patients needed a higher level of disease activity at baseline in order to have the opportunity to achieve the 4-point reduction on the 100 point SELENA–SLEDAI scale needed to meet the SRI end point.[4] Patients with severe kidney disease or CNS lupus were excluded. The primary endpoint was the composite SRI response rate at week 52, which was a weak definition of response as previously described. More patients who received SC belimumab 200 mg once a week were SRI responders at week 52 than those who received placebo ([61.4% versus 48.4% respectively; OR 1.68; 95% CI 1.25–2.25]; p=0.0006; NNT =

8).[4] A secondary endpoint was the number of patients with reduction in corticosteroid dosage. No statistical difference could be found in the number of patients able to reduce their corticosteroid dosage by more than 25% (to less than 7.5mg per day) during weeks 40 through 52 with belimumab compared to placebo (18.2% versus 11.9% respectively; OR 1.65; 95% CI 0.95–2.84; p = 0.0732).[4]

Limitations

Efficacy of belimumab has not been studied in patients with severe active lupus nephritis or severe active CNS lupus. Belimumab has not been studied as monotherapy in treatment of SLE, nor has it been studied in combination with other biologics or IV cyclophosphamide. Therefore, the use of belimumab is not recommended in these situations.[5] Some fluctuations in background standard of care therapy was allowed during the belimumab IV infusion trials which may have created some imbalance between groups. Prednisone could be increased during the first 24 weeks and immunosuppressive therapy could be increased during the first 16 weeks of study. After that, doses needed to be close to baseline doses. However prednisone taper was encouraged if possible, possibly resulting in a known imbalance with more belimumab-treated patients achieving a steroid sparing endpoint.[26] Use of immunosuppressive drugs was not similar across geographical regions in BLISS-52. Use of antimalarial drugs was less in eastern Europe (54%) compared to Latin America (69%) and Asia-Pacific regions (69%).[26] High dose prednisone (>7.4 mg/day) was greater in Latin America (73%) compared to Asia-Pacific regions (60%).[26] The range of corticosteroid use permitted at baseline varied widely from 0 to 40 mg per day. Use of rescue medications for infusion-related reactions was not mentioned or defined. Patients were removed from the trial and considered non-responders if they started a prohibited medication (e.g., angiotensin converting enzyme-inhibitor, angiotensin receptor blocker, or statin). Starting a prohibited medication occurred more frequently in the placebo arm compared to treatment arm during BLISS-52 (17% placebo vs. 9% 1mg/kg vs. 10% 10 mg/kg) and BLISS-76 (11% placebo vs. 7% 1mg/kg vs. 6% 10mg/kg).[26] Imputing these withdrawn patients as efficacy failures could bias the treatment effect in the primary efficacy endpoint in favor of belimumab.[26] Finally, the composite primary endpoint of SRI not previously used in clinical trials is problematic. The 3 assessments overstated the response to therapy, consisted of subjective assessments and were inadequately reported. These issues may have led to an overstatement of how well belimumab alleviated symptoms of SLE in clinical trials.

Clinical Safety:

The most common adverse reactions that occurred in greater than 5% of subjects who received IV belimumab during Phase 2 and 3 clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine and pharyngitis.[5] Discontinuation of belimumab therapy due to any adverse reaction was 6.2% versus 7.1% in the belimumab and placebo arms respectively.[5] The most common reasons for discontinuation were infusion reactions, lupus nephritis and infections. The most common infusion reactions (> 3%) noted in patients receiving belimumab included headache, nausea and skin reactions.[5] Adverse events occurring on the same day of the infusion were reported in 17% (251/1458) and 15% (99/675) of patients receiving belimumab and placebo, respectively.[5] Serious infusion reactions (except hypersensitivity reactions) were reported in 0.5% vs. 0.4% in the belimumab and placebo arms, respectively.[5] Serious reactions included bradycardia, myalgia, headache, rash, urticaria and hypotension.

In the SC belimumab trial, 449 patients in the belimumab group (80.8%) and 236 patients in the placebo group (84.3%) experienced at least 1 adverse effect.[4] The most frequent adverse events were infections and infestations (55.4% belimumab vs 56.8% placebo); gastrointestinal disorders (22.5% belimumab vs 24.3% placebo); musculoskeletal and connective tissue disorders (22.3% belimumab vs 23.6% placebo); nervous system disorders (20.0% belimumab vs 18.9% placebo) and skin and subcutaneous disorders (14.4% belimumab vs 21.4% placebo).[4] Serious adverse events were reported for 10.8% of belimumab patients and 15.7% of placebo patients.[4] Serious adverse events included infections and infestations, renal and urinary disorders, and nervous system disorders. Treatment-related adverse effects were reported for 31.1% of the belimumab patients and 26.1% of the placebo patients.[4] Local injection site reactions occurred in 34 patients in the belimumab group (6.1%) and 7 patients in the placebo group (2.5%).[4] All local injection site reactions were mild or moderate in severity, and no serious or severe injection site reactions were reported. The incidence of hypersensitivity reactions was similar between treatment groups. Three deaths were reported in

the belimumab group (0.5%) and 2 were reported in the placebo group (0.7%).[4] Fifteen patients in the belimumab group (2.7%) and 10 patients in the placebo group (3.6%) experienced depression; none of these episodes were serious.[4]

Look-alike / Sound-alike Error Risk Potential:
Generic name (belimumab): basilixumab, bevacizumab, belatacept
Brand name (Benlysta): Evista, Benylin, Bentyl, Bendamustine

Table 3. Pharmacology and Pharmacokinetic Properties after IV infusion of belimumab 10mg/kg

Parameter	
Mechanism of Action	Binds to soluble human BLyS which results in decreased numbers of B-lymphocytes
Distribution	Volume of Distribution: 5.29 liters
Clearance	215 ml/day
Half-Life	19.4 hours

Abbreviations: BLyS = B-lymphocyte stimulator; ml = milliliters

Comparative Clinical Efficacy:

1) Symptom and disease activity control
2) Prevention of complications
3) Mortality
4) Quality of Life
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1). Improvement in SRI at week 52

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. Navarra et al[24] (BLISS-52) Phase 3 RCT, DB, PC, PG, MC in Latin America (50%), Asia-Pacific (38%) and eastern Europe (13%)	1. Belimumab 1 mg/kg IV 2. Belimumab 10 mg/kg IV 3. Placebo IV Drug or placebo administered on Days 0, 14 and 28	Demographics: -Mean age: 35.5 y -Female: 95% -White: 27% -Asian: 42% -Mean SELENA-SLEDAI score ≥10: 48-55% -Disease duration: 5 y -Prednisone >7.5 mg/d: 46%	ITT: 1.288 2.290 3.287 PP: 1.240 2.241 3.226	Primary Endpoint: Proportion of patients with improvement in composite SRI at week 52: 1. 148 (51%) OR 1.55; 95% CI 1.10 to 2.19; p=0.0129 vs 3 2. 167 (58%) OR 1.83; 95% CI 1.30 to 2.59; p=0.0006 vs 3 3. 125 (44%)	7%/15 14%/8	AE: 1.264 (92%) 2.266 (92%) 3.263 (92%) SAE: 1.47 (16%) 2.41 (14%) 3.36 (13%) Discontinuation due to SAE:	NA NA NA	**Trial Quality: Fair** **Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Central IVRS assigned 1:1:1 ratio, stratified according to SELENA-SLEDAI score (6-9 vs ≥10), extent of proteinuria, and ethnic origin. Baseline characteristics similar across groups. Performance Bias: UNCLEAR: Blinding strategy not discussed. Standard of care regimen may have had some regional variability – prednisone doses were tapered based on provider clinical judgement. Use of high dose

	and then every 28 days for 48 weeks in combination with SOC therapy. There were also restrictions to standard care, including that the prednisone dose return to within 25% or 5 mg greater than the baseline dose at 24 weeks and for the remainder of the study, and that the addition of a new immunosuppressive or biological drug at any time or a new antimalarial after 4 months was prohibited.	<u>Key Inclusion Criteria</u>: -Age ≥18 y -Active SLE (≥6 on SELENA-SLEDAI) -Positive ANA titer (≥1:80) -Stable regimen of prednisone (0-40mg/day) or NSAID, antimalarial or immunosuppressive drug for ≥30 days <u>Key Exclusion Criteria</u>: -Active lupus nephritis or CNS lupus -Pregnancy -Prior treatment with B-lymphocyte targeted drug -IV cyclophosphamide within 6 months -IVIG or prednisone > 100 mg/day within 3 months	<u>Attrition</u>: 1. 48 (16.6%) 2. 49 (16.8%) 3. 61 (21.3%)	<u>Secondary Endpoints</u>: 1. ≥4-point reduction in SELENA-SLEDAI score at week 52: 1. 153 (53%) OR 1.51; 95% CI 1.07 to 2.14; p=0.0189 vs 3 2. 169 (58%) OR 1.71; 95% CI, 1.21 to 2.41; p=0.0024 vs 3 3. 132 (46%) 2. No worsening BILAG at week 52: 1. 226 (78%) OR 1.38; 95% CI 0.93 to 2.04; p=0.1064 vs 3 2. 236 (81%) OR 1.62; 95% CI, 1.09 to 2.42; p=0.0181 vs 3 3. 210 (73%) 3.No worsening in PGA at week 52: 1. 227 (79%) OR 1.68; 95% CI 1.15 to 2.47; p=0.0078 vs 3 2. 231 (80%) OR 1.74; 95% CI 1.18 to 2.55; p=0.0048 vs 3 3. 199 (69%)	7%/15 12%/9 NS 8%/13 10%/10 11%/9	1.16 (6%) 2.15 (5%) 3.19 (7%) Deaths: 1.2 (< 1%) 2.4 (1%) 3.3 (1%) Infection: 1.197 (68%) 2.194 (67%) 3.183(64%) Infusion Reactions: 1.47 (16%) 2.48 (17%) 3.49 (17%)	NA NA NA	prednisone (>7.5mg/day) was higher in Latin America. <u>Detection Bias</u>: LOW: Patients, investigators, study coordinators, and sponsors masked to treatment assignment. Pharmacists that prepared study drug were not blinded to trial assignments. <u>Attrition Bias</u>: UNCLEAR. Higher attrition rate in placebo arm vs drug arms (21% vs 17%). Patients that withdrew or required med changes not per protocol were considered treatment failures in the analysis. <u>Reporting Bias</u>: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline. GSK also assisted in drafting the article and interpreting data. **Applicability**: <u>Patient</u>: Narrow inclusion criteria (serologically active SLE, no severe disease, 1/3 on low dose prednisone) limits generalization to sicker patients: 50% of patients had SELENA-SLEDAI scores ≥ 10. Most of the patients were Asian, limiting applicability to other races, in particular, people of African descent. <u>Intervention</u>: Belimumab 1 mg/kg compared to 10mg/kg and placebo at all sites. Use of immunosuppressive drugs was not similar across regions. Use of antimalarial drugs was less in eastern Europe (54%) vs Latin America (69%) and Asia-Pacific (69%). High dose prednisone (>7.4 mg/day) was greater in Latin America (73 %) vs Asia-Pacific (60%). <u>Comparator</u>: Placebo appropriate to determine efficacy on background SOC. <u>Outcomes</u>: The choice of a reduction from the baseline score ≥ 4 points on the SELENA-SLEDAI was chosen as clinically relevant, whereas a minimum of 6 points had been defined as such by an ACR expert panel.

								Setting: 90 centers in 13 countries: Latin America (50%), Asia-Pacific (38%), and eastern Europe (13%).
2. Furie et al[25] (BLISS-76) Phase 3 RCT, DB, PC, PG, MC Conducted at 136 centers located in 19 countries in North America (53%) and Europe (36%) and Latin America (11%)	1. Belimumab 1 mg/kg IV 2. Belimumab 10 mg/kg IV 3. Placebo IV Administered on days 0,14 and 28 and then every 28 days for 76 weeks	Demographics: -Mean age: 40 y -Female: 94% -White: 65% -Mean SELENA-SLEDAI score ≥10: 50% -Disease duration: 7.5 y -Prednisone dose > 7.5 mg/day: 69% Key Inclusion Criteria: -Age ≥18 y -SLE w/ SELENA-SLEDAI score ≥6 -Positive ANA -Stable regimen of prednisone (0-40mg/day) or NSAID, antimalarial or immunosuppressive drug for ≥30 days prior to study -Stable regimen of ACE-I, ARB, or statin 3≥30 days Key Exclusion Criteria: -Active lupus nephritis or CNS lupus -Pregnancy -Prior treatment with B-lymphocyte targeted drug (rituximab)	ITT: 1. 271 2. 273 3. 275 PP: 1. 199 2. 191 3. 186 Attrition: 1. 72 (26%) 2. 82 (30%) 3. 89 (32%)	Primary Endpoint: SRI Response Rate at week 52: 1. 110 (40.6%) OR 1.34; 95% CI 0.94 to 1.91; p=0.1041 2. 118 (43.2%) OR 1.52; 95% CI 1.07 to 2.15; p=0.0207 3. 92 (33.5%) Secondary Endpoints: 1. ≥4-point reduction in SELENA-SLEDAI score at week 52: 1. 116 (42.8%) OR 1.36 (95% CI 0.96 to 1.93; p=0.869) 2. 127 (46.5%) OR 1.63 (95% CI 1.15 to 2.32; p=0.0062) 3. 97 (35.3%) 2. No worsening in BILAG at week 52: 1. 203 (74.9%) OR 1.63 (95% CI 1.12 to 2.37; p=0.0108) 2. 189 (69.2%) OR 1.20 (95% CI 0.92 to 1.90; p=0.3193) 3. 180 (65.5%) 2.No worsening in PGA at week 52 compared to placebo 1. 197 (72.7%) OR 1.6 (95% CI 1.11 to 2.30; p=0.0120) 2. 190 (69.6%) OR 1.32 (95% CI 0.92 to 1.90; p=0.1258)	 NS 10%/10 NS 11%/9 9%/11 NS 10%/10 NS	AE: 1. 202 (74.5%) 2. 202 (74%) 3. 190 (69.1%) SAE: 1.51 (18.8%) 2.54 (19.8%) 3.52 (18.9%) Discontinuation due to SAE: 1.18 (6.6%) 2.23 (8.4%) 3.23 (8.4%) Deaths: 1.2 (< 1%) 2.1 (< 1%) 3.0 Infection: 1.202 (74.5%) 2.202 (74%) 3.190(69.1%) Infusion Reactions: 1.42 (15.5%) 2.37 (13.6%) 3.27 (9.8%)	NA NA NA NA NA NA	**Trial Quality: Fair** **Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Random assignment 1:1:1 via IVRS. Stratified by according to SELENA-SLEDAI score (6-9 vs ≥10), proteinuria (< 2 gm vs ≥2gm/24hrs), and ethnic origin. Baseline characteristics similar across groups. Performance Bias: UNCLEAR: methods of blinding not described. Standard of care regimen may have had some regional variability. Detection Bias: LOW: Patients, investigators, study coordinators, and sponsors masked to treatment assignment. Pharmacists that prepared study drug were not blinded to trial assignments. Attrition Bias: HIGH. High attrition rate (> 26% for all 3 arms). Patients who withdrew or had changes in concomitant medications restricted by protocol were considered treatment failures and last observation was carried forward for imputation. Reporting Bias: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline. **Applicability**: Patient: Narrow inclusion criteria Intervention: Belimumab 1 mg/kg not approved by FDA. Efficacy established with 10 mg/kg. Comparator: Placebo appropriate to establish efficacy Outcomes: The choice of a reduction from the baseline score ≥ 4 points on the SELENA-SLEDAI was chosen as clinically relevant, whereas a minimum of 6 points had been defined as such by an ACR expert panel. Setting: Primarily in North America (53%), Europe (36%) and Latin America (11%)

		-Prior treatment with IV cyclophosphamide -Prior treatment with IVIG or prednisone > 100 mg/day -New start of ACE-I, ARB or statin within 60 days		3. 173 (62.9%) SRI response rate at week 76: 1. 106 (39.1%) OR 1.34 (95% CI 0.94 to 1.91; p=0.1050) 2. 105 (38.5%) OR 1.31 (95% CI 0.92 to 1.87; p=0.1323) 3. 89 (32.4%)	 NS NS			
3.Stohl et al[4] (BLISS-SC) RCT, DB, PC, MC. Conducted in 177 sites in 30 countries in Central and South America 20%), Eastern Europe (21%), Asia (22%); Australia/Western Europe/Israel (7%), United States (30%).	1.Belimumab 200 mg SC once weekly 2.Placebo once weekly In addition to SOC over 52 weeks	<u>Demographics:</u> -Mean age: 39 years -Female 94% -Hispanic or Latino: 29% -Mean SELENA-SLEDAI score ≥10: 60% -Mean PGA: 1.5 -Disease duration: 4 years <u>Key Inclusion Criteria:</u> -Age ≥18 y -SLE (SELENA-SLEDAI score ≥8 -Stable SLE medication regimen 30 days prior to study enrollment <u>Key Exclusion Criteria:</u> -Active lupus nephritis or CNS lupus	<u>ITT:</u> 1.556 2.280 <u>PP:</u> 1. 463 2. 214 <u>Attrition:</u> 1. 93 (16.7%) 2. 66 (23.6%)	<u>Primary Endpoint:</u> SRI response rate at week 52 1. 61.4% 2. 48.4% OR 1.68 (95% CI 1.25 to 2.25; p=0.0006) <u>Secondary Endpoint:</u> Number of patients with reduction in corticosteroid dosage at weeks 40-52: 1. 18.2% 2. 11.9% OR 1.65 (95% CI 0.95 to 2.84; p=0.07)	 13%/8 NS	AE: 1. 449 (80.8%) 2. 236 (84.3%) SAE: 1. 60 (10.8%) 2. 44 (15.7%) Discontinuation due to SAE: 1. 40 (7.2%) 2. 25 (8.9%)	NA NA NA	**Trial Quality: Poor** Risk of Bias (low/high/unclear): <u>Selection Bias</u>: UNCLEAR. Randomized 2:1, not clear how randomization was completed. Subjects stratified according to SELENA-SLEDAI score, complement level, and race. <u>Performance Bias</u>: UNCLEAR. Not clear how investigators were blinded and if protocol was standardized. <u>Detection Bias</u>: UNCLEAR. Blinding of outcome assessors was by the GSK physicians. <u>Attrition Bias</u>: HIGH. Higher attrition rate in placebo arm vs drug arms (23.6% vs 16.7%) <u>Reporting Bias</u>: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline Applicability: <u>Patient</u>: Patients had more severe disease as assessed by SELENA-SLEDAI score ≥ 8 than BLISS trials (≥ 6). <u>Intervention</u>: 200 mg once per week selected to achieve AUC similar to 10 mg/kg IV every 4 weeks <u>Comparator</u>: Placebo <u>Outcomes</u>: Composite SRI index with limitation as noted above <u>Setting</u>: 177 sites in 30 countries including: Central and South America (20%), Eastern Europe (21%), and Asia (22%). Western Europe, Australia and Israel (7%). 30% of the sites were in the United States.

Abbreviations: ACE-I = angiotensin converting enzyme inhibitors; ACR = American College of Rheumatology; AE =Adverse Event; ANA = antinuclear antibody; ARB = angiotensin receptor blocker; ARR = absolute risk reduction; BILAG = British Isles Lupus Assessment Group; CI = confidence interval; Double Blind = DB; ITT = intention to treat; IV = intravenous; IVIG = intravenous immunoglobulin IVRS = interactive voice response system; MC = Multi-Center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OR = Odds Ratio; PG = Parallel Group; PC = Placebo controlled; PGA = Physician's Global Assessment; PP = per protocol; RCT = Randomized Controlled Trial; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SAE = Serious Adverse Event; SC = subcutaneous; SLE = Systemic Lupus Erythematosus; SOC = standard of care; SRI = Systemic Lupus Erythematosus Responder Index

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Appendix 1: Prescribing Information Highlights

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

BENLYSTA (belimumab) for injection, for intravenous use
BENLYSTA (belimumab) injection, for subcutaneous use

Initial U.S. Approval: 2011

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

Dosage and Administration, Subcutaneous Dosing Instructions (2, 2.2)	07/2017
Warnings and Precautions (5)	07/2017

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

BENLYSTA is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. (1)

Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations. (1)

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

Intravenous Administration
- 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute, and administer as an intravenous infusion over a period of 1 hour. (2.1)
- Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions. (2.1)

Subcutaneous Administration
- 200 mg once weekly. (2.2)

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

Intravenous Infusion
For Injection: 120 mg or 400 mg lyophilized powder in single-dose vials for reconstitution and dilution prior to intravenous infusion. (3)
Subcutaneous Injection
Injection: 200 mg/mL single-dose prefilled autoinjector or single-dose prefilled syringe. (3)

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

Previous anaphylaxis to belimumab. (4)

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

- Mortality: There were more deaths reported with BENLYSTA than with placebo during the controlled period of clinical trials. (5.1)
- Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Use with caution in patients with severe or chronic infections. Consider interrupting therapy with BENLYSTA if patients develop a new infection during treatment with BENLYSTA. (5.2)
- Progressive Multifocal Leukoencephalopathy (PML): Patients presenting with new-onset or deteriorating neurological signs and symptoms should be evaluated for PML by an appropriate specialist. If PML is confirmed, consider discontinuation of immunosuppressant therapy, including BENLYSTA. (5.2)
- Hypersensitivity Reactions, including Anaphylaxis: Serious and fatal reactions have been reported. BENLYSTA for intravenous use should be administered by healthcare providers prepared to manage anaphylaxis. Monitor patients during and for an appropriate period of time after intravenous administration of BENLYSTA. (2.1, 5.3)
- Depression: Depression and suicidality have been reported in trials with BENLYSTA. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes. (5.5)
- Immunization: Live vaccines should not be given concurrently with BENLYSTA. (5.7)

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

- Common adverse reactions (≥5%): nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, and injection site reactions (subcutaneous administration). (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-877-423-6597 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2017

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:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. 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:** Approve for 6 months**.**

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 condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *3/18 (DM)*
Implementation: *TBD*

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

Drug Class Update with New Drug Evaluation: Fluoroquinolones

Date of Review: March 2018
Generic Name: delafloxacin

End Date of Literature Search: 12/30/2017
Brand Name (Manufacturer): Baxdela™
Dossier Received: yes

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

Purpose for Class Update:
The purpose of this class update is to review new comparative evidence for efficacy and safety of oral fluoroquinolones (FQs) and to evaluate the evidence and place in therapy of the recently approved fluoroquinolone, delafloxacin.

Research Questions:
1. Is there new comparative evidence that oral fluoroquinolones differ in efficacy/effectiveness in the clinical cure of acute bacterial infections?
2. Is there new comparative evidence that oral FQs differ in serious adverse events or tolerability when used to manage acute bacterial infections?
3. Are there specific subpopulations for which one oral fluoroquinolone is more effective or better tolerated than other FQs?

Conclusions:
- There is no new moderate or high-quality comparative evidence that suggests of a difference in effectiveness of FQs to susceptible bacterial pathogens.
- There is insufficient evidence to determine if one FQ antibiotic is more effective or safer than other antibiotics in the treatment of diabetic foot infections.
- FQs should be reserved for serious infections requiring broad-spectrum coverage. Due to potential side effects (tendinitis and tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system), FQs should be avoided as first-line treatment for uncomplicated infections.
- There is low quality evidence that delafloxacin is noninferior to vancomycin plus aztreonam in clinical response of acute bacterial skin and skin structure infections (ABSSSIs) based on two noninferior trials with high risk of bias and low applicability.
- Delafloxacin is the first FQ with activity against methicillin resistant *Staphylococcus aureus (*MRSA) and should be reserved for serious infections requiring braod spectrum antibiotics.

Recommendations:
- Continue to maintain at least one FQ with broad coverage of gram-negative bacteria and at least one 'respiratory' FQ as preferred options.
- Review comparative drug costs in executive session.

Previous Conclusions:

- Moderate quality evidence continues to support previous conclusions that there is no difference in effectiveness of fluoroquinolones (FQs) to susceptible bacteria.
- Low quality evidence suggests there may be some differences in harms between FQs. In particular, ofloxacin may be associated with highest risk of tendon injury while levofloxacin may be associated with least risk. Levofloxacin may be associated with higher risk of hyperglycemia or hypoglycemia and moxifloxacin may be associated with no risk for dysglycemia. Ciprofloxacin and levofloxacin appear to have little risk for QT-interval prolongation relative to other FQs. Levofloxacin may be associated with the least risk for neurotoxicity-related adverse events. All FQs are associated with Clostridium difficile infection and there does not appear to be any differences in risk among this class.

Previous Recommendations:

- Continue to maintain at least one FQ with broad coverage of gram-negative bacteria (ciprofloxacin, levofloxacin) and at least one "respiratory" third-generation FQ (gemifloxacin, levofloxacin, moxifloxacin).

Background:

Fluoroquinolones antibiotics interfere with bacterial DNA synthesis by inhibiting topoisomerase II (DNA gyrase) in gram-negative organisms and topoisomerase IV in gram-positive organisms.[1] Fluoroquinolones are bactericidal and exhibit post-antibiotic effects of inhibition of bacterial growth even after the plasma concentration falls below the minimum inhibitory concentration (MIC). They have good oral bioavailability and penetrate most body tissues. Other than moxifloxacin, the FQs are eliminated through the kidneys via active tubular secretion.[1] FQs have a broad spectrum of activity, including against *Pseudomonas aeruginosa* and *Staphylococci*. FQs are classified by generation based on their antimicrobial spectrum of activity and intended use (Table 1). Due to the broad-spectrum activity of FQs, there is widespread incentive to preserve the efficacy of these drugs by reserving them as second-line when narrow-spectrum antibiotics can be utilized first. Resistance to FQs is also increasing rapidly and is considered a major concern in the clinical setting.[2]

Table 1: Characteristics of Fluoroquinolones by Generation[3]

Generation	Agents	Spectrum of Activity	Indications
First Generation	Nalidixic acid	*Enterobacteriaceae*	Not used for systemic infections, uncomplicated UTI only
Second Generation	Norfloxacin, ofloxacin, ciprofloxacin	*Enterobacteriaceae*, atypical pathogens, *P. aeruginosa* (Cipro only), *Pneumococci*	UTI, gastroenteritis, prostatitis, nosocomial infections, STDs
Third Generation	Levofloxacin	*Enterobacteriaceae*, atypical pathogens, *Streptococci*, *Pneumoccoci*	UTI, gastroenteritis, prostatitis, nosocomial infections, STDs, community acquired pneumonia
Fourth Generation	Moxifloxacin, gemifloxacin	*Enterobacteriaceae*, *P. aeruginosa*, atypical pathogens, MSSA, *Streptococc*i, anaerobes, *Pneumoccoci*	UTI, gastroenteritis, prostatitis, nosocomial infections, STDs, community acquired pneumonia, intra-abdominal infections
Abbreviations: MSSA = methicillin-susceptible *Staphylococcus aureus;* UTI: urinary tract infection; STD: sexually transmitted disease			

Delafloxacin is a recently approved FQ, which has shown good *in vitro* and *in vivo* activity against major pathogens associated with community acquired pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI). It has been studied in both infections, but is currently only approved for ABSSSI.[4] It also shows good activity against a broad spectrum of microorganisms, including Gram-positive, Gram-negative, atypical and anaerobic organisms. Delafloxacin is the first FQ with activity against methicillin resistant *Staphylococcus aureus (*MRSA). It is available in oral and intravenous (IV) formulations.

ABSSSIs are classified as simple or complicated, purulent or nonpurulent, and can involve the skin, subcutaneous fat, fascial layers and musculotendinous tissues.[5] Current guidelines from the Infectious Disease Society of America (IDSA) recommend treatment with antibiotics based on severity, location, presence of purulence, and degree of systemic signs of infection.[6] While most community-acquired cases are caused by *S. aureus* and *Streptococci*, gram negative bacteria (*Enterococcus*, *E. coli, P. aeruginosa)* are often localized from diabetic lower limb infections and necrotizing infections which can be polymicrobial and involve anaerobes. In the IDSA guidelines, FQs are specifically recommended for the following: 1) in combination with metronidazole for surgical site infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract; and 2) treatment of necrotizing infection of the skin, fascia and muscle.[6] In less severe skin and soft tissue infections (SSTI), narrow-spectrum agents are recommended to target appropriate bacterial pathogens.

The FDA guidance defines ABSSSI types that can be enrolled in ABSSSI trials as a bacterial infection of the skin with a lesion size of at least 75 cm^2 and includes cellulitis/erysipelas, wound infection, and major cutaneous abscess.[7] The ABSSSI indications excludes deeper infections such as necrotizing infections, ulcerations and diabetic foot infections. Outcomes of interest in the treatment of ABSSSI include ABSSSI-related mortality, clinical cure (resolution of symptoms and signs) and microbiological cure, or eradication of bacteria.

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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

Systematic Reviews:

A systematic review from Cochrane Collaboration was performed to determine the efficacy and safety of systemic antibiotics in the treatment of diabetic foot infections.[8] It is unknown whether one antibiotic treatment, including FQs, is more effective or safer than another antibiotic regimen for the treatment of diabetic foot infections due to heterogeneous data of clinical trials with unclear or high risk of bias due to industry funding, unclear allocation concealment, and high risk of detection bias.

Two additional systematic reviews[9,10] were identified and excluded due to poor quality evidence, high heterogeneity, and wrong study design of trials included. In one of these reviews, the investigators found the data insufficient to make strong conclusions on the absolute risk of arrhythmias with FQs.[10]

New Guidelines:
The Infectious Disease Society of America (IDSA) and American Thoracic Society published a clinical practice guideline on the management of adults with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in 2016.[11] The guideline panel required conflict of interest (COI) disclosures and had an adequate management plan for COI. Panelists were categorized as cleared for full participation, allowed to participate with recusal for certain aspects, or disqualified from participation. The co-chairs remained free of any financial COI.

Fluoroquinolones are recommended in the following instances:

- Levofloxacin is recommended as a treatment option for empiric treatment of VAP and HAP when coverage for methicillin-susceptible *Staphylococcus aureus* (MSSA) is indicated (weak recommendation, very low-quality evidence) noting that FQ resistance is slightly more common in MSSA versus other treatment options. Therapy should be narrowed once a bacterial pathogen has been isolated.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:
In May 2016, the FDA issued new safety warnings regarding the risk of adverse effects including tendinitis and tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects with FQs.[12] The FDA advised FQs be reserved for uncomplicated infections (sinusitis, bronchitis, and uncomplicated urinary tract infections) for which the risk of these adverse events outweighs the benefit. A boxed warning was added to drug labeling for FQs.

In May 2017, FDA confirmed that current data do not support reports that FQs may cause retinal detachment, aortic aneurysm or aortic dissection.[12]

Randomized Controlled Trials:
A total of 25 citations were manually reviewed from the initial literature search. After further review, 24 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 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
Postma, et al.[13] Cluster, RCT, non-inferiority	Beta-lactam monotherapy (BL) vs. Beta-lactam + macrolide (BL/MC) vs. FQ monotherapy	Hospitalized adults with CAP (n=2283)	All-cause mortality within 90 days of admission	<u>All-cause 90 day mortality</u> BL: 59 (9.0%) BL/MC: 82 (11.1%) FQ: 78 (8.8%) *BL vs. BL/MC:* Treatment difference 1.9% (90% CI -0.6 to 4.4)

				BL vs. FQ: Treatment difference 0.6% (90% CI -2.8 to 1.9)
Abbreviations: BL: Beta-lactam; CAP: community acquired pneumonia; FQ: fluoroquinolone; MC: macrolide; RCT: randomized controlled trial				

NEW DRUG EVALUATION: Baxdela® (delafloxacin)

Delafloxacin is a FQ antibiotic indicated for adults for the treatment of ABSSSI caused by susceptible bacteria. 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:
Prior phase 2 studies showed that delafloxacin is well tolerated and has similar clinical efficacy compared with tigecycline, linezolid and vancomycin.[14,15] A post-hoc analysis demonstrated superior clinical success rates in obese patients with delafloxacin compared to vancomycin in one Phase 2 study which led to an enrichment of the following phase 3 trials with subjects with BMIs ≥ 30 .[7]

Delafloxacin was approved based on two Phase 3, multicenter, randomized, double-blind, noninferiority trials with high risk of bias comparing delafloxacin to vancomycin plus aztreonam in the treatment of moderate to severe ABSSSI. Only one of these trials is currently published and can be fully assessed for quality.[16] Both studies were similarly designed with the key difference being study 302 included delafloxacin IV only and study 303 included IV to oral switch. Inclusion and exclusion criteria were almost identical except study 302 excluded patients with a creatinine clearance (CrCl) < 30 mL/min and body weight > 140 kg, while 303 excluded those with CrCl < 15 mL/min and body weight > 200 kg. Specific inclusion and exclusion criteria are included in the evidence table below. The key characteristics of the two studies were consistent with the recommendations in the FDA guidance on ABSSSI studies including infection type, lesion size, use of prior ineffective antibacterial drugs, and endpoints.[8] The primary outcome in both studies was clinical response defined as ≥ 20% reduction in erythema of the ABSSSI lesion at 48-72 hours. The FDA guidance defined non-inferiority acceptable if the lower limit of the 95% CI was greater than -10%.

In the published noninferiority study (study 302) with high risk of bias, 331 patients were randomized to IV delafloxacin and 329 patients were randomized to IV vancomycin plus aztreonam. Patients in this trial had the following infections: cellulitis (39%), wound infection (35%), major cutaneous abscess (25%), and burn infection (1%). Patients continued on IV therapy for the entire duration of therapy and aztreonam was discontinued once baseline cultures did not reveal gram-negative organisms. Although patients on delafloxacin received an IV placebo infusion instead of aztreonam, it is unclear how the investigators maintained blinding with variability in vancomycin dosing schedules based on trough levels. Overall, *S. aureus* was identified in approximately 66% of cases; MRSA was found in 32% of patients the delafloxacin group and 36.8% of patients in the vancomycin/aztreonam group.

Intravenous delafloxacin was found to be noninferior to IV vancomycin plus aztreonam in clinical response (78.2% vs. 80.9%; treatment difference -2.6%; 95% CI -8.78 to 3.57%) and investigator-assessed cure (52% vs. 50.5%; treatment difference 1.5%; 95% CI -6.11 to 9.11%), with the lower limit of the 95% CI greater than -10% for both outcomes.

Study 303 remains unpublished and could not be fully assessed for quality and risk of bias. Much of the information from the evidence table comes from the FDA review.[7] In this study, 423 patients were randomized to delafloxacin and 427 patients were randomized to vancomycin plus aztreonam. This trial implemented a mandatory switch from IV delafloxacin to oral therapy after 48 hours (6 doses). The patients in the vancomycin arm were switched to an oral

placebo and IV placebo infusions were used to maintain blinding. Patients in this trial had the following infections: cellulitis (48%), wound infection (26%), major cutaneous abscess (25%), and burn infection (1%).

Consistent with the previous trial, IV to oral delafloxacin was found to be noninferior to IV vancomycin plus aztreonam for clinical response (83.7% vs. 80.6% treatment difference 3.1%; 95% CI -2.0 to 8.3%) with the lower limit of the 95% CI greater than -10% non-inferiority margin.

In both trials, approximately 90% of baseline isolates were Gram-positive organisms and over 60% were *S. aureus* (56% MSSA and 44% MRSA). Gram-negative isolates were uncommon but most were from polymicrobial infections that included Gram-positive organisms. In both trials, the microbiologic response rates by baseline organisms did not differ significantly between the delafloxacin and vancomycin/aztreonam arms (Table 2).

Table 2. Pooled Outcomes by Baseline Pathogens (MITT population)[9]

	Clinical Response at 48-72 hours[a]		Investigator-Assessed Success at Follow-up[b]	
Pathogen	Delafloxacin, n/N (%)	Comparator, n/N (%)	Delafloxacin, n/N (%)	Comparator, n/N (%)
Staphylococcus aureus Methicillin-susceptible Methicillin-resistant	271/319 (85.0%) 149/177 (84.2%) 125/144 (86.8%)	269/324 (83.0%) 148/180 (80.9%) 121/141 (85.8%)	275/319 (86.2%) 154/177 (87.0%) 122/144 (84.7%)	269/324 (83.0%) 153/183 (83.6%) 116/141 (82.3%)
Streptococcus pyogenes	17/23 (73.9%)	9/18 (50.0%)	21/23 (91.3%)	16/18 (88.9%)
Streptococcus agalactiae	10/14 (71.4%)	9/12 (75.0%)	12/14 (85.7%)	11/12 (91.7%)
Escherichia coli	12/14 (85.7%)	16/20 (80.0%)	12/14 (85.7%)	18/20 (90.0%)
Klebsiella pneumoniae	19/22 (86.4%)	22/23 (95.7%)	20/22 (90.9%)	21/23 (91.3%)
Pseudomonas aeruginosa	9/11 (81.8%)	11/12 (91.7%)	11/11 (100.0%)	12/12 (100.0%)

[a] Objective clinical response was defined as 20% or greater decrease in lesion size as determined by digital planimetry of the leading edge of erythema at 48 to 72 hours after initiation of treatment.
[b] Investigator-assessed success was defined as complete or near resolution of signs and symptoms, with no further antibacterial needed at Follow-up Visit (Day 14±1).

Applicability of these studies is low since exclusion criteria was extensive and included many comorbidities commonly seen in patients at risk for ABSSSI (underlying skin condition, impaired arterial blood supply to extremities, peripheral neuropathy, liver disease, renal disease). In addition, less than 10% of patients in the studies had diabetes which is lower than what is seen in practice. More than 90% of pathogens identified were gram-positive organisms, mainly *Staphylococcus* and *Streptococcus* species. Thus, delafloxacin provides broad-spectrum gram-negative coverage that may not be necessary for most ABSSSIs. In the trials, cellulitis/erysipelas accounted for the majority of ABSSSI infections across most regions and countries except for the U.S. where wound infections accounted for the majority of infections. However, many of the designated wound infections resulted from the puncturing of skin with syringes in IV drug users. This is inconsistent with the definition of wound infection and it is unknown how many of these patients may have actually had an abscess.

More studies are needed to adequately assess the place in therapy of delafloxacin. There is currently an ongoing study comparing delafloxacin to moxifloxacin in patients with community acquired pneumonia.

Clinical Safety

No significant safety concerns emerged for 741 patients included in the two Phase 3 trials. The common adverse reactions reported in the clinical trials included nausea, diarrhea, headache, transaminase elevations and vomiting (table 3). There were no reports of tendinitis or tendon rupture, peripheral neuropathy or myopathy; however, post marketing data will be necessary to determine the risks associated with delafloxacin.

Table 3. Most Common Adverse Reactions Occurring in ≥2% of Patients Receiving Delafloxacin[18]

Adverse Reactions	Delafloxacin, N = 741 (%)	Comparator, N = 751 (%)
Nausea	8%	6%
Diarrhea	8%	3%
Headache	3%	6%
Transaminase Elevations*	3%	4%
Vomiting	2%	2%

*include hypertransaminasemia, increased transaminases, and increased ALT and AST

Serious adverse events (SAEs) were reported by 27 (3.6%) patients in the delafloxacin arm and 16 (3.5%) patients in the comparator arm. SAEs that were reported in more than one delafloxacin-treated patient included cellulitis/erysipelas/skin infection (n=4), sepsis/septic shock (n=2) and pulmonary embolism (n=2). Discontinuation of study drug due to treatment emergent adverse events was reported in 13 (1.8%) patients in the delafloxacin arm and in 26 (3.5%) in the comparator arm.

Table 4. Pharmacology and Pharmacokinetic Properties[7,18]

Parameter	
Mechanism of Action	Fluoroquinolone class of antibacterial drug whose antibacterial activity is due to the inhibition of both bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes which are required for bacterial DNA replication, transcription, repair, and recombination. It exhibits concentration-dependent bactericidal activity against gram-positive and gram-negative bacteria in vitro.
Oral Bioavailability	Bioavailability of 450 mg oral tablet administered as a single dose = 58.8%
Distribution and Protein Binding	$V_{d,ss}$ = 30 to 48 L Plasma protein binding = 84%
Elimination	Mean CL following single IV 300 mg administration = 16.3 L/h (SD 3.7 L/h) CLr = 35 to 45% of total clearance
Half-Life	Mean $t_{1/2}$ for single-dose IV administration = 3.7 hours (SD 0.7 hour) Mean $t_{1/2}$ for multiple oral administration = 4.2 to 8.5 hours
Metabolism	Primarily glucuronidation with oxidative metabolism representing 1% of administered dose;

	Glucuronidation mediated by UGT1A1, UGT1A3, and UGT2B15

Abbreviations: CL = clearance; CLr = renal clearance; $t_{1/2}$ = half-life; SD = standard deviation; $V_{d,ss}$ = steady state volume of distribution; UGT = glucuronosyltransferase

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:
1) Clinical cure
2) Clinical response
3) Treatment failure
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:
1) Clinical Response (≥20% reduction in erythema)
2) Investigator-assessed cure at follow up (complete or near resolution of signs and symptoms, with no further antibiotics needed)

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. Pullman et al. (Study 302)[16] Phase 3 MC, MN, DB, NI, RCT	1. DFX 300 mg IV Q12h and placebo infusion IV Q12h 2. IV VANC 15 mg/kg and AZT 2 g IV Q12h Duration 5-14 days, at investigator discretion	Demographics: Male: 62.9% White: 91.1% Mean age: 45.8 yo Mean BMI: 28.1 kg/m^2 (32.4% of patients with BMI ≥30kg/m^2); Mean duration: 5 days S. aureus identified (66%) MRSA (34%) Key Inclusion Criteria: Adult (≥18 yo) with ABSSSI, and ≥2 signs of systemic infection Key Exclusion Criteria: Receipt of systemic abx in the 14 days prior to enrollment with some exceptions, chronic or underlying skin condition, DFI, osteomyelitis, animal bite, necrotizing infection, septic	ITT: 1. 331 2. 329 Safety: 1. 324 2. 326 Attrition: 1. 55 2. 58	Primary Endpoint: Clinical Response: 1. 259/331 (78.2%) vs. 2. 266/329 (80.9%), MD -2.6% (95% CI, -8.78 to 3.57) Secondary Endpoints: Investigator-assessed cure at FU: 1. 172/331 (52.0%) vs. 2. 166/329 (50.5%), MD 1.5% (95% CI, -6.11 to 9.11) Investigator-assessed cure at LFU: 1. 233/331 (70.4%) vs. 2. 219/329 (66.6%), MD 3.8% (95% CI, -3.27 to 10.89)	 NS NS NS	DC due to AE: 1. 3(<1%) 2. 9 (2.7%) Overall serious AEs: 1. 12/324 (3.7%) 2. 12/326 (3.7%)	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized (1:1) to treatment or comparator using interactive web response system. Treatment assignments obtained from unblinded pharmacist. More obese patients in DFX group. Higher rate of prior abx use in VANC/AZT group. Performance Bias: UNCLEAR. Double-blind, placebo infusion given in combination with DFX to maintain blinding. However, potential of vancomycin dosing variability to unblind treatment. Detection Bias: UNCLEAR. Unclear blinding of evaluators. Attrition Bias: HIGH. Overall attrition was 17.1% (16.6% in DFX and 17.6% in VANC/AZT) Reporting Bias: HIGH. The work was funded by Melinta Therapeutics and some of the authors are employees of Melinta Therapeutics. **Applicability**: Patient: Narrow ethnic diversity. Excludes comorbidities commonly seen in practice as risk factors for skin and soft tissue infections (diabetes, poor circulatory status, peripheral

		arthritis, endocarditis, severely impaired arterial blood supply to extremity with ABSSSI or poor circulatory status, severely compromised immune system, liver disease, CrCl < 30 ml/min, peripheral neuropathy, > 140 kg, other severe underlying comorbidities						neuropathy). Significant exclusion criteria limits generalizability to real-world patients. Intervention: Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections. Comparator: Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections. Outcomes: Outcome appropriate based on FDA guidance for ABSSSI. Could be at risk for subjective variability. Setting: Multiple centers in seven countries, including Croatia, Israel, Latvia, Russian Federation, Spain, Ukraine, and United States. ~80% from the U.S.
2. Study 303[7] Phase 3 MC, DB, NI, RCT	1. DFX 300 mg IV Q12h for 6 doses, then PO DFX 450 mg Q12h 2. VANC 15 mg/kg IV + AZT 2 g Q12h; after 6 doses, included PO placebo Duration 5-14 days, at investigator discretion	Demographics: Male: 63.3% White: 82.7% Mean age: 50.7 yo Mean BMI: 30.5 kg/m^2 (50.0% of patients with BMI ≥30kg/m^2) Key Inclusion Criteria: Adult (≥18 yo) with ABSSSI, and ≥2 signs of systemic infection Key Exclusion Criteria: Receipt of systemic abx in the 14 days prior to enrollment with some exceptions, chronic or underlying skin condition, DFI, osteomyelitis, animal bite, necrotizing infection, septic arthritis, endocarditis, severely impaired arterial blood supply to extremity with ABSSSI or poor circulatory status, severely	ITT: 1. 423 2. 427 Safety: 1. 417 2. 425 Attrition: 1. 57 2. 59	Primary Endpoint: Clinical Response: 1. 354/423 (83.7%) 2. 344/427 (80.6%), MD 3.1% (95% CI, -2.0 to 8.3) Secondary Endpoints: Investigator-assessed cure at FU: 1. 244/423 (57.7%) 2. 255/427 (59.7%) MD: -2.0% (95% CI, -8.6 to 4.6) Investigator-assessed cure at LFU: 1. 287/423 (67.8%) 2. 303/427 (71.0%) MD:-3.1% (95% CI, -9.3 to 3.1)	NS NS NS	DC due to AE: 1. 10 2. 17 Overall serious AEs: 16/417 (3.8%) vs. 17/425 (4.0%)	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR; unpublished. No available information on randomization and allocation concealment. Groups similar at baseline. Performance Bias: UNCLEAR. Double-blind, placebo infusion given in combination with DFX to maintain blinding. However, potential of vancomycin dosing variability to unblind treatment. Detection Bias: UNCLEAR Attrition Bias: HIGH. Overall attrition was 13.6% but similar between groups. (13.5% in DFX and 13.8% in VANC/AZT) Reporting Bias: UNCLEAR. The work was funded by Melinta Therapeutics. **Applicability**: Patient: Narrow ethnic diversity. Excludes comorbidities commonly seen in practice as risk factors for skin and soft tissue infections (diabetes, poor circulatory status, peripheral neuropathy). Significant exclusion criteria limits generalizability to real-world patients. Intervention: Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections.

		compromised immune system, liver disease, CrCl < 15ml/min, peripheral neuropathy, > 200 kg, other severe underlying comorbidities						Comparator: Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections. Outcomes: Outcome appropriate based on FDA guidance for ABSSSI. Could be at risk for subjective variability. Setting: Multiple centers in 16 countries in North America, Latin America, Eastern Europe, and Asia.

*Systemic signs of ABSSSI included lymph node enlargement, elevated C-reactive protein (>10x upper limit of normal), elevated white blood cell count (≥10,000 cell/µL), fever (≥38°C), and lymphangitis
Abbreviations [alphabetical order]: ABSSI = acute bacterial skin and skin structure infections; ABW = actual body weight; abx = antibiotic; AE = adverse event; ARR = absolute risk reduction; AZT = aztreonam; BMI = body mass index; CI = confidence interval; combo = combination; DB = double-blind; DC = discontinuation; DD = double-dummy; DFX = delafloxacin; FU = follow-up (day 14); ITT = intention to treat; IV = intravenous; LFU = late follow-up (days 21-28); MC= multicenter; MD = mean difference; MN = multinational; MSA = minimum surface area; N = number of subjects; NA = not available; NI = noninferiority; NNH = number needed to harm; NNT = number needed to treat; PO = oral; Q12h = every 12 hours; RCT = randomized controlled trial; SA = short-acting; SD = standard deviation; SI = systemic infection; tx = therapy; VANC = vancomycin; yo = years old

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Appendix 1: Current Preferred Drug List

PDL	Generic	Brand	Route	Form
Y	CIPROFLOXACIN HCL	CIPRO	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPRO	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	LEVOFLOXACIN	LEVAQUIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVAQUIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVAQUIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	SOLUTION
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	SOLUTION
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	SOLUTION
Y	CIPROFLOXACIN	CIPRO	ORAL	SUS MC REC
Y	CIPROFLOXACIN	CIPROFLOXACIN	ORAL	SUS MC REC
Y	CIPROFLOXACIN	CIPRO	ORAL	SUS MC REC
Y	CIPROFLOXACIN	CIPROFLOXACIN	ORAL	SUS MC REC
N	OFLOXACIN	OFLOXACIN	ORAL	TABLET
N	OFLOXACIN	OFLOXACIN	ORAL	TABLET
N	MOXIFLOXACIN HCL	AVELOX	ORAL	TABLET
N	MOXIFLOXACIN HCL	MOXIFLOXACIN HCL	ORAL	TABLET
N	CIPROFLOXACIN/CIPROFLOXA HCL	CIPROFLOXACIN ER	ORAL	TBMP 24HR
N	CIPROFLOXACIN/CIPROFLOXA HCL	CIPROFLOXACIN ER	ORAL	TBMP 24HR

Appendix 2: Abstracts of Comparative Clinical Trials

Postma DF, van Werkhoven CH, van Elden LJ, et al.. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med.* 2015 Apr 2;372(14):1312-23.

BACKGROUND: The choice of empirical antibiotic treatment for patients with clinically suspected community-acquired pneumonia (CAP) who are admitted to non-intensive care unit (ICU) hospital wards is complicated by the limited availability of evidence. We compared strategies of empirical treatment (allowing deviations for medical reasons) with beta-lactam monotherapy, beta-lactam-macrolide combination therapy, or fluoroquinolone monotherapy.

METHODS: In a cluster-randomized, crossover trial with strategies rotated in 4-month periods, we tested the noninferiority of the beta-lactam strategy to the beta-lactam-macrolide and fluoroquinolone strategies with respect to 90-day mortality, in an intention-to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

RESULTS: A total of 656 patients were included during the beta-lactam strategy periods, 739 during the beta-lactam-macrolide strategy periods, and 888 during the fluoroquinolone strategy periods, with rates of adherence to the strategy of 93.0%, 88.0%, and 92.7%, respectively. The median age of the patients was 70 years. The crude 90-day mortality was 9.0% (59 patients), 11.1% (82 patients), and 8.8% (78 patients), respectively, during these strategy periods. In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% confidence interval [CI], -0.6 to 4.4) with the beta-lactam-macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, -2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated noninferiority of the beta-lactam strategy. The median length of hospital stay was 6 days for all strategies, and the median time to starting oral treatment was 3 days (interquartile range, 0 to 4) with the fluoroquinolone strategy and 4 days (interquartile range, 3 to 5) with the other strategies.

CONCLUSIONS: Among patients with clinically suspected CAP admitted to non-ICU wards, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies with a beta-lactam-macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality. (Funded by the Netherlands Organization for Health Research and Development; CAP-START ClinicalTrials.gov number, NCT01660204.).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 4 2017
1 exp Fluoroquinolones/ 32406
2 exp Ciprofloxacin/ 13269
3 exp Levofloxacin/ 3115
4 exp Ofloxacin/ 7237
5 moxifloxacin.mp. 4038
6 gemifloxacin.mp. 446
7 exp Norfloxacin/ 2518
8 delafloxacin.mp. 39
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 33539
10 limit 9 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 380
11 Administration, Oral/ or oral.mp.
12 oral.mp*
13 11 or 12
14 10 and 13
15 from 14 keep 1-2, 4, 8, 12, 16-17, 21… 25

Appendix 4: Prescribing Information Highlights[4]

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

BAXDELA (delafloxacin) tablets, for oral use
BAXDELA (delafloxacin) for injection, for intravenous use
Initial U.S. Approval: 2017

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS, and EXACERBATION OF MYASTHENIA GRAVIS
See full prescribing information for complete boxed warning.

Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:

- **Tendinitis and tendon rupture (5.2)**
- **Peripheral neuropathy (5.3)**
- **Central nervous system effects (5.4)**

Discontinue BAXDELA immediately and avoid the use of fluoroquinolones, including BAXDELA, in patients who experience any of these serious adverse reactions. (5.1)

- **Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid BAXDELA in patients with known history of myasthenia gravis. (5.5)**

----------INDICATIONS AND USAGE ----------
BAXDELA is a fluoroquinolone antibacterial indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. (1.1)

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

---------- DOSAGE AND ADMINISTRATION ----------
- Administer BAXDELA for injection 300 mg by intravenous infusion over 60 minutes, every 12 hours, or a 450-mg BAXDELA tablet orally every 12 hours for 5 to 14 days total duration. (2.1)
- Dosage for patients with renal impairment is based on the estimated glomerular filtration rate (eGFR) (2.3)

Estimated Glomerular Filtration Rate (eGFR)(mL/min/1.73m^2)[a]	Recommended Dosage Regimen for BAXDELA[c]	
	Oral	Intravenous[b]
30-89	No dosage adjustment	No dosage adjustment
15-29	No dosage adjustment	200 mg every 12 hours
End Stage Renal Disease (ESRD) (<15 including hemodialysis)	Not Recommended[d]	

a. Estimate of GFR based on a Modification of Diet in Renal Disease (MDRD) equation.
b. All intravenous doses of BAXDELA are administered over 60 minutes.
c. For a total treatment duration of 5 to 14 days.
d. Not recommended due to insufficient information to provide dosing recommendations.

---------- DOSAGE FORMS AND STRENGTHS ----------
- For Injection: 300 mg of delafloxacin (equivalent to 433 mg delafloxacin meglumine) as a lyophilized powder in a single dose vial for reconstitution and further dilution before intravenous infusion. (3)
- Oral Tablets: 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine). (3)

---------- CONTRAINDICATIONS ----------
Known hypersensitivity to BAXDELA or other fluoroquinolones (4, 5.6)

---------- WARNINGS AND PRECAUTIONS ----------
- Hypersensitivity Reactions: May occur after first or subsequent doses of BAXDELA. Discontinue BAXDELA at the first sign of a skin rash or any other sign of hypersensitivity. (5.7)
- *Clostridium difficile*-associated diarrhea: Evaluate if diarrhea occurs. (5.8)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥ 2%) are nausea, diarrhea, headache, transaminase elevations and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Melinta Therapeutics at (844) 635-4682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- USE IN SPECIFIC POPULATIONS ----------
Renal Impairment: Closely monitor serum creatinine levels in patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) receiving intravenous delafloxacin. If serum creatinine level increases occur, consider changing to oral delafloxacin. Discontinue BAXDELA if eGFR decreases to <15 mL/min/1.73 m^2 (8.6).