Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 24, 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)
	II. CONSENT AGENDA TOPICS	T. Klein (Chair)
1:20 PM	A. Approval of Agenda and Minutes	
	B. Topical Antibiotics Class Update with Xepi™ (ozenoxacin) New Drug Evaluation	
	C. Glaucoma Class Update with Rhopressa™ (netarsudil) and Vyzulta™ (latanoprostene) New Drug Evaluations	
	1. Public Comment	
	III. DUR OLD BUSINESS	
1:25 PM	A. Exclusion List	D. Weston (OHA)
	1. Prior Authorization Criteria Clarification	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
	IV. DUR ACTIVITIES	
1:35 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. What's New with Biologic Agents for Inflammatory Disease?
    b. Second Generation Antipsychotic Use in Major Depressive Disorder
2. Future Topic Recommendations

V. PREFERRED DRUG LIST NEW BUSINESS

2:05 PM	A. 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)
2:25 PM	B. 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)
2:45PM	BREAK	
2:55 PM	C. *Clostridium Difficile* Drugs Class Update 1. Class Update/Prior Authorization Criteria 2. Zinplava® (bezlotoxumab) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:15 PM	D. Botulinum Toxins Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	J. Page (OSU)

VI. DUR NEW BUSINESS

3:30 PM	A. Methadone Drug Use Evaluation 1. Drug Use Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	T. Tsai (OSU)
3:45 PM	B. Gabapentin Drug Use Evaluation 1. Drug Use Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	P. Engelder (OSU)

4:00 PM VII. EXECUTIVE SESSION

A. Topical Antibiotics
B. Glaucoma Drugs
C. Fluoroquinolones
D. Clostridium Difficile Drugs
E. Short-acting Opioid Patient Cases

4:45 PM VIII. RECONVENE for PUBLIC RECOMMENDATIONS

4:50 PM IX. Short-acting Opioid PA criteria clarification based upon review of protected health information in executive session

1. Public Comment
2. Discussion of Clinical Recommendations to OHA

X. ADJOURN

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Oregon Pharmacy and Therapeutics Committee – Appointed members

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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 22, 2018, 1:00-5:00 PM
DXC 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 Levine, PhD; William Origer, MD; Rich Clark, MD, MPH; Walter Hardin, DO, MBA; Jim Slater, PharmD; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD; Cathy Zehrung, RPh

Members Present by Phone: Kelley Burnett, DO

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Trevor Douglass, DC, MPH; Sarah Servid, PharmD; Lindsay Newton; Julia Page, PharmD; Jonnaliz Corbett; Deanna Moretz, PharmD; Paige Hook; Emily Hull, PharmD Candidate

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

Audience: Rick Frees, Vertex; Chris Stanfield, Supernus; *Amy Everitt, Sunovion; *Kim Laubmeier, Sunovion; Svetlana Cooper, Salud Medical Center; Paul Bonham, Avexis; *Dan Allen, Genzyme; Anthony Wheeler, Eli Lilly; John Goddard, GSK; Tim McFerron, Alkermes; C Johnson, Spark; Diann Matthews, Merck; *Lillian Chen, Spark; Samantha Sweeney, Otsuka; Lisa Boyle, WVP Health; Margaret Olman, Abbvie; *A. Baig, Pfizer; Catie Schlechter, OHSU; *Paul Yang, MD, OHSU; Jeana Colabianchi, Sunovion; Joseph So, Melinta; Jennifer Jordon, Melinta

(*) Provided verbal testimony

Written testimony provided:

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:04 pm. Introductions were made by Committee members and staff. No new conflict of interests were declared.
B. Mr. Douglass provided a department update and legislative update.

C. Ms. Servid provided discussion around the P&T Operating Procedures.

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

II. CONSENT AGENDA TOPICS

A. Approval of agenda and November minutes presented by Mr. Citron. (pages 9-12)

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

B. Antiepileptics Literature Scan (pages 13-30)
   1. No further review or research needed at this time.
   2. Review in executive session.

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

III. DUR Activities

A. Quarterly Utilization Reports (pages 31-36)
B. ProDUR Report (pages 37-40)
C. RetroDUR Report (pages 41-44)
D. Oregon State Drug Reviews
   1. Recently published reviews:
      i. Marketing Claims of Newer Drugs and the Evidence (pages 45-47)
      ii. Current Landscape of the Antidepressant Class (pages 48-50)
   2. Future Topic Recommendations

IV. Preferred Drug List New Business

A. Bone Metabolism drugs class update (pages 51 - 71)
Dr. Moretz presented the class update and recommended:

1. Maintain ablaloparatide as a non-preferred agent.
2. Update clinical PA criteria for bone metabolism agents to include abaloparatide and limit use to women and inclusion criteria from trial including: age of 49-86 years; and fracture and T-score requirements.

ACTION: Committee recommended modifying the proposed PA criteria to add a question after #3 to require a trial or documented contraindication to oral bisphosphonate; add specific language in #8 to include exclusion criteria for abaloparatide from trial (i.e. anticonvulsant use, corticosteroid use) Motion to approve, 2nd. Majority in favor, one opposed. Approved.

B. Oral First and Second Generation Antipsychotics Class Update (pages 72-94)
Dr. Servid presented the class update and recommended:

1. No changes to the PDL or safety edits based on the clinical information

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

C. Luxturna™ (voretigene neparvovec) New Drug Evaluation (pages 95-105)
Dr. Servid presented the evaluation and proposed PA criteria to:
1. Limit use to the population studied.

ACTION: Committee recommended modify the proposed PA criteria to limit approval to requests from a Center of Excellence with confirmation that it will be administered per protocol. Motion to approve, 2nd. Majority in favor, one opposed. Approved. The Committee also recommended referring voretigene neparvovec to the HERC for prioritization consideration as a drug with high cost and marginal benefit. Motion to approve, 2nd. All in favor. Approved.

D. Atopic Dermatitis DERP Summary (pages 106-138)
Dr. Moretz presented the summary with the following recommendations:
1. Revise PA criteria for topical antipsoriatic drugs to include agents used to manage atopic dermatitis. Categorize these 2 classes as "atopic dermatitis drugs" and "antipsoriatics, topical" on the PDL.
2. Designate dupilumab as non-preferred and apply PA criteria to limit use to:
    a. Moderate-severe atopic dermatitis
    b. Age ≥ 18 years
    c. Prescribed by a dermatologist or allergist
    d. History of inadequate response to ≥ 2 first line agents

ACTION: Committee recommended modifying the proposed PA criteria to require a trial and failure or contraindication to all 3 of the following: topical steroids; topical calcineurin inhibitors; and systemic immunomodulators. Motion to approve, 2nd. All in favor. Approved.

E. Keveyis® (dichlorphenamide) Drug Evaluation (pages 139-154)
Ms. Hill presented the evaluation with the following recommendations:
1. Recommend implementation of PA criteria for dichlorphenamide.

ACTION: Committee recommended modifying the proposed PA criteria to require trial and failure of acetazolamide. Motion to approve, 2nd. All in favor. Approved. The Committee also recommended referring dichlorphenamide to the HERC for prioritization consideration as a drug with high cost and marginal benefit. Motion to approve, 2nd. All in favor. Approved.

F. Anti-Parkinson's Agents Class Update (pages 155-176)
Dr. Page presented the class update with the following recommendations:
1. Modify the PA criteria to:
    a. Add specific clinical criteria for safinamide which limits use to FDA-approved indication and
    b. Add renewal criteria which requires physician attestation of condition improvement.
    c. .

ACTION: Committee recommended modifying the proposed PA criteria to move question #8 prior to #7. Motion to approve, 2nd. All in favor. Approved.

V. EXECUTIVE SESSION

VI. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Antiepileptics Literature Scan (pages 13-30)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

B. Bone Metabolism drugs class update (pages 51 - 71)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

C. Oral First and Second Generation Antipsychotics Class Update (pages 72-94)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

D. Atopic Dermatitis DERP Summary (pages 106-138)
*__ACTION:__ Make tacrolimus 0.03% ointment, tacrolimus 0.1% ointment, and pimecrolimus 1% cream preferred.
Motion, 2nd, All in Favor. Approved.

E. Anti-Parkinson's Agents Class Update (pages 155-176)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

VII. ADJOURN

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Drug Class Update with New Drug Evaluation: Topical Antibiotics

Date of Review: May 2018
Generic Name: ozenoxacin

End Date of Literature Search: 01/09/2018
Brand Name (Manufacturer): Xepi™ (Medimetriks)
Dossier Received: Yes

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

Purpose for Class Update:
To define place in therapy for a new topical quinolone antibiotic (ozenoxacin) recently approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of impetigo. In addition, new comparative evidence for existing topical antibiotics for management of skin and soft tissues infections will be reviewed.

Research Questions:
1. Is there new comparative evidence that topical antibiotics differ in efficacy or effectiveness?
2. Is there any new comparative evidence the topical antibiotics differ in harms?
3. Are there specific subpopulations for which one agent is better tolerated or more effective than other available agents?

Conclusions:
- There is no new comparative evidence that demonstrates differences in efficacy or safety between topical antibiotics.
- Infectious Disease Society of America (IDSA) recommendations support treatment of impetigo with topical mupirocin or retapamulin for five days.[1]
- The efficacy of ozenoxacin compared to placebo in treating impetigo was demonstrated in one published, moderate quality trial.[2] The clinical success after 5 days of therapy was 34.8% in the ozenoxacin group and 19.2% in the placebo group (treatment difference = 15.6%; 95% Confidence Interval [CI] 5.8 to 25.3; p = 0.002, number needed to treat [NNT] =6).[2]
- Adverse effects with topical ozenoxacin are relatively rare. Of the 362 patients who were treated with ozenoxacin in clinical trials, only one adult reported adverse effects of rosacea and seborrheic dermatitis.[3] To date, no serious adverse events have been reported with ozenoxacin use.[3]
- There is insufficient evidence to evaluate comparative efficacy of ozenoxacin with mupirocin or retapamulin.

Recommendations:
- No preferred drug list (PDL) recommendations for ozenoxacin based on efficacy/safety data.
- Evaluate costs in executive session.

Author: Deanna Moretz, PharmD, BCPS

Previous Conclusions:

- There is no new clinical evidence that can further inform PDL decisions for topical antibiotics.

Previous Recommendations:

- No further review or research needed. After evaluation of comparative drugs costs in the executive session, no changes to the Preferred Drug List (PDL) recommended.

Background:

Impetigo is a contagious skin infection that occurs commonly in children aged 2 to 5 years, although older children and adults may also be affected.[4] It is estimated that at any one time, 162 million children in the world have impetigo.[5] There are two principal types of impetigo: non-bullous (70% of cases) and bullous (30% of cases).[4] Nonbullous impetigo is caused by *Staphylococcus aureus* (*S. aureus*) or *Streptococcus pyogenes* (*S. pyogenes*), and is characterized by erosions covered with golden-colored crusts on the face and extremities.[4] Bullous impetigo, which is caused exclusively by *S. aureus*, results in large, flaccid blister-like sores filled with pus and is more likely to affect the trunk, extremities and intertriginous areas.[4] Both forms of impetigo are highly contagious through skin-to-skin contact or contact with articles that have touched the lesions.[6] Impetigo usually occurs in warm, humid conditions.[6] Risk factors for contracting impetigo include poverty, crowding, poor hygiene, or underlying scabies.[7] Impetigo itself is not usually serious and often improves within a week of treatment or within a few weeks without treatment.[6] Complications of impetigo include cellulitis, septicemia, osteomyelitis, and post-streptococcal glomerulonephritis.[6] Although glomerulonephritis following a streptococcal infection is relatively rare, it is a severe adverse event associated with impetigo.[6]

A gram stain and culture of pus or exudate is recommended to identify whether *S. aureus* or *S.pyogenes* is the cause of impetigo.[1] However, treatment may be initiated without obtaining cultures in patients with typical impetigo clinical presentation.[1] According to 2014 Infectious Diseases Society of America (IDSA) recommendations, treatment of impetigo includes topical antibiotics such as mupirocin or retapamulin twice daily for 5 days.[1] A 7-day regimen of oral antibiotic therapy can be used for impetigo with large bullae or when topical therapy is impractical.[1] Amoxicillin/clavulanate, dicloxacillin, cephalexin, clindamycin, and erythromycin are oral options for impetigo treatment.[1] However, there is increasing evidence of bacterial strains resistant to penicillin, erythromycin, cloxacillin, clindamycin, cephalexin, and more recently, mupirocin.[6] Patients with suspected or confirmed methicillin-resistant *S. aureus* (MRSA) infections can be treated with doxycycline, clindamycin, or trimethoprim-sulfamethoxazole, provided the isolate is susceptible to the selected antibiotic.[8]

During the fourth quarter of 2017 (10/1/17 to 12/3/17) there were over 500 claims for mupirocin (a preferred topical antibiotic) in the Medicaid Fee-for-Service (FFS) population. The current manufacturer of retapamulin has not signed a rebate agreement with the Centers for Medicare/Medicaid Services (CMS), so it is currently not included on the Oregon Health Plan (OHP) Preferred Drug List (PDL).

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:
A 2017 Canadian Agency for Drugs and Technologies in Health (CADTH) Rapid Response report reviewed the evidence and guidelines supporting the clinical effectiveness of topical antibiotics for patients with impetigo.[9] Evidence was evaluated for the following topical antibiotics: polymixin B-bacitracin, polymixin B-gramicidin, polymixin B-bacitracin-gramicidin, bacitracin, mupirocin, silver sulfadiazine, and fusidic acid compared to each other, placebo or oral antibiotics. The search was limited to English language documents published between January 1, 2007 and January 23, 2017. The literature included in the report consists of one systematic review, one Cochrane meta-analysis, one health technology assessment from Provider Synergies, and two guidelines. The evidence evaluated for the CADTH publication supports the clinical efficacy of topical mupirocin and fusidic acid for the treatment of impetigo.[9] Fusidic acid has not been reviewed by the FDA and is not available in the U.S. Insufficient evidence was identified to support the clinical efficacy of bacitracin and a lack of evidence was identified on other topical antibiotics of interest.[9] The evidence identified for the systemic treatment of impetigo supports the superiority of topical mupirocin over oral erythromycin (10 RCTs; pooled Relative Risk (RR) 1.07; 95% Confidence Interval (CI) 1.01 to 1.13; p = 0.032).[9] However, the evidence also suggests existing local antimicrobial resistance patterns may strongly influence this comparative efficacy assessment.[9] Guidelines from Australia (Joanna Briggs Institute) and the United States (National Athletic Trainers' Association) contain impetigo treatment recommendations for the use of topical mupirocin and topical fusidic acid consistent with the clinical evidence identified in the rapid response report.[9] Both of the guidelines referenced in the CADTH report were described as having significant quality limitations including very little methodological information on the literature search, broad focus and research question, no information on stakeholder involvement, and no conflict of interest statement.[9]

Guidelines:
A 2014 publication updated the 2005 IDSA practice guidelines for the diagnosis and management of skin and soft tissue infections (SSTIs).[1] The recommendations discuss a wide range of SSTIs from minor superficial infections to life-threating infections. The guidelines were developed to be concordant with 2014 IDSA recommendations for treatment of MRSA infections. Evaluation and treatment of impetigo are discussed as part of the SSTI recommendations. Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection.[1] Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for 5 days.[1] Oral therapy for impetigo should be a 7-day regimen with an agent active against *S.aureus* unless cultures yield streptococci alone (in which case oral penicillin is the recommended agent).[1] Because *S.aureus* isolates from impetigo are usually methicillin susceptible, dicloxacillin or cephalexin is recommended.[1] When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.[1]

New Formulations or Indications:
None identified.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 57 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

NEW DRUG EVALUATION: Ozenoxacin

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:
Ozenoxacin is a non-fluorinated quinolone FDA-approved for the topical treatment of impetigo due to *S.aureus* or *S.pyogenes* in adult and pediatric patients 2 months of age and older.[3] Two phase 3 trials have been conducted to assess the efficacy of ozenoxacin 1% cream in treating impetigo compared to placebo or retapamulin. One trial has been published,[2] while the study details for the second trial are only available at the clinicaltrials.gov website.[10] Both trials were submitted to the FDA by the manufacturer for approval of ozenoxacin.[11]

The first trial was a multicenter, randomized, placebo-controlled, parallel, blinded, three-arm trial comparing ozenoxacin cream to placebo; the third arm with retapamulin ointment was included to test internal validity. The trial was conducted in patients with a clinical diagnosis of nonbullous or bullous impetigo.[2] The trial was double-blinded for the ozenoxacin cream versus placebo comparison and investigator-blinded for retapamulin ointment versus placebo because of the different formulation appearances. Treatments in each of the 3 arms were administered twice daily for 5 days. The study was performed in 27 centers in 5 countries including Germany, Romania, South Africa, Ukraine, and the U.S.[2] Most patients (67%) were from South Africa and 6% were from the U.S.[11] Evaluation of efficacy was based upon a clinical assessment by the investigator using a 7-point skin infection rating scale (SIRS). The signs or symptoms evaluated via the SIRS included: 1) exudate/pus, 2) crusting, 3) erythema/inflammation, 4) tissue warmth, 5) edema, 6) itching and 7) pain. Each component was rated on a scale of 0 to 6: a score of 0 = absent, 1-2 = mild, 3 or 4 = moderate, 5 or 6 = severe symptoms; with a maximum score of 42.[2] Clinical improvement was defined as a decrease in total SIRS score of greater than 10% compared with baseline.[2] The primary efficacy end point was clinical response measured by the SIRS by the third follow-up visit on day 6 or 7.[2] Clinical cure at visit 3 was defined as SIRS score zero for exudates/pus, crusting, tissue warmth and pain and no more than one each for erythema/inflammation, tissue edema and itching and no additional antimicrobial therapy of the baseline lesion required.[2] The clinical cure rate at end of therapy was 34.8% in the ozenoxacin group and 19.2% in the placebo group (treatment difference=15.6%; 95% CI 5.8 to 25.3; p = 0.002; NNT=6).[2] Clinical success was observed in 37% of the patients who received retapamulin, which supported the internal validity of the trial.[2] The trial was not powered to compare the efficacy of ozenoxacin with retapamulin.

One limitation of this trial is funding by the manufacturer, possibly increasing the risk of bias in the results. Two of the study authors are employees of the manufacturer. Another limitation is that ozenoxacin was not analyzed for comparative efficacy to retapamulin due to insufficient power. Finally, a small proportion (6%) of patients were enrolled from the U.S. Most of the patients were from South Africa (67%), which may limit the applicability to the Oregon Medicaid population as well as the U.S. population as a whole.

The second manufacturer-sponsored trial compared ozenoxacin cream with placebo; in each arm the treatments were administered twice daily for 5 days.[10] Four hundred and twelve patients were randomized 1:1 with similar inclusion and exclusion criteria as the published trial. However, a different version of the SIRS scale was used in this trial both in evaluation and scoring. Response to treatment was based on five-point SIRS scale: 1) blistering, 2) exudate/pus, 3)

crusting, 4) erythema/inflammation, and 5) itching/pain. The rating scale ranged from 0 to 3: a score of 0 = absent, 1 = mild, 2= moderate, and 3 = severe; the maximum score was 15.[11] Clinical cure, the primary endpoint, was defined differently than the previous trial. In the unpublished trial, clinical cure was defined as having a SIRS score of 0 for blistering, exudate/pus, crusting, itching/pain, and 0 or 1 for erythema/inflammation and no additional antimicrobial therapy of the baseline lesion required.[11] The reported clinical cure rate was 54.4% for ozenoxacin and 37.9% for placebo (treatment difference = 16.5%, 95% CI 6.9 to 25.8; p <0.001, NNT = 6).[11] Limitations of this trial include manufacturer funding and sponsorship. The trial results have not been published in a peer reviewed journal. Utilization of a different version of the SIRS tool to assess impetigo improvement limits comparison to other trials.

Clinical Safety:
The safety profile reported by the manufacturer is supported by administration of ozenoxacin cream in 362 adults and pediatric patients 2 months of age and older. Adverse reactions (rosacea and seborrheic dermatitis) were reported in 1 adult patient.[3]

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

Comparative Endpoints:

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 Endpoint:
1) Clinical cure (SIRS score 0-1)

Table 1. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Non-fluorinated quinolone antibiotic
Absorption	Minimally absorbed after topical administration, therefore minimal pharmacokinetic data studies were completed by the manufacturer
Protein Binding	80-85% independent of concentration
Metabolism	Minimally metabolized by hepatocytes

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. Gropper et al.[2] Phase 3, DB, PC, RCT N=465	1. Ozenoxacin 1% cream BID x 5 days 2. Placebo BID x 5 days 3. Retapamulin 1% ointment BID x 5 days Duration: 6-7 days	Demographics: -Mean age: 16 years (68% of patients were 2-12 yo) -Male: 62% -Black: 50% -White: 12% -Nonbullous: 79% -Mean SIRS score: 15 Key Inclusion Criteria: -Aged 2 years or older -Clinical diagnosis of impetigo that covers 1-100 cm^2 of total BSA - SIRS of at least 8 with a pus/exudate score at least 1 Key Exclusion Criteria: -Bacterial infection not suitable for topical therapy -No systemic signs of infection	ITT: 1.155 2.156 3.154 PP: 1.153 2.150 3.152 Attrition: 1.2 (1%) 2.6 (4%) 3.2 (1%)	Primary Endpoint: Response to treatment (cure) by day 6 – 7: SIRS score of 0-1 1.34.8% (n=54) 2.19.2% (n=30) 3.37.7% (n=58) 1 vs. 2: Difference in cure rates: 15.6%, 95% CI (5.8 to 25.3); p = 0.002 2 vs. 3: Difference in cure rates:18.4%, 95% CI (8.5 to 28.2); p <0.001 Secondary Endpoints: Microbiologic response at visit 2 (Day 3-4) and visit 3 (Day 6-7) Visit 2: 1.70.8% 2. 38.2% Difference 32.6%; 95% CI NR; p<0.0001 Visit 3: 1.79.2% 2.56.6% Difference 22.6%; 95% CI NR; p<0.0001	15.6%/6 18.4%/6 32.6/4 22.6/4	TEAE (nasopharyngitis and rhinitis) 1. 4 2. 0 3. 7 Application Site Reaction 1.0 2.0 3.2 Serious AE 1.0 2.0 3.0	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized 1:1:1 via IVRS, stratified into age subsets. Performance Bias: LOW. Ozenoxacin and placebo creams did not differ in appearance. Since retapamulin is an ointment, it could not be included in the double-blind design, but was administered in investigator-blinded fashion. Detection Bias: UNCLEAR. Investigators were blinded to treatment arms. Ozenoxacin and placebo were creams, retapamulin in ointment form, which may have resulted in unblinding during assessment to therapy. Attrition Bias: LOW. Attrition rates were very low (1-4%). Reporting Bias: HIGH. Funded by manufacturer. Two of the authors is are employees of the manufacturer. **Applicability**: Patient: 68% of patients were pediatric patients. Baseline SIRS scores were also on average 15/42 likely indicating less severe disease. Intervention: Placebo controlled trial, would have been more meaningful to use mupirocin as an active comparator. Comparator: Retapamulin response rates were used as internal control, but assessment in efficacy differences between ozenoxacin and retapamulin would have provided more meaningful data. Outcomes: SIRS scale is a subjective assessment. Setting: 27 centers in 5 countries: Germany (4) , Romania (2), South Africa (13) Ukraine (5), U.S. (3). 67% of the patients were from South Africa, 6% were from the U.S. May limit applicability to Oregon Medicaid and U.S. population.

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BID = twice daily; BSA = body surface area; CI = confidence interval; DB = double blind; ITT = intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SIRS = skin infection rating scale; TEAE = treatment=emergent adverse effect; YO = years old

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Appendix 1: Current Preferred Drug List

Route	Form	Generic	Brand	PDL
TOPICAL	OINT. (G)	BACITRACIN/POLYMYXIN B SULFATE	DOUBLE ANTIBIOTIC	Y
TOPICAL	OINT. (G)	MUPIROCIN	CENTANY	Y
TOPICAL	OINT. (G)	MUPIROCIN	MUPIROCIN	Y
TOPICAL	CREAM (G)	GENTAMICIN SULFATE	GENTAMICIN SULFATE	Y
TOPICAL	OINT. (G)	BACITRACIN	BACITRACIN	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC	ANTIBIOTIC	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC	BACITRACIN ZINC	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC/POLYMYXIN B	DOUBLE ANTIBIOTIC	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC/POLYMYXIN B	POLY BACITRACIN	Y
TOPICAL	OINT. (G)	NEOMYCIN/BACITRACIN/POLYMYXINB	TRIPLE ANTIBIOTIC	Y
TOPICAL	GEL (GRAM)	ERYTHROMYCIN/BENZOYL PEROXIDE	BENZAMYCIN	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN/BENZOYL PEROXIDE	ERYTHROMYCIN-BENZOYL PEROXIDE	N
TOPICAL	KIT	MUPIROCIN	CENTANY AT	N
TOPICAL	OIN/PF APP	MUPIROCIN	MUPIROCIN	N
TOPICAL	OINT. (G)	GENTAMICIN SULFATE	GENTAMICIN SULFATE	N
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOSPHATE	CLEOCIN T	N
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	SOLUTION	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	LOTION	CLINDAMYCIN PHOSPHATE	CLEOCIN T	N
TOPICAL	LOTION	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLEOCIN T	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLINDACIN ETZ	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLINDACIN P	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	FOAM	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	FOAM	CLINDAMYCIN PHOSPHATE	EVOCLIN	N
TOPICAL	PACKET	BACITRACIN	BACITRACIN	N
TOPICAL	PACKET	BACITRACIN ZINC	BACITRACIN ZINC	N
TOPICAL	CREAM (G)	MUPIROCIN CALCIUM	MUPIROCIN	N
TOPICAL	MED. SWAB	ERYTHROMYCIN BASE/ETHANOL	ERY	N
TOPICAL	MED. SWAB	ERYTHROMYCIN BASE/ETHANOL	ERYTHROMYCIN	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN BASE/ETHANOL	ERYGEL	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN BASE/ETHANOL	ERYTHROMYCIN	N
TOPICAL	SOLUTION	ERYTHROMYCIN BASE/ETHANOL	ERYTHROMYCIN	N
TOPICAL	CREAM (G)	NEOMYCIN/POLYMYXIN B/PRAMOXINE	ANTIBIOTIC PLUS	N

TOPICAL	OINT PACK	NEOMYCIN/BACITRACIN/POLYMYXINB	TRIPLE ANTIBIOTIC	N
TOPICAL	OINT. (G)	NEOMYCN/BACITRC/POLYMYX/PRAMOX	TRIPLE ANTIBIOTIC EXTRA	N
TOPICAL	OINT. (G)	NEOMYCN/BACITRC/POLYMYX/PRAMOX	TRIPLE ANTIBIOTIC PLUS	N
TOPICAL	KIT	CLINDAMYCIN PHOS/SKIN CLNSR 19	CLINDACIN ETZ	N
TOPICAL	KIT	CLINDAMYCIN PHOS/SKIN CLNSR 19	CLINDACIN PAC	N

Appendix 2: Medline Search Strategy

1	bacitractin.mp.	1
2	Neomycin	7947
3	Erythromycin/	14440
4	Clindamycin/	5772
5	Gentamicin/	18916
6	retapamulin.mp.	98
7	Mupirocin/	1180
8	Polymixin b.mp.	260
9	Chlorhexidine/	8037
10	Metronidazole/	12874
11	Sulfacetamide/	365
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	65780
13	limit 12 to yr="2016 -Current"	2199
14	Administration, Topical/	38858
15	13 and 14	66
16	limit 15 to (english language and humans)	57

Appendix 3: Prescribing Information Highlights

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

XEPI™ (ozenoxacin) cream, for topical use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
XEPI is a quinolone antimicrobial indicated for the topical treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in adult and pediatric patients 2 months of age and older (1).

----------DOSAGE AND ADMINISTRATION----------
- Apply a thin layer of XEPI topically to the affected area twice daily for 5 days (2).
- Affected area may be up to 100 cm^2 in adult and pediatric patients 12 years of age and older or 2% of the total body surface area and not exceeding 100 cm^2 in pediatric patients less than 12 years of age (2).
- For topical use only (2).
- Not for oral, ophthalmic, intranasal, or intravaginal use (2).

----------DOSAGE FORMS AND STRENGTHS----------
Cream: Each gram contains 10 mg of ozenoxacin (1%) (3).

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

----------WARNINGS AND PRECAUTIONS----------
Potential for Microbial Overgrowth: Prolonged use of XEPI may result in overgrowth of nonsusceptible bacteria and fungi. If such infections occur, discontinue use and institute alternative therapy (5).

----------ADVERSE REACTIONS----------
Adverse reactions (rosacea and seborrheic dermatitis) were reported in 1 adult patient treated with XEPI (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Medimetriks at 866-262-0222 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2017

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Class Update with New Drug Evaluation: Glaucoma Drugs

Date of Review: May 2018

Generic Name: latanoprostene bunod
Generic Name: netarsudil dimesylate

Date of Last Review: January 2015
End Date of Literature Search: 02/26/2018
Brand Name (Manufacturer): Vyzulta (Bausch & Lomb, Inc)
Brand Name (Manufacturer): Rhopressa (Aerie Pharmaceuticals, Inc)
Dossier Received: yes – Vyzulta / no - Rhopressa

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

Purpose for Class Update:
This class update was prompted by the approval of two new treatments for glaucoma, latanoprostene bunod (LB) and netarsudil. The evidence used for these approvals will be evaluated in addition to any new comparative evidence published for glaucoma therapies since the last review.

Research Questions:
1. Are there comparative efficacy differences between glaucoma treatments based on outcomes such as intraocular pressure (IOP), loss of vison, or blindness?
2. Are there differences in harms between treatments for glaucoma that would have a clinical impact on patient care and should be factored into treatment decisions?
3. Are there subgroups of patients in which LB, netarsudil or other glaucoma treatments are safer or more effective than other available ophthalmic treatments for glaucoma?

Conclusions:
- No meaningful differences were found after evaluation of the evidence for comparative efficacy differences between treatments for glaucoma. Guidance from National Institute for Health and Care Excellence (NICE) recommends the use of generic prostaglandins first line in adult patients with chronic open angle glaucoma (OAG) or ocular hypertension (OH).[1]
- Canadian Agency for Drugs and Technology in Health (CADTH) studied the comparative efficacy and harms of bimatoprost compared to other prostaglandins.[2] Moderate strength of evidence found combination therapy with bimatoprost to be more effective in lowering IOP than other combinations; however, despite statistically significant differences in some cases the small difference between treatments (up to a maximal difference of 2mmHg) is unlikely to be clinically significant. Monotherapy comparisons of bimatoprost, travoprost and latanoprost demonstrated similar IOP lowering. Bimatoprost, used as monotherapy or combination therapy, was associated with the highest incidence of hyperemia. Latanoprost was found to have the most benefit with least risk of harms amongst the comparisons.

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- *Latanoprostene*: There was low strength of evidence of IOP lowering of 7-9 mmHg in patients treated with LB compared to 6-8 mmHg in patients treated with timolol, with OAG or OH diagnosis, based on two poor quality, noninferiority studies.[3,4]
- *Netarsudil*: There was low strength of evidence of IOP lowering in patients treated with netarsudil based on two poor quality, noninferiority studies in patients with OAG and OH.[5] IOP decreases from baseline ranged from 3.3 to 5.0 mmHg in the netarsudil once daily group (approved dose), 4.1 to 5.4 mmHg in the netarsudil twice daily group and 3.7 to 5.1 mmHg in the timolol group.
- Hyperemia was more common with LB and netarsudil compared to timolol. LB was associated with up to an 8% higher incidence of hyperemia than timolol and netarsudil was associated with up to a 45% higher incidence compared to timolol.[3–5]

Recommendations:
- No changes to the PDL for glaucoma drugs are recommended based on efficacy or safety data.
- Evaluate comparative drug costs in executive session.

Current Policy:
- The Oregon Health Plan (OHP) provides coverage for glaucoma with the current policy preferring treatments from each class of treatments; miotics, alpha-adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogues. Previous reviews, including the last update in January of 2015, have not found meaningful differences in efficacy/effectiveness within drug classes of ophthalmic medications used to treat glaucoma. Cost effectiveness and differences in harms data have been the driving forces for preferring specific therapies (**Appendix 1**). Newer fixed-combination products have not shown to provide substantial clinical benefit over the use of individual components. There are currently no prior authorization criteria for this class; however, utilization of PDL agents is high. There are approximately 3,000 Oregon Health Plan (OHP) fee-for-service patients with a diagnosis of glaucoma with a minimal impact on overall OHP healthcare costs.

Background:
Glaucoma is the second leading cause of blindness in the world.[6] Glaucoma is characterized by two variations: OAG and angle-closure glaucoma. A 2016 guideline estimates the incidence of OAG to be 2.2 million people in the United States, representing a 2% prevalence in adults.[7] The suggested incidence of angle-closure glaucoma is 20 million people worldwide.[8] Open-angle glaucoma is more common in individuals of European and African decent and the incidence of angle-closure glaucoma is higher in people of Asian heritage. Risk factors for the development of open-angle glaucoma include: age, black race, family history, and elevated IOP. Hypertension and diabetes have also been associated with an increased risk of OAG. Risk factors for development of visual loss and progression to blindness are not fully known.[6] Risk factors for patients with angle-closure glaucoma are family history, age over 60 years, female, hyperopia (farsightedness), certain medications, race and pseudoexfoliation.

Open-angle glaucoma causes peripheral visual field loss due to optic neuropathy. Open-angle glaucoma is often associated with elevated IOP levels and reduction in IOP is important to prevent the progression to loss of vision.[1] Elevated IOP is the result of increased aqueous production or decreased aqueous outflow. The increased pressure can result in “cupping” of the optic nerve causing loss of ganglion cell axons. The pathogenesis of OAG is not clear but thought to be a combination of circulatory or extracellular matrix factors, variation in axon susceptibility and systemic factors. If left untreated OAG can cause visual field loss and irreversible blindness.[6] Angle-closure glaucoma is the result of narrowing or closure of the anterior chamber angle. This chamber is responsible for drainage of the aqueous humor, which is the fluid that fills the eyeball. Prevention of drainage from this pathway can cause increased IOP with subsequent damage to the optic nerve. Angle-closure glaucoma is caused by certain anatomical traits of the eye. Acute blockage of the entire angle in angle-closure glaucoma can cause rapidly rising IOP and subsequent vision loss and potential blindness if not treated. Chronic angle-closure glaucoma can occur over time and

result in scarring of the optic nerve.[6] Secondary glaucoma can be caused by uveitis, trauma, glucocorticoids, vasoproliferative retinopathy, or ocular syndromes (i.e., pigment dispersion or pseudoexfoliation).

The consensus for initiating treatment in patients with open-angle glaucoma are 2 IOP readings of more than 22 mmHg, with normal ranges of IOP being 8-21 mmHg.[6] Treatment options for lowering IOP include medications, laser or surgery; however, pharmacotherapy or laser are preferred. If medical treatment is used, prostaglandins (e.g., latanoprost, travoprost, bimatoprost) are recommended as the first-line based on once-daily dosing, improved efficacy and low incidence of side-effects compared to beta-blockers (e.g., betaxolol, carteolol, timolol), carbonic anhydrase inhibitors (e.g., brinzolamide, dorzolamide), and alpha adrenergic agonists (e.g., brimonidine, apraclonidine).[1] Beta-blockers are commonly used as a second-line treatment option due to side effects such as bradycardia, worsening heart failure and increased airway resistance. Alpha adrenergic agonists have been shown to have similar efficacy to beta-blockers in lowering IOP but a higher incidence of ocular side effects prevents it from being an initial treatment option. Topical carbonic anhydrase inhibitors have been shown to be less effective than other options and associated with burning, stinging and allergy.[1] Miotics (e.g., pilocarpine) are associated with fixed, small pupils, myopia, and increased visual disturbances and are therefore not widely used. If monotherapy is not effective, combination therapy of beta blockers plus prostaglandin or beta blocker plus carbonic anhydrase inhibitor have been shown to lower IOP more than single therapy. Fixed-dose combination products are offered most commonly with timolol and an additional agent.[1]

Acute treatment of angle-closure glaucoma includes methods to lower quickly reduce IOP.[6] A regimen of topical ophthalmic drops consisting of a beta-blocker, an alpha agonist and treatment to produce miosis (i.e., pilocarpine) is often recommended. Systemic treatment with acetazolamide, mannitol or oral glycerol or isosorbide is also recommended. Once IOP is reduced, laser peripheral iridotomy is used to prevent future elevations of IOP. Peripheral iridotomy is the treatment of choice for patients with angle-closure glaucoma. Secondary angle-closure glaucoma is treated with removing the offending cause if possible and utilizing medications recommended for open-angle glaucoma if necessary.

Outcomes used to track response to therapy are IOP, visual field changes, condition of the optic nerve and progression to blindness.[7] The goal of treating open-angle glaucoma is to lower IOP to a level to prevent further eye damage. The magnitude of IOP lowering is dependent upon the degree of optic nerve damage, rate of progression, family history, age or presence of disc hemorrhages.[7] There is no standard IOP target; however, IOP lowering of 25-30% (approximately 6-7 mmHg) below IOP at presentation has been suggested.[6,7] Evidence has shown that lowering IOP slows progression of visual impairment associated with elevated IOP levels.

For the glaucoma class of medication there is approximately 95% preferred drug utilization within the fee-for-service population. As expected, the highest utilization is within the prostaglandin class followed by alpha-2 agonists.

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, 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:

CADTH – Prostaglandins for Ophthalmic Use: Rapid Response Report

CADTH completed a systematic review of the evidence on prostaglandin use in adult patients with glaucoma in July 2015.[2] The focus of the review was on the comparative efficacy and harms of bimatoprost compared to other ocular prostaglandins (latanoprost, tafluprost, or travoprost). Eighteen publications were considered in the review which included systematic reviews and randomized controlled trials. The mean ages reported in the identified literature were 46 to 68 years and 37% to 64% were females.

One systematic review of 7 adequate quality trials compared fixed combinations of bimatoprost and timolol (B/T) to travoprost and timolol (TR/T) or latanoprost and timolol (L/T) in patients with glaucoma.[2] Diurnal IOP reduction difference favored bimatoprost combinations; -1.94 mmHg (95% confidence interval [CI], 0.19 to 3.68) for B/T compared to TR/T and -0.88 (95% CI, 0.42 to 1.33) for B/T compared to L/T ($p<0.05$ for both comparisons). The incidence of conjunctival hyperemia was higher in both groups of patients treated with B/T compared to TR/T or L/T, with odds ratios [OR] of 1.65 (95% CI, 0.48 to 5.70) and 1.85 (95% CI, 1.09 to 3.13), respectively.[2]

A 2012 Agency for Healthcare Research and Quality (AHRQ) systematic review was included in the CADTH rapid response report. Fair to moderate quality evidence, found more IOP lowering with bimatoprost compared with travoprost (RR 1.19; 95% CI, 1.00 to 1.42).[2] Weighted mean differences were statistically significant in favor of bimatoprost for time periods 8 am and 12 pm, 1.02 mmHg (95% CI, 0.32 to 1.72) and 0.86 mmHg (95% CI, 0.12 to 1.59). A meta-analysis found bimatoprost to lower IOP more than latanoprost (RR 1.70; 95% CI, 1.44 to 2.02). The weighted mean difference between the groups ranged from 0.50 to 1.17 mmHg ($p<0.05$ at all time periods) in favor of more IOP lowering with bimatoprost.[2] The small differences in IOP lowering demonstrated in this systematic review are unlikely to be clinically meaningful. Hyperemia was more common with bimatoprost compared to other treatments in both comparisons. There were no meaningful differences between the prostaglandins studied in the incidence of ocular irritation, inflammation, cystoid macular edema and iris pigmentation.

Monotherapy Active Treatment Comparisons

Six randomized, fair to good quality, monotherapy trials compared bimatoprost, travoprost and latanoprost.[2] Intraocular pressure reduction was the primary outcome in all the studies. Most of the studies found small differences in IOP reduction between groups; however, one study found bimatoprost to statistically significantly lower IOP compared to travoprost and latanoprost with reductions at 12 weeks of 8.8 mmHg, 7.6 mmHg and 7.3 mmHg, respectively. Small differences in IOP lowering are of unknown clinical significance.[2] Four randomized controlled trials comparing bimatoprost to travoprost found no difference in one study, travoprost to be noninferior to bimatoprost in one study and in two studies bimatoprost was found to be superior to travoprost. The incidence of hyperemia was found to be similar between bimatoprost, travoprost and latanoprost in three of the randomized controlled trials. The other two trials that reported on hyperemia found a higher incidence with bimatoprost compared to travoprost and latanoprost; however, statistical significance was not reported.

Monotherapy Bimatoprost and Travoprost Treatment Comparisons

Bimatoprost was compared to travoprost in four, fair quality randomized-controlled trials. Two trials found bimatoprost to lower IOP more than travoprost, 7% more in one trial and by 0.7 mmHg in another ($p<0.05$ for both comparisons).[2] One study found a travoprost to be non-inferior to bimatoprost and a second study found no difference between treatments. Hyperemia was more common in patients using bimatoprost but the numerical results were not reported.

Combination Therapy Comparison

One good quality randomized controlled trial found the combination of bimatoprost and timolol to be similar in lowering IOP compared to travoprost and timolol.[2] A randomized controlled trial which compared bimatoprost, latanoprost and travoprost (all in combination with timolol) found similar IOP values at 3-months to be 12.10 mmHg, 11.59 mmHg and 14.00 mmHg, respectively ($p=0.0$ for all comparisons). The incidence of hyperemia was 23.8% with bimatoprost + timolol compared to 10% with travoprost + timolol (p-value not provided).[2]

New Guidelines:

NICE – Glaucoma: Diagnosis and Management

In 2017 NICE issued guidance on the management of chronic OAG and OH in adults ages 18 and older.[1] Assessment, diagnosis and treatment strategies were presented. Strategies for the treatment of angle closure glaucoma were not included in this review. Evidence was evaluated using the GRADE technique. Effectiveness of prostaglandins and beta-blockers were analyzed via a network meta-analysis, which is low quality evidence. For the purposes of this review, only the pharmacological treatment recommendations are provided.

2017 NICE recommendations for the treatment of OH:[1]

1. Generic prostaglandin analogs are recommended for patients with an IOP of 24 mmHg or more if they are at risk of visual impairment within their lifetime.
2. Treatment should not be offered to patients who are not at risk of visual impairment within their lifetime.
3. Patients who cannot tolerate their current treatment should be offered a different pharmacological option if IOP is 24 mmHg or higher. An alternative generic prostaglandin is recommended first line and a beta-blocker should be considered if prostaglandins are not tolerated. If neither of the previous options are tolerated then the following should be considered: non-generic prostaglandin, carbonic anhydrase inhibitor, sympathomimetic, miotics or combination of treatments.
4. In patients with an IOP of 24 mmHg or greater whose current treatment is failing to reduce IOP to a sufficient level, recommend a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to prevent risk of sight loss. Reduction of IOP may require topical treatments from different therapeutic classes.
5. Patients who have elevated IOP despite pharmacologic therapy should be referred to an ophthalmologist to discuss other treatment options.
6. Preservative-free eye drops should be used in patients with an allergy to preservatives and clinically significant and symptomatic ocular surface disease if they are high risk of conversion to chronic OAG.

2017 NICE recommendations for suspected chronic OAG:[1]

1. Patients with IOP less than 24 mmHg and suspected OAG should not receive treatment. Patients with an IOP of 24 mmHg or higher with suspected OAG should be offered a generic prostaglandin.

2017 NICE recommendations for patients with chronic OAG:[1]

1. Generic prostaglandins are recommended first line in patients with chronic OAG.

2. Patients that have advanced OAG should be offered surgery in addition to pharmacotherapy.
3. Patients who present with advanced chronic OAG should be offered a generic prostaglandin while awaiting surgery.
4. A change in pharmacological therapy should be considered in the following circumstances: IOP is not reduced to the extent to prevent the progression to loss of sight, there is progression in optic nerve head damage, there is progression of visual field defect, or drug intolerance.
5. Patients who fail to have successful IOP lowering should be assessed for adherence and proper technique. If adherence and instillation technique is appropriate then one of the following options are recommended: offer a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or combination therapy with drugs from different therapeutic classes; laser trabeculoplasty; surgery with adjunctive pharmacotherapy.
6. Surgery and pharmacotherapy should be recommended in patients with chronic open angle glaucoma who are at risk of progressing to loss of sight despite pharmacotherapy.
7. Patients who cannot tolerate a drug from one therapeutic class should be offered a drug from a different therapeutic class or preservative-free eye formulation if an allergy is suspected or clinically significant and symptomatic ocular surface disease is suspected
8. Patients who fail treatment from 2 therapeutic classes should be considered for surgery with pharmacotherapy augmentation.
9. Patients who have had surgery but still have elevated IOP may need pharmacotherapy, including multiple drugs from different pharmacological classes.
10. Patients who have chronic OAG who are not candidates for surgery should be offered pharmacological treatment, including treatment from multiple classes if needed. Laser trabeculoplasty or cyclodiode laser treatment may also be an option.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 127 citations were manually reviewed from the initial literature search. After further review, 123 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the evidence tables below.

NEW DRUG EVALUATION: Latanoprostene Bunod
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:
The clinical efficacy of LB comes from two, randomized, multi-center, phase 3, double-blind, noninferiority studies (**Table 2**). In both studies LB 0.024% once daily was compared to timolol 0.5% twice daily in adult patients with OAG or OH.[3,4] The primary endpoint was the decrease in IOP from baseline at 8AM, 12PM and 4PM at week 2, week 6 and month 3 measured in the intent-to-treat (ITT) population, with missing data imputed using last observation carried forward (LOCF), for both studies. Noninferiority was determined in the ITT population if the upper limit of the CI for the difference did not exceed 1.5 mmHg at all 9 time points

and did not exceed 1.0 mmHg for more than 5 of the 9 time points. Superiority was tested if noninferiority was met. Superiority was achieved if the upper limit of the 95% CI did not exceed 0 mmHg at all 9 time points. Analysis was also performed on the per protocol population to substantiate results.

In the first study (n=417), patients meeting the inclusion criteria (i.e., adult patients with OAG or OH) were a mean age of 64 years, 58% female, predominately European or African ancestry with a mean baseline IOP of 26.6 mmHg.[3] Seventy-two percent of patients had history of prior use of topical IOP-lowering therapy. LB was associated with more IOP lowering compared to timolol at all 9 time points in the ITT study population, with mean IOP values after treatment of 17.8 mmHg to 18.7 mmHg and 19.1 mmHg to 19.8 mmHg, respectively. LB was found to be noninferior to timolol with the upper limit of the 95% CI for the difference between the two treatments being less than 1.0 mmHg for all 9 time points. Since noninferiority was met, superiority was also analyzed and LB was found to be superior to timolol since the upper limit of the 95% CI was less than or equal to 0 mmHg for all 9 time points. Per-protocol results were not given but were stated to support the ITT results. For the secondary endpoint of proportion of patients with an IOP less than 18 mmHg at all 9 time points, 23% of patients treated with LB obtained this endpoint compared to 11% patients treated with timolol (mean difference [MD] 12%; 95% CI, 4.3 to 18.9; p=0.005; ARR 12/NNT 9).[3] Thirty-five percent of patients treated with LB had an IOP reduction greater than 35% from baseline at all 9 time points compared to 20% of patients treated with timolol (MD 15%; 95% CI, 6.6 to 24.0; p=0.001; ARR 15/NNT 7).

The second study was very similar to the first study in methodology and baseline characteristics of included patients (n=387).[4] Patients had moderate levels of IOP elevations (mean baseline IOP 26.6 mmHg), mean age of 65 years and 58% were female. Seventy-two percent of patients had used some type of topical therapy for IOP lowering. Mean IOP levels after treatment for LB ranged from 17.7 to 19.2 mmHg and from 18.8 to 19.6 mmHg for timolol.[4] LB was found to be noninferior to timolol based on the upper limit of the mean difference of the 95% CI not exceeding 1.0 mmHg at any of the 9 time points. LB was not superior to timolol since one of the nine time points exceeded 0 mmHg. Authors stated that per-protocol results were consistent with ITT findings but specific data were not provided.

Limitations to this evidence include the use of an ITT analysis for the primary endpoint in a noninferiority study which can bias the results in direction of no difference between treatments. A more appropriate analysis would be on the per-protocol population which was done but the results were not reported in the published trial. The FDA medical review did contain the per protocol results which do substantiate the ITT findings.[9] The timing of testing may have also influenced the results in favor of LB. The maximal effect of timolol has been shown to be 2 hours post-dose which was not studied in the trials; however, the maximal effect of LB would have been captured at the pre-specified time points.[9] The FDA analysis concluded that there was no clinically significant difference between LB and timolol. Three-month study design prevents long-term conclusions on safety and efficacy. Both of the above studies have open-label extension studies that will help to inform the safety of long-term use.

Clinical Safety:
The number of patients who discontinued LB due to adverse events was 1.4% in both studies compared to 0.7% to 3.0% for placebo.[3,4] The most common adverse reactions seen in 2% or more of patients treated with LB are conjunctival pain, hyperemia, eye irritation, eye pain and instillation pain.[10] LB carries a warning for pigmentation changes to the tissues which may be irreversible in some cases. Increases in length, thickness and number of lashes or hairs have also be seen with LB treatment, as well as other prostaglandin therapy.

Table 1. Pharmacology and Pharmacokinetic Properties.[4,10]

Parameter

Mechanism of Action	Prostaglandin analog which increases the outflow of aqueous humor through the trabecular meshwork and uveoscleral routes. Latanoprostene is metabolized to latanoprost acid (prostaglandin) and butanediol mononitrate (nitic-oxide donating moiety).
Oral Bioavailability	Not applicable
Distribution and Protein Binding	No distribution studies performed
Elimination	Not provided
Half-Life	Not provided
Metabolism	Liver

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Visual disturbance
2) Blindness
3) Intraocular pressure
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Reduction in intraocular pressure from baseline

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. Weinreb, et al[3] (Apollo) Phase 3, DB, MC, PG, NI, RCT	1. Latanoprostene Bunod 0.024% once daily at night (L) 2. Timolol 0.5% twice daily (T) 3-month study	Demographics: Mean age: 64 years Female: 58% White: 78% Treatment naïve to topical IOP-lowering therapy: 28% Mean baseline IOP: 26.6 mmHg Key Inclusion Criteria: - OAG or OH in one or both eyes - 18 years of age or older - IOP ≥26 mmHg at a minimum of 1 time point, ≥24 mmHg at a minimum of 1 time point, ≥22 mmHg at 1 time point in the same eye and IOP ≤36 mmHg at all 3 measurement time points in both eyes at baseline - BCVA of +0.7 logarithm of the minimum angle of	ITT: 1. 284 2. 133 PP: 1. 192 2. 80 Attrition: 1. 92 (32%) 2. 53 (40%)	Primary Endpoint: Mean IOP (mmHg) at 8 AM, 12 AM and 4 PM at weeks 2, 6 and month 3 visits: **Week 2 – 8AM** L: 18.6 T: 19.8 MD -1.2 (95% CI, -0.5 to -1.9) **Week 2 – 12PM** L: 18.0 T: 19.4 MD -1.4 (95% CI, -0.7 to -2.1) **Week 2 – 4PM** L: 18.1 T: 19.2 MD -1.1 (95% CI, -0.5 to -1.8) P<0.001 for all comparisons **Week 6 – 8AM** L: 18.6 T: 19.6 MD -1.0 (95% CI, -0.4 to -1.7); P = 0.002 **Week 6 – 12PM**	 NA NA NA NA	Discontinuations due to adverse events: L: 4 (1.4%) T: 4 (3.0%) P-value not reported Eye Irritation: L: 11 (3.9%) T: 3 (2.2%) P-value not reported Conjunctival Hyperemia: L: 8 (2.8%) T: 2 (1.5%) P-value not reported	 NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) Randomized 2:1 by an unmasked statistician using SAS software. Performance Bias: (low) Each product was packaged the same to mask treatment assignment. Detection Bias: (unclear) Details of blinding were not provided. Attrition Bias: (high) Very high attrition was seen in both groups. Analysis was done on the ITT population which can bias results in favor of no difference between groups. Reporting Bias: (low) Industry funded study. Outcomes were reported as described. **Applicability**: Patient: Patients had moderately increased IOP and the majority had been previously treated with

		resolution or better in either eye. Key Exclusion Criteria: - Participation in any clinical trial within 30 days - Central corneal thickness >600 µm in either eye - Advanced glaucoma - Significant ophthalmic disease - Modification of medication known to affect IOP		L: 17.8 T: 19.1 MD -1.3 (95% CI, -0.6 to -1.9); P<0.001 **Week 6 – 4PM** L: 17.8 T: 19.1 MD -1.3 (95% CI, -0.6 to -2.0); P<0.001 **Month 3 – 8AM** L: 18.7 T: 19.7 MD -1.0 (95% CI, -0.4 to -1.7); P = 0.002 **Month 3 – 12PM** L: 17.9 T: 19.2 MD -1.3 (95% CI, -0.6 to -1.9); P<0.001 **Month 3 – 4PM** L: 17.8 T: 19.1 MD -1.3 (95% CI, -0.6 to -2.0); P<0.001 Secondary Endpoints: Proportion of patients with IOP ≤18 mmHg at all 9 time points: L: 22.9% T: 11.3% MD 11.6% (95% CI, 4.3-18.9); P=0.005 Proportion of patients with IOP reduction ≥25% from baseline at all time points: L: 34.9% T: 19.5% MD 15.3% (95% CI, 6.6-24.0); P=0.001	NA NA NA NA 12/9 15/7			a topical IOP-lowering therapy. The number of patients with an OAG diagnosis versus OH diagnosis was not provided. Intervention: Approved dose of latanoprostene treatment was used. Comparator: Timolol twice daily is an appropriate OAG treatment. Outcomes: IOP is an accepted surrogate outcome measure for patients with glaucoma. Setting: Forty-five sites in the United States and Europe.
2. Medeiros, et al[4] (Lunar) Phase 3, DB, MC, PG, NI, RCT	1. Latanoprostene Bunod 0.024% once daily at night (L) 2. Timolol 0.5% twice daily (T) 3-month study	Demographics: Mean age: 65 years Female: 58% White: 71% Treatment naïve to topical IOP-lowering therapy: 28% Mean baseline IOP: 26.5 mmHg Key Inclusion Criteria:	ITT: 1. 278 2. 136 PP: 1. 259 2. 128 Attrition: 1. 19 (7%) 2. 8 (6%)	Primary Endpoint: Mean IOP (mmHg) at 8 AM, 12 AM and 4 PM at weeks 2, 6 and month 3 visits: **Week 2 – 8AM** L: 19.2 T: 19.6 MD -0.4 (95% CI, -1.1 to 0.3); P=0.216 **Week 2 – 12PM** L: 18.5 T: 19.2 MD -0.8 (95% CI, -1.4 to -0.1); P=0.022	NS NA	Discontinuations due to adverse events: L: 4 (1.4%) T: 1 (0.7%) P-value not reported Eye Irritation: L: 20 (7.2%) T: 6 (4.4%) P-value not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 2:1 by statistician prior to any study enrollment. Drug allocation was determined by Interactive Response Technology. Performance Bias: (low) See Apollo. Detection Bias: (low) Patients and study site personnel were masked to treatment assignments.

		- OAG or OH in one or both eyes - 18 years of age or older - IOP ≥26 mmHg at a minimum of 1 of 3 time points, ≥24 mmHg at a minimum of 1 time point, ≥22 mmHg at 1 time point in the same eye and IOP ≤36 mmHg at all 3 measurement time points in both eyes at baseline - BCVA of +0.7 logarithm of the minimum angle of resolution or better in either eye. Key Exclusion Criteria: - Participation in any clinical trial within 30 days - Central corneal thickness >600 µm in either eye - Advanced glaucoma - Significant ophthalmic disease - Modification of medication known to affect IOP - Unable to discontinue contact lens use or other eye drop medications during and 15 min following study drug administration		**Week 2 – 4PM** L: 18.1 T: 18.8 MD -0.7 (95% CI, -1.3 to -0.1); P=0.025 **Week 6 – 8AM** L: 18.7 T: 19.6 MD -0.9 (95% CI, -1.6 to -0.3); P = 0.005 **Week 6 – 12PM** L: 18.0 T: 18.9 MD -0.8 (95% CI, -1.5 to -0.2); P=0.007 **Week 6 – 4PM** L: 17.9 T: 18.9 MD -1.0 (95% CI, -1.6 to -0.4); P=0.003 **Month 3 – 8AM** L: 18.7 T: 19.6 MD -0.9 (95% CI, -1.5 to -0.3); P = 0.006 **Month 3 – 12PM** L: 17.9 T: 19.2 MD -1.3 (95% CI, -1.9 to -0.7); P<0.001 **Month 3 – 4PM** L: 17.7 T: 19.1 MD -1.3 (95% CI, -2.0 to -0.7); P<0.001 Secondary Endpoints: Proportion of patients with IOP ≤18 mmHg at all 9 time points: L: 17.1% T: 11.1% MD 6.6% (95% CI, -0.4 to 13.5); P=0.84 Proportion of patients with IOP reduction ≥25% from baseline at all time points: L: 31.0% T: 18.5% MD 12.5% (95% CI, 4.0-21.1); P=0.007	NA NA NA NA NA NA 7/15 13/8	Conjunctival Hyperemia: L: 25 (9.0%) T: 1 (0.7%) P-value not reported		Attrition Bias: (high) Attrition was low (<10%); however, analysis was performed on the ITT (LOCF) population which is likely to show no difference between treatments in a noninferiority study and can bias the results. Reporting Bias: (low) See Apollo. **Applicability**: Patient: See above. Of the 72% of patients using IOP-lowering medication at enrollment, 81% were for prostaglandins followed by 24% for beta-blockers. Intervention: See Apollo. Comparator: See Apollo. Outcomes: See Apollo. Setting: Forty-six sites in the United States (40) and European Union (6).

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BCVA = best-corrected visual acuity; CI = confidence interval; IOP = intraocular pressure; ITT = intention to treat; LOCF = last observation carried forward; MC = multicenter; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; NI = noninferiority; OH = ocular hypertension; OAG = open angle glaucoma; PG = parallel group; PP = per protocol

NEW DRUG EVALUATION: Netarsudil Dimesylate

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:

Netarsudil was studied in 2 published, double-blind, phase 3, multicenter, active treatment trials in patients with OAG or OH.[5] The studies, ROCKET-1 and ROCKET-2, employed the same methodology. Both studies were non-inferiority trials which reported results up to 3 months. The delta for non-inferiority was determined to be within 1.5 mmHg for all time points and 1.0 mmHg at a majority of time points (at least 5 of 9) for both trials.[11] The per-protocol population analysis was used for the primary analysis in both studies. Patients were included after screening, qualification 1 (medication washout if needed) and qualification 2 (stable IOP without medication) study visits. The primary endpoint was the decrease in IOP from baseline at 8AM, 10AM and 4PM at week 2, week 6 and month 3.

In the first study, ROCKET-1, netarsudil 0.02% once daily at night was compared to timolol 0.5% given twice daily (**Table 4**).[5] Patients (n=411) were predominately female (61%), mean age of 65 years, 66% had an open-angle diagnosis and the baseline IOP was 22.37 mmHg. Prior use of prostaglandins was found in 51% of patients. Patients were analyzed based on the per-protocol population with a maximum baseline IOP of 27 mmHg. Decreases from baseline in the netarsudil group ranged from 3.3-5.0 mmHg (15-22%) and 3.7 to 5.1 mmHg (17-22%) in the timolol group.[5] Netarsudil was not found to be non-inferior to timolol. In a post-hoc analysis, patients with an IOP of less than 25 were analyzed and netarsudil was found to be non-inferior to timolol. An analysis of the ITT population was not specifically reported but the authors mention that the results were similar to the per-protocol population.

The second study, ROCKET-2, compared netarsudil 0.02% daily and netarsudil 0.02% twice daily to timolol 0.5% twice daily (**Table 4**).[5] Patients enrolled in the trial were predominately white females with a mean age of 64 years. The mean baseline IOP for all groups was 21.46 mmHg. Sixty-six percent of patients had an OAG diagnosis and 34% were diagnosed with OH. Forty-eight percent of patients had previously used prostaglandins. Only patients with IOP less than 25 mmHg were included in the primary endpoint analysis. At month 3, the mean IOP decreases from baseline were 3.3 to 4.6 mmHg (16-21% reduction) in the netarsudil once daily group, 4.1 to 5.4 mmHg (22-24%) in the netarsudil twice daily group and 3.7 to 5.1 mmHg (18-23%) in the timolol group.[5] Netarsudil met the requirements for non-inferiority to timolol. An analysis of the ITT population was not specifically reported but the authors mention that the results were similar to the per-protocol population.

A third study was not published but was included in the FDA medical summary and will be briefly described.[11] The study was a phase 3, randomized, controlled trial in 708 adult patients with elevated IOP greater than 20 mmHg and less than 27 mmHg at the first qualification visit and greater than 17 mmHg and less than less than 27 mmHg at the second qualification visit. The study methodology was similar to the first two trials. Netarsudil 0.02% at night was compared to timolol 0.5% twice daily in both eyes. The primary endpoint was the decrease in IOP from baseline at 8AM, 10AM and 4PM at week 2, week 6 and month 3 analyzed in the per-protocol population in patients with a maximum baseline IOP of less than 30 mmHg. Netarsudil was found to be non-inferior to timolol for the primary analysis of IOP of less than 30 mmHg in the per-protocol population but not in the ITT population.[11]

As discussed above, the use of a non-inferiority trial doesn't prove superior efficacy to existing products suggests that a new product is no worse than the comparator. The short-term duration of all the trials prevents conclusions on long-term use for netarsudil, in which chronic use is to be expected. Limited evidence would suggest that netarsudil is effective in patients with mild IOP elevations (less than 25 mmHg) and use in patients with more severe IOP is not known. The FDA summary found inconsistencies in supportive ITT analyses in netarsudil and timolol comparisons. Results that demonstrated non-inferiority in

the per-protocol population were found to be inferior for ITT (LOCF) analyses in patients with higher baseline IOP values (27 mmHg or less in studies one and two and 30 mmHg or less in study 3). This reinforces the lack of robust data to support non-inferiority for netarsudil to timolol in populations with higher baseline IOP.

Clinical Safety:

The most common adverse reactions seen in trials of netarsudil were conjunctival hyperemia which occurred in 53% of patients treated with netarsudil compared to 8-10% of patients treated with timolol.[5] Other common adverse events seen in greater than 20% of patients treated with netarsudil were: corneal verticillata, instillation site pain, and conjunctival hemorrhage.[12] Conjunctival verticillata (deposits) are rarely seen with topical treatment but have been associated with systemic treatments such as amiodarone. They rarely cause visual disturbances and are usually reversible upon drug discontinuation. Discontinuations due to adverse events ranged from 10-30% in the netarsudil groups compared to 1-2% in timolol treated patients.

Table 3. Pharmacology and Pharmacokinetic Properties.[12]

Parameter	
Mechanism of Action	Netarsudil is a Rho kinase (ROCK) inhibitor. The exact mechanism is unknown but netarsudil is thought to work by reducing IOP via increased outflow of aqueous humor through the tubular network.
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Not applicable
Elimination	Not applicable
Half-Life	Not provided
Metabolism	Metabolized via eye esterases

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Visual disturbance
2) Blindness
3) Intraocular pressure
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Reduction in intraocular pressure from baseline

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. Serle, et al[5] (ROCKET-1) DB, RCT, NI, MC, PG	1. Netarsudil 0.02% ophthalmic solution once daily at night (N) 2. Timolol 0.5% ophthalmic solution twice daily (T) 3 months	Demographics: Mean Age: 65 years Female: 61% White: 75% Prior prostaglandin therapy: 51% OAG Diagnosis: 66% Mean baseline IOP: 22.37 mmHg Key Inclusion Criteria: - Open-angle glaucoma OR ocular hypertension - Age 18 years or older OR children 0-2 years with bilateral OAG or OH - Unmedicated IOP >20 mmHg and <27 mmHg in at least one eye at first qualification visit and >17 mmHg and <27 mmHg at the second visit - Corrected visual acuity via ETDRS of +1.0 logMAR or better Key Exclusion Criteria: - Current use of >2 ocular hypertensive medicines - Pseudoexfoliation or pigment dispersion glaucoma - Iridocorneal angle abnormalities - Prior glaucoma surgery - Significant ocular disease - Pregnancy, nursing	ITT: N: 202 T: 209 PP: N: 182 T: 188 Attrition: N: 20 (10%) T: 21 (10%)	Primary Endpoint: Mean IOP (mmHg) at 8 AM, 10 AM and 4 PM at weeks 2, 6 and month 3 visits in patients with baseline IOP <27 mmHg: **Week 2 – 8AM** N: 18.68 T: 18.33 MD 0.35 (95% CI, -0.27 to 0.96) **Week 2 – 10AM** N: 17.29 T: 17.55 MD -0.26 (95% CI, -0.87 to 0.36) **Week 2 – 4PM** N: 17.24 T: 17.70 MD -0.45 (95% CI, -1.08 to 0.17) **Week 6 – 8AM** N: 19.35 T: 18.24 MD 1.11 (95% CI, 0.42 to 1.80) **Week 6 – 10AM** N: 18.14 T: 17.44 MD 0.70 (95% CI, 0.04 to 1.36) **Week 6 – 4PM** N: 17.86 T: 17.71 MD 0.15 (95% CI, -0.52 to 0.83) **Month 3 – 8AM** N: 19.81 T: 18.47 MD 1.33 (95% CI, 0.64 to 2.03) **Month 3 – 10AM** N: 18.92 T: 17.96 MD 0.96 (95% CI, 0.26 to 1.66) **Month 3 – 4PM** N: 18.48 T: 17.74	NA for all due to methodology of NI trial	Ocular Adverse Events: N: 156 (77%) T: 92 (44%) p-value not reported Discontinuations due to Adverse Events: N: 20 (10%) T: 4 (2%) p-value not reported Conjunctival Hyperemia: N: 108 (53%) T: 17 (8%) P<0.0001 Conjunctival Hemorrhage: N: 27 (13%) T: 1 (0.5) P<0.0001 Conjunctival Verticillata: N: 11 (5%) T: 0 P=0.0004	NA NA 45/3 13/8 5/20	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized via a computer model. Performance Bias: (unclear) Vehicle bottle was provided for AM dosing of netarsudil once-daily treatment group. Masking of products was not described. Detection Bias: (low) Patients and study site personnel were blinded to treatment assignments. Attrition Bias: (low) Attrition was low in the both groups. Analysis was on the per-protocol population. Reporting Bias: (low) The study was funded by industry. Endpoints reported as originally designed. **Applicability**: Patient: Baseline IOP values would suggest mild IOP elevations. Results would be most applicable to white females with OAG. Post-hoc analysis of patients with an IOP <25 mmHg to showed more benefit than patients with higher IOP values. Intervention: Netarsudil dose is the FDA approved dose. Comparator: Timolol twice daily is an appropriate OAG treatment. Outcomes: IOP is an accepted surrogate outcome measure for patients with glaucoma. Setting: United States treatment centers.

				MD 0.74 (95% CI, 0.07 to 1.42)				
2. Serle, et al[5] (ROCKET-2) DB, RCT, NI, MC, PG	1. Netarsudil 0.02% ophthalmic solution once daily at night (N) 2. Netarsudil 0.02% ophthalmic solution twice daily (N2) 3. Timolol 0.5% ophthalmic solution twice daily (T) 3 months (study duration up to 12 months and will be reported separately)	Demographics: Mean Age: 64 years Female: 61% White: 69% Prior prostaglandin therapy: 48% OAG: 66% Mean baseline IOP: 21.46 mmHg Key Inclusion Criteria: - >20 mmHg and <25 mmHg in at least one eye Key Exclusion Criteria: - See Rocket-1	ITT: N: 251 N2: 253 T: 251 PP: N: 206 N2: 209 T: 217 Attrition: N: 45 (18%) N2: 44 (17%) T: 34 (14%)	Primary Endpoint: Mean IOP at 8 AM, 10 AM and 4 PM at weeks 2, 6 and month 3 visits in patients with baseline IOP <25 mmHg: **Week 2 – 8AM** N: 18.07 N2: 17.21 T: 17.69 *N vs. T:* MD 0.37 (95% CI, -0.25 to 0.99) *N2 vs. T: M*D -0.48 (-1.19 to 0.22) **Week 2 – 10AM** N: 16.72 N2: 16.35 T: 16.93 *N vs. T:* MD -0.21 (95% CI, -0.82 to 0.41) *N2 vs. T:* MD -0.57 (-1.24 to 0.09) **Week 2 – 4PM** N: 16.68 N2: 15.65 T: 16.83 *N vs. T:* MD -0.15 (95% CI, -0.75 to 0.46) *N2 vs. T:* MD -1.18 (-1.82 to -0.54) **Week 6 – 8AM** N: 17.95 N2: 17.64 T: 17.46 *N vs. T:* MD 0.49 (95% CI, -0.13 to 1.12) *N2 vs. T:* MD 0.17 (-0.51 to 0.86) **Week 6 – 10AM** N: 16.95 N2: 16.28 T: 16.63 *N vs. T:* MD 0.32 (95% CI, -0.31 to 0.95) *N2 vs. T:* MD -0.34 (-1.02 to 0.2=33) **Week 6 – 4PM** N: 17.00 N2: 15.75 T: 16.60 *N vs. T:* MD 0.40 (95% CI, -0.22 to 1.02) *N2 vs. T:* MD -0.85 (-1.53 to -0.17)	NA for all due to methodology of NI trial	Ocular Adverse Events: N: 182 (73%) N2: 213 (84%) T: 102 (41%) p-value not reported Discontinuations due to adverse events: N: 31 (12%) N2: 77 (30%) T: 2 (1%) p-value not reported Conjunctival Hyperemia: N: 126 (50%) N2: 149 (59%) T: 27 (11%) N vs. T: P<0.0001 N2 vs. T: P<0.0001 Conjunctival Hemorrhage: N: 37 (15%) N2: 43 (17%) T: 0 (0) N vs. T: P<0.0001 N2 vs. T: P<0.0001 Conjunctival Verticillata: N: 22 (9%) N2: 37 (15%) T: 1 (0.4%)	NA NA 39/3 48/2 15/7 17/6	**Risk of Bias (low/high/unclear)**: Selection Bias: See ROCKET-1 Performance Bias: See ROCKET-1 Detection Bias: See ROCKET-1 Attrition Bias: (high) Attrition was high in all groups. Per-protocol analysis was used to analyze data. Reporting Bias: See ROCKET-1 **Applicability**: Patient: Baseline IOP values would suggest mild IOP elevations. Results would be most applicable to white females with OAG. Intervention: See ROCKET-1 Comparator: See ROCKET-1 Outcomes: See ROCKET-1 Setting: See ROCKET-1

				Month 3 – 8AM N: 18.24 N2: 17.58 T: 17.47 *N vs. T:* MD 0.77 (95% CI, 0.03 to 1.50) *N2 vs. T:* MD 0.11 (-0.64 to 0.86) **Month 3 – 10AM** N: 17.03 N2: 16.94 T: 16.92 *N vs. T:* MD 0.10 (95% CI, -0.59 to 0.80) *N2 vs. T:* MD 0.02 (-0.72 to 0.77) **Month 3 – 4PM** N: 17.13 N2: 16.51 T: 16.95 *N vs. T:* MD 0.18 (95% CI, -0.55 to 0.91) *N2 vs. T:* MD -0.44 (-1.16 to 0.27)		N vs. T: P<0.0001 N2 vs. T: P<0.0001	23%/5 15%/7	
Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; ITT = intention to treat; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; OAG = open-angle glaucoma; OH = ocular hypertension; PG = parallel group; PP = per protocol								

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Appendix 1: Current Preferred Drug List

Route	FormDesc	Brand	Generic	PDL
OP	DROPS	BETAXOLOL HCL	BETAXOLOL HCL	Y
OP	DROPS	ALPHAGAN P	BRIMONIDINE TARTRATE	Y
OP	DROPS	BRIMONIDINE TARTRATE	BRIMONIDINE TARTRATE	Y
OP	DROPS SUSP	AZOPT	BRINZOLAMIDE	Y
OP	DROPS	CARTEOLOL HCL	CARTEOLOL HCL	Y
OP	DROPS	COSOPT	DORZOLAMIDE HCL/TIMOLOL MALEAT	Y
OP	DROPS	DORZOLAMIDE-TIMOLOL	DORZOLAMIDE HCL/TIMOLOL MALEAT	Y
OP	DROPERETTE	COSOPT PF	DORZOLAMIDE/TIMOLOL/PF	Y
OP	DROPS	LATANOPROST	LATANOPROST	Y
OP	DROPS	XALATAN	LATANOPROST	Y
OP	DROPS	VYZULTA	LATANOPROSTENE BUNOD	Y
OP	DROPS	ISOPTO CARPINE	PILOCARPINE HCL	Y
OP	DROPS	PILOCARPINE HCL	PILOCARPINE HCL	Y
OP	GEL (GRAM)	PILOPINE HS	PILOCARPINE HCL	Y
OP	DROPS	TIMOLOL MALEATE	TIMOLOL MALEATE	Y
OP	DROPS	TIMOPTIC	TIMOLOL MALEATE	Y
OP	DROPS	TRAVATAN	TRAVOPROST	Y
OP	DROPS	TRAVATAN Z	TRAVOPROST	Y
IO	KIT	MIOCHOL-E	ACETYLCHOLINE CHLORIDE	N
OP	DROPS	APRACLONIDINE HCL	APRACLONIDINE HCL	N
OP	DROPERETTE	IOPIDINE	APRACLONIDINE HCL	N
OP	DROPS	IOPIDINE	APRACLONIDINE HCL	N
OP	DROPS SUSP	BETOPTIC S	BETAXOLOL HCL	N
OP	DROPS	BIMATOPROST	BIMATOPROST	N
OP	DROPS	LUMIGAN	BIMATOPROST	N
OP	DROPS	ALPHAGAN P	BRIMONIDINE TARTRATE	N
OP	DROPS	COMBIGAN	BRIMONIDINE TARTRATE/TIMOLOL	N
OP	DROPS SUSP	SIMBRINZA	BRINZOLAMIDE/BRIMONIDINE TART	N
IO	VIAL	MIOSTAT	CARBACHOL	N
OP	DROPS	DORZOLAMIDE HCL	DORZOLAMIDE HCL	N
OP	DROPS	TRUSOPT	DORZOLAMIDE HCL	N
OP	DROPS	PHOSPHOLINE IODIDE	ECHOTHIOPHATE IODIDE	N
OP	DROPS	BETAGAN	LEVOBUNOLOL HCL	N
OP	DROPS	LEVOBUNOLOL HCL	LEVOBUNOLOL HCL	N
OP	DROPERETTE	ZIOPTAN	TAFLUPROST/PF	N
OP	DROPS	BETIMOL	TIMOLOL	N
OP	DROP DAILY	ISTALOL	TIMOLOL MALEATE	N

OP	DROP DAILY	TIMOLOL MALEATE	TIMOLOL MALEATE	N
OP	SOL-GEL	TIMOLOL MALEATE	TIMOLOL MALEATE	N
OP	SOL-GEL	TIMOPTIC-XE	TIMOLOL MALEATE	N
OP	DROPERETTE	TIMOPTIC OCUDOSE	TIMOLOL MALEATE/PF	N
OP	DROPS	VYZULTA	LATANOPROSTENE BUNOD	N
OP	DROPS	RHOPRESSA	NETARSADIL DIMESYLATE	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to February Week 5 2018

Search Strategy:

#	Searches	Results
1	betaxolol.mp. or BETAXOLOL/	924
2	brimonidine.mp. or Brimonidine Tartrate/	1547
3	brinzolamide.mp.	258
4	carteolol.mp. or CARTEOLOL/	426
5	dorzolamide.mp.	885
6	latanoprost.mp.	1628
7	latanoprostene.mp.	9
8	pilocarpine.mp. or PILOCARPINE/	8380
9	TIMOLOL/ or timolol.mp.	4439
10	travoprost.mp. or TRAVOPROST/	546
11	acetylcholine.mp. or ACETYLCHOLINE/	87341
12	apraclonidine.mp.	430
13	bimatoprost.mp. or BIMATOPROST/	592
14	brimonidine.mp. or Brimonidine Tartrate/	1547
15	carbachol.mp. or CARBACHOL/	18323
16	echothiophate iodine.mp.	2
17	levobunolol.mp. or LEVOBUNOLOL/	292
18	tafluprost.mp.	139
19	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	116804
20	limit 19 to (english language and humans and yr="2014 -Current")	3868
21	limit 20 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or systematic reviews)	127

Appendix 3: Prescribing Information Highlights

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

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%, for topical ophthalmic use
Initial U.S. Approval: 2017

----------**INDICATIONS AND USAGE**----------
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

----------**DOSAGE AND ADMINISTRATION**----------
One drop into the affected eye(s) once daily in the evening. (2)

----------**DOSAGE FORMS AND STRENGTHS**----------
Ophthalmic solution containing 0.2 mg/mL of netarsudil. (3)

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

----------**ADVERSE REACTIONS**----------
The most common adverse reaction is conjunctival hyperemia (53%). Other common adverse reactions, approximately 20% include: corneal verticillata, instillation site pain, and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aerie Pharmaceuticals, Inc. at 1-800-xxx-xxxx, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2017

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

VYZULTA (latanoprostene bunod ophthalmic solution) 0.024%, for topical ophthalmic use
Initial U.S. Approval: 2017

---------- **INDICATIONS AND USAGE** ----------
VYZULTA is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

---------- **DOSAGE AND ADMINISTRATION** ----------
One drop in the affected eye(s) once daily in the evening. (2)

---------- **DOSAGE FORMS AND STRENGTHS** ----------
Topical ophthalmic solution: 0.24 mg/mL latanoprostene bunod (0.024%) (3)

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

---------- **WARNINGS AND PRECAUTIONS** ----------
- Pigmentation: Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. (5.1)
- Eyelash changes: Gradual changes to eyelashes including increased length, increased thickness and number of eyelashes. Usually reversible upon discontinuation of treatment. (5.2)

---------- **ADVERSE REACTIONS** ----------
Most common ocular adverse reactions with incidence ≥ 2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2017

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Pharmacy Utilization Summary Report: October 2016 - September 2017

Eligibility	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
Total Members (FFS & Encounter)	990,652	980,593	969,749	956,495	953,093	978,100	991,147	991,908	994,823	982,276	963,901	959,096	975,986
FFS Members	155,740	139,906	142,728	144,554	140,575	146,756	144,374	130,857	135,409	143,784	127,100	130,304	140,174
OHP Basic with Medicare	32,844	32,823	32,859	32,850	32,815	33,065	33,156	33,179	33,308	33,513	33,453	33,651	33,126
OHP Basic without Medicare	13,382	12,478	12,602	12,851	12,507	12,526	12,803	12,559	12,546	12,903	12,546	12,333	12,670
ACA	109,514	94,605	97,267	98,853	95,253	101,165	98,415	85,119	89,555	97,368	81,101	84,320	94,378
Encounter Members	834,912	840,687	827,021	811,941	812,518	831,344	846,773	861,051	859,414	838,492	836,801	828,792	835,812
OHP Basic with Medicare	40,531	40,691	40,697	40,501	40,586	40,562	40,614	40,798	40,843	40,894	40,986	41,036	40,728
OHP Basic without Medicare	67,357	67,819	67,277	67,089	67,386	67,328	67,031	67,125	66,631	63,104	62,676	62,828	66,138
ACA	727,024	732,177	719,047	704,351	704,546	723,454	739,128	753,128	751,940	734,494	733,139	724,928	728,946

Gross Cost Figures for Drugs	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	YTD Sum
Total Amount Paid (FFS & Encounter)	$68,568,897	$68,779,524	$69,468,003	$72,948,816	$69,152,918	$77,031,623	$69,085,807	$76,739,593	$75,672,311	$71,651,239	$74,925,130	$69,374,183	$863,398,047
Mental Health Carve-Out Drugs	$7,589,702	$7,798,638	$7,806,076	$8,124,349	$7,710,837	$8,460,981	$7,737,043	$8,400,181	$8,177,022	$7,999,820	$8,124,790	$7,107,794	$95,037,231
OHP Basic with Medicare	$571	$263	$1,066	$1,485	$1,159	$3,173	$954	$912	$37	$52	$117	$28	$9,816
OHP Basic without Medicare	$3,146,033	$3,327,973	$3,324,446	$3,427,309	$3,256,589	$3,538,455	$3,171,817	$3,442,137	$3,334,781	$3,268,287	$3,296,451	$2,949,544	$39,483,824
ACA	$4,385,772	$4,405,657	$4,419,682	$4,633,011	$4,390,194	$4,840,303	$4,492,656	$4,876,115	$4,767,871	$4,653,663	$4,746,754	$4,102,395	$54,714,075
FFS Physical Health Drugs	$3,617,542	$3,470,318	$3,232,545	$3,784,754	$3,459,044	$3,744,944	$3,271,874	$3,495,982	$3,155,553	$2,858,244	$2,973,141	$2,966,532	$40,030,473
OHP Basic with Medicare	$277,259	$295,141	$203,069	$302,380	$290,114	$264,834	$238,682	$243,141	$230,225	$221,081	$229,559	$226,743	$3,022,228
OHP Basic without Medicare	$1,040,162	$924,704	$880,054	$1,009,187	$927,575	$1,275,703	$1,054,072	$1,121,346	$954,044	$859,691	$1,008,119	$1,051,988	$12,106,645
ACA	$2,193,802	$2,149,825	$2,064,744	$2,355,676	$2,133,470	$2,083,596	$1,823,740	$2,004,592	$1,813,766	$1,656,112	$1,604,917	$1,565,131	$23,449,373
FFS Physician Administered Drugs	$1,716,011	$1,718,203	$2,372,806	$2,889,215	$2,737,539	$2,609,165	$1,864,418	$2,872,642	$2,865,259	$2,037,180	$2,503,458	$1,720,970	$27,906,866
OHP Basic with Medicare	$337,821	$320,603	$321,557	$373,360	$364,872	$442,700	$435,203	$424,610	$334,041	$542,101	$468,952	$333,267	$4,699,086
OHP Basic without Medicare	$340,455	$232,663	$209,043	$325,987	$390,658	$391,838	$251,044	$1,247,266	$1,230,759	$447,963	$306,496	$233,719	$5,607,890
ACA	$820,618	$937,796	$1,094,624	$1,728,441	$1,320,437	$1,331,160	$769,557	$895,817	$918,691	$796,468	$837,130	$923,980	$12,374,717
Encounter Physical Health Drugs	$45,297,444	$46,888,576	$46,115,239	$47,314,442	$44,637,435	$50,872,609	$45,805,929	$50,234,614	$49,448,081	$47,696,231	$49,750,965	$46,877,358	$570,938,923
OHP Basic with Medicare	$141,004	$130,960	$116,418	$122,046	$116,400	$122,034	$115,048	$116,672	$110,047	$111,071	$116,004	$106,295	$1,423,999
OHP Basic without Medicare	$12,397,059	$12,811,332	$12,921,970	$13,137,124	$12,459,281	$13,698,524	$12,357,349	$13,548,810	$13,253,821	$13,234,688	$13,886,643	$12,750,349	$156,456,951
ACA	$32,318,795	$33,424,738	$32,526,502	$33,514,102	$31,471,416	$36,426,143	$32,744,382	$35,867,427	$35,405,854	$33,677,676	$35,004,885	$33,244,119	$405,626,039
Encounter Physician Administered Drugs	$10,348,199	$8,903,788	$9,941,338	$10,836,057	$10,608,063	$11,343,925	$10,406,543	$11,736,175	$12,026,395	$11,059,765	$11,572,776	$10,701,529	$129,484,554
OHP Basic with Medicare	$181,847	$197,460	$214,774	$235,689	$226,316	$272,321	$201,545	$262,234	$210,109	$220,659	$208,202	$176,547	$2,607,703
OHP Basic without Medicare	$2,416,899	$2,205,645	$2,594,041	$2,609,369	$2,360,634	$2,235,402	$2,407,881	$2,598,956	$2,366,106	$2,660,741	$2,635,815	$2,219,683	$29,311,172
ACA	$7,311,887	$6,270,159	$6,880,556	$7,797,632	$7,773,741	$8,655,618	$7,627,805	$8,607,115	$9,281,402	$8,047,684	$8,524,439	$8,132,994	$94,911,032

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: April 25, 2018

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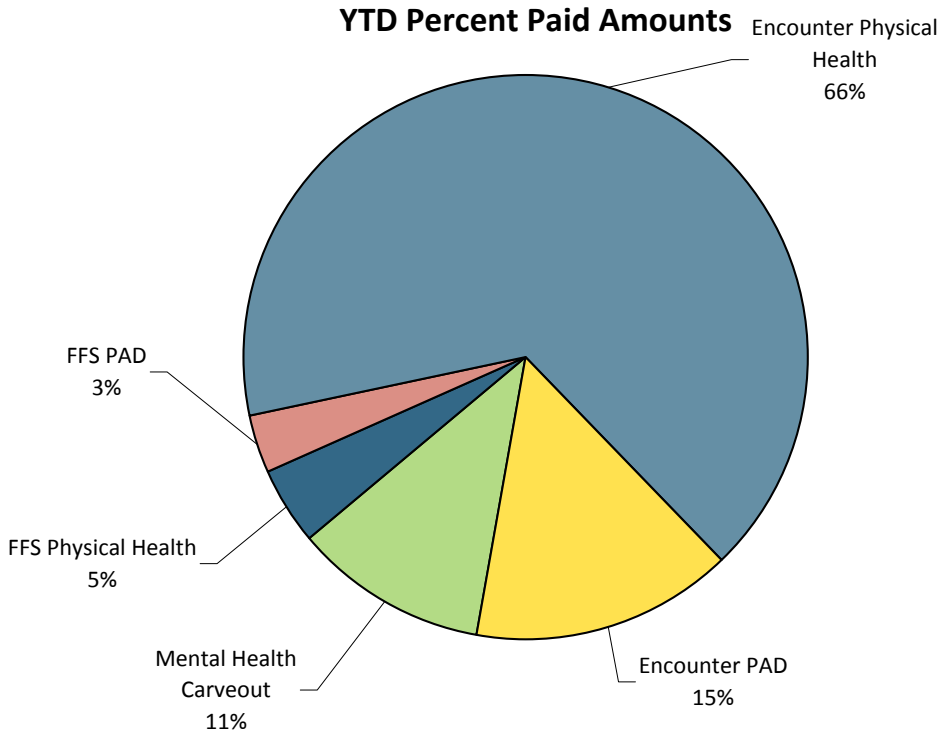
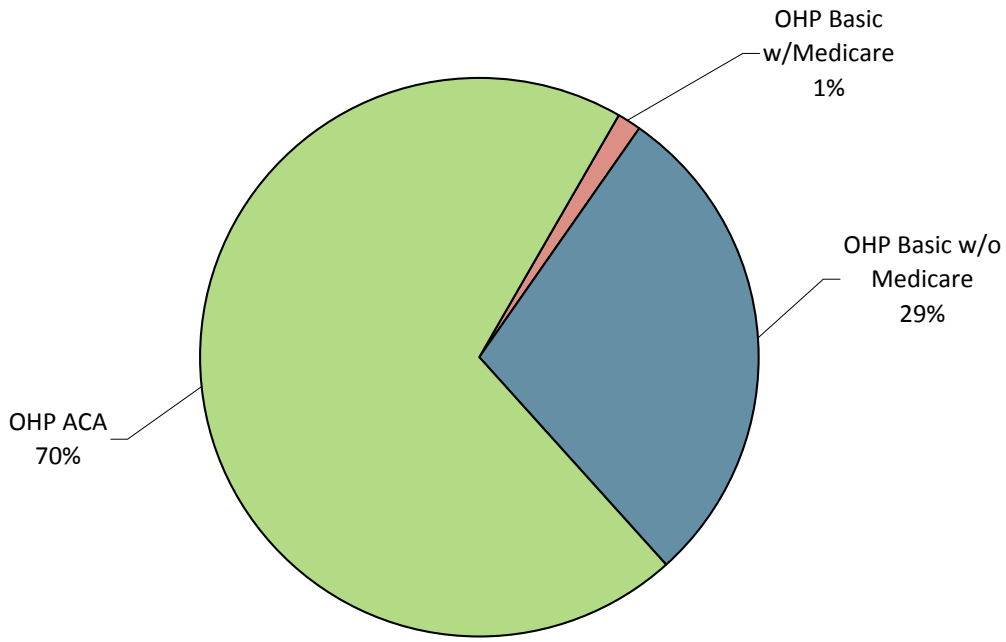
Pharmacy Utilization Summary Report: October 2016 - September 2017





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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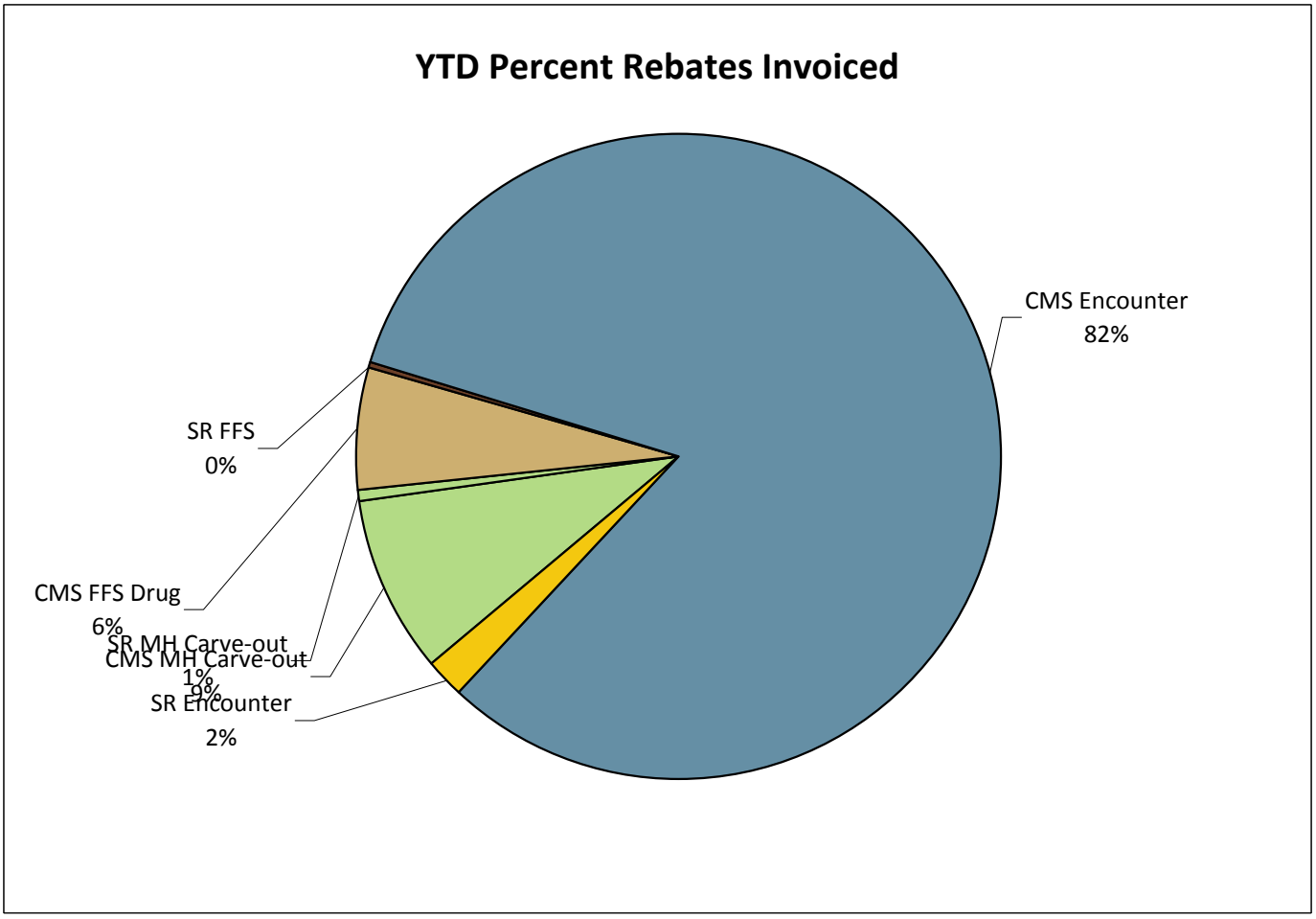
Quarterly Rebates Invoiced	2016-Q4	2017-Q1	2017-Q2	2017-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$100,266,996	$105,615,196	$147,487,521	$99,290,271	$452,659,983
CMS MH Carve-out	$9,516,816	$10,790,702	$10,294,983	$9,385,491	$39,987,992
SR MH Carve-out	$512,346	$634,141	$594,672	$609,692	$2,350,852
CMS FFS Drug	$6,388,318	$7,922,007	$7,566,755	$6,524,342	$28,401,423
SR FFS	$272,718	$207,986	$217,224	$171,620	$869,549
CMS Encounter	$82,129,232	$83,888,481	$125,514,244	$80,468,615	$372,000,572
SR Encounter	$1,447,566	$2,171,878	$3,299,643	$2,130,510	$9,049,597

Quaterly Net Drug Costs	2016-Q4	2017-Q1	2017-Q2	2017-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$106,549,429	$113,518,162	$74,010,190	$116,660,282	$410,738,064
Mental Health Carve-Out Drugs	$13,165,253	$12,871,323	$13,424,591	$13,237,220	$52,698,387
FFS Phys Health + PAD	$9,466,389	$11,094,668	$9,741,749	$8,363,562	$38,666,368
Encounter Phys Health + PAD	$83,917,787	$89,552,171	$50,843,850	$95,059,499	$319,373,308



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

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Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$69.22	$70.14	$71.64	$76.27	$72.56	$78.76	$69.70	$77.37	$76.07	$72.94	$77.73	$72.33	$73.73
Mental Health Carve-Out Drugs	$7.66	$7.95	$8.05	$8.49	$8.09	$8.65	$7.81	$8.47	$8.22	$8.14	$8.43	$7.41	$8.11
FFS Physical Health Drugs	$23.23	$24.80	$22.65	$26.18	$24.61	$25.52	$22.66	$26.72	$23.30	$19.88	$23.39	$22.77	$23.81
FFS Physician Administered Drugs	$11.02	$12.28	$16.62	$19.99	$19.47	$17.78	$12.91	$21.95	$21.16	$14.17	$19.70	$13.21	$16.69
Encounter Physical Health Drugs	$54.25	$55.77	$55.76	$58.27	$54.94	$61.19	$54.09	$58.34	$57.54	$56.88	$59.45	$56.56	$56.92
Encounter Physician Administered Drugs	$12.39	$10.59	$12.02	$13.35	$13.06	$13.65	$12.29	$13.63	$13.99	$13.19	$13.83	$12.91	$12.91

Claim Counts	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
Total Claim Count (FFS & Encounter)	1,012,017	1,007,848	989,256	1,034,218	974,533	1,096,045	1,013,504	1,084,234	1,034,174	984,541	1,025,470	979,026	1,019,572
Mental Health Carve-Out Drugs	146,332	146,370	144,464	148,818	138,426	156,086	146,706	158,936	152,223	147,115	153,298	144,365	148,595
FFS Physical Health Drugs	68,313	67,933	68,123	71,987	67,880	72,373	63,939	67,292	64,193	61,458	62,892	58,889	66,273
FFS Physician Administered Drugs	16,952	16,891	17,444	25,003	22,142	22,617	17,049	17,232	16,671	17,237	17,644	16,551	18,619
Encounter Physical Health Drugs	675,708	675,651	659,486	683,946	644,617	733,823	680,022	732,976	698,266	654,721	682,705	653,741	681,305
Encounter Physician Administered Drugs	104,712	101,003	99,739	104,464	101,468	111,146	105,788	107,798	102,821	104,010	108,931	105,480	104,780

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$67.75	$68.24	$70.22	$70.54	$70.96	$70.28	$68.17	$70.78	$73.17	$72.78	$73.06	$70.86	$70.57
Mental Health Carve-Out Drugs	$51.87	$53.28	$54.03	$54.59	$55.70	$54.21	$52.74	$52.85	$53.72	$54.38	$53.00	$49.23	$53.30
FFS Physical Health Drugs	$52.96	$51.08	$47.45	$52.58	$50.96	$51.75	$51.17	$51.95	$49.16	$46.51	$47.27	$50.37	$50.27
FFS Physician Administered Drugs	$101.23	$101.72	$136.02	$115.55	$123.64	$115.36	$109.36	$166.70	$171.87	$118.19	$141.89	$103.98	$125.46
Encounter Physical Health Drugs	$67.04	$69.40	$69.93	$69.18	$69.25	$69.33	$67.36	$68.54	$70.82	$72.85	$72.87	$71.71	$69.85
Encounter Physician Administered Drugs	$98.83	$88.15	$99.67	$103.73	$104.55	$102.06	$98.37	$108.87	$116.96	$106.33	$106.24	$101.46	$102.94

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$27.06	$27.50	$28.03	$27.47	$27.43	$27.03	$26.32	$26.44	$26.76	$26.82	$26.95	$26.58	$27.03
Mental Health Carve-Out Drugs	$33.82	$33.79	$33.92	$34.23	$34.25	$33.24	$30.95	$30.20	$30.04	$30.32	$28.97	$24.71	$31.54
FFS Physical Health Drugs	$22.58	$23.41	$22.28	$24.04	$23.48	$22.82	$21.01	$21.34	$20.95	$21.36	$21.27	$22.54	$22.26
Encounter Physical Health Drugs	$25.98	$26.49	$27.27	$26.29	$26.32	$26.07	$25.77	$26.06	$26.55	$26.52	$27.00	$27.38	$26.48

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$590.58	$634.43	$635.58	$635.53	$649.08	$657.64	$653.86	$669.36	$683.79	$712.39	$686.09	$618.07	$652.20
Mental Health Carve-Out Drugs	$762.38	$781.59	$793.10	$800.67	$807.82	$808.01	$837.60	$852.43	$864.59	$873.78	$878.97	$878.22	$828.26
FFS Physical Health Drugs	$448.64	$429.23	$389.66	$422.71	$425.32	$446.12	$460.34	$471.08	$438.90	$403.79	$402.34	$394.56	$427.72
Encounter Physical Health Drugs	$591.98	$642.70	$647.60	$644.89	$658.89	$665.93	$656.57	$671.57	$689.80	$725.53	$694.23	$616.15	$658.82

Multi-Source Drug Use Percentage	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
Multi-Source Drug Use Percentage	93.5%	93.8%	93.8%	93.8%	93.9%	93.9%	94.0%	94.0%	94.0%	94.0%	93.8%	93.3%	93.8%
Mental Health Carve-Out Drugs	97.5%	97.4%	97.4%	97.3%	97.2%	97.3%	97.3%	97.2%	97.2%	97.1%	97.2%	97.1%	97.3%
FFS Physical Health Drugs	92.9%	93.2%	93.1%	92.8%	93.2%	93.2%	93.1%	93.2%	93.3%	93.4%	93.2%	92.5%	93.1%
Encounter Physical Health Drugs	92.7%	93.0%	93.1%	93.1%	93.2%	93.2%	93.4%	93.4%	93.3%	93.4%	93.1%	92.5%	93.1%

Preferred Drug Use Percentage	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Avg Monthly
Preferred Drug Use Percentage	85.45%	85.15%	85.11%	86.68%	86.67%	86.64%	86.58%	86.43%	86.30%	86.42%	86.19%	87.08%	86.2%
Mental Health Carve-Out Drugs	76.24%	76.05%	76.03%	75.90%	75.80%	75.68%	75.65%	75.30%	75.10%	74.83%	74.81%	74.73%	75.5%
FFS Physical Health Drugs	95.25%	95.54%	95.44%	95.41%	95.34%	95.31%	95.16%	95.27%	95.24%	95.41%	95.40%	95.55%	95.4%
Encounter Physical Health Drugs	86.48%	86.11%	86.05%	88.09%	88.10%	88.12%	88.14%	88.01%	87.89%	88.14%	87.87%	89.03%	87.7%

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: April 25, 2018

Drug Use Research & Management Program
DHS - Health Systems Division
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Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,280,938	14.9%	4,423	$1,194	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,059,104	5.8%	1,129	$1,824	V
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$972,603	2.7%	531	$1,832	Y
4	REXULTI	Antipsychotics, 2nd Gen	$833,951	2.3%	876	$952	V
5	FLUOXETINE HCL	Antidepressants	$616,736	1.7%	31,183	$20	Y
6	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$612,107	1.7%	1,589	$385	V
7	ATOMOXETINE HCL	ADHD Drugs	$598,580	1.7%	4,933	$121	Y
8	VRAYLAR	Antipsychotics, 2nd Gen	$550,325	1.5%	506	$1,088	V
9	SAPHRIS	Antipsychotics, 2nd Gen	$539,281	1.5%	813	$663	Y
10	INVEGA TRINZA	Antipsychotics, Parenteral	$502,536	1.4%	92	$5,462	V
11	DULOXETINE HCL	Antidepressants	$501,350	1.4%	28,296	$18	V
12	SERTRALINE HCL	Antidepressants	$491,031	1.4%	41,056	$12	Y
13	TRAZODONE HCL	Antidepressants	$431,480	1.2%	37,635	$11	
14	BUPROPION XL	Antidepressants	$421,825	1.2%	20,973	$20	V
15	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$388,899	1.1%	458	$849	Y
16	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$358,018	1.0%	2,254	$159	
17	VIIBRYD	Antidepressants	$357,281	1.0%	1,377	$259	V
18	VENLAFAXINE HCL ER	Antidepressants	$354,792	1.0%	1,801	$197	V
19	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$352,701	1.0%	1,650	$214	V
20	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$350,297	1.0%	14,049	$25	V
21	TRINTELLIX	Antidepressants	$326,425	0.9%	892	$366	V
22	MAKENA*	Progestational Agents	$296,380	0.8%	162	$1,830	Y
23	AMITRIPTYLINE HCL	Antidepressants	$269,602	0.8%	15,745	$17	Y
24	LAMOTRIGINE	Antiepileptics (oral & rectal)	$265,406	0.7%	21,957	$12	Y
25	ESCITALOPRAM OXALATE	Antidepressants	$264,056	0.7%	22,734	$12	Y
26	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$255,147	0.7%	16,622	$15	
27	SPINRAZA*	Oligonucleotides for Muscular Disorders	$250,000	0.7%	2	$125,000	
28	CITALOPRAM HBR	Antidepressants	$240,693	0.7%	23,826	$10	Y
29	ARISTADA	Antipsychotics, Parenteral	$234,979	0.7%	134	$1,754	Y
30	HUMIRA PEN*	Biologics for Autoimmune Conditions	$220,926	0.6%	69	$3,202	Y
31	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$211,185	0.6%	53	$3,985	Y
32	VENLAFAXINE HCL ER	Antidepressants	$199,860	0.6%	14,673	$14	Y
33	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$199,124	0.6%	14,830	$13	Y
34	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$191,540	0.5%	655	$292	V
35	FETZIMA	Antidepressants	$186,991	0.5%	484	$386	V
36	Rituximab Injection	Physican Administered Drug	$181,150	0.5%	61	$2,970	
37	ORKAMBI*	Cystic Fibrosis	$178,290	0.5%	15	$11,886	N
38	METHYLPHENIDATE ER*	ADHD Drugs	$170,497	0.5%	1,217	$140	N
39	Infliximab Not Biosimil 10mg	Physican Administered Drug	$165,866	0.5%	118	$1,406	
40	CLOZAPINE	Antipsychotics, 2nd Gen	$160,798	0.5%	2,911	$55	Y
		Top 40 Aggregate:	**$21,042,750**		**332,784**	**$4,217**	
		All FFS Drugs Totals:	**$35,533,055**		**679,589**	**$493**	

*** 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) - First Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$358,018	2.9%	2,254	$159	
2	MAKENA*	Progestational Agents	$296,380	2.4%	162	$1,830	Y
3	SPINRAZA*	Oligonucleotides for Muscular Disorders	$250,000	2.0%	2	$125,000	
4	HUMIRA PEN*	Biologics for Autoimmune Conditions	$220,926	1.8%	69	$3,202	Y
5	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$211,185	1.7%	53	$3,985	Y
6	Rituximab Injection	Physican Administered Drug	$181,150	1.4%	61	$2,970	
7	ORKAMBI*	Cystic Fibrosis	$178,290	1.4%	15	$11,886	N
8	METHYLPHENIDATE ER*	ADHD Drugs	$170,497	1.4%	1,217	$140	N
9	Infliximab Not Biosimil 10mg	Physican Administered Drug	$165,866	1.3%	118	$1,406	
10	LANTUS	Diabetes, Insulins	$150,920	1.2%	492	$307	Y
11	ADVAIR DISKUS	Corticosteroids/LABA Combination, Inhaled	$138,467	1.1%	451	$307	Y
12	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$135,355	1.1%	2,173	$62	Y
13	GENVOYA	HIV	$132,882	1.1%	57	$2,331	Y
14	ADVATE	Antihemophilia Factors	$127,346	1.0%	10	$12,735	
15	LANTUS SOLOSTAR*	Diabetes, Insulins	$127,185	1.0%	365	$348	Y
16	VENTOLIN HFA	Beta-Agonists, Inhaled Short-Acting	$124,954	1.0%	2,325	$54	Y
17	Inj Pembrolizumab	Physican Administered Drug	$122,580	1.0%	34	$3,605	
18	VYVANSE	ADHD Drugs	$120,264	1.0%	716	$168	Y
19	NUVARING	STC 63 - Oral Contraceptives	$110,756	0.9%	451	$246	
20	PULMOZYME	Cystic Fibrosis	$109,379	0.9%	72	$1,519	Y
21	Factor Viii Recombinant Nos	Physican Administered Drug	$108,810	0.9%	3	$36,270	
22	Injection, Nivolumab	Physican Administered Drug	$106,199	0.8%	79	$1,344	
23	NOVOLOG FLEXPEN	Diabetes, Insulins	$106,018	0.8%	210	$505	Y
24	Drugs Unclassified Injection	Physican Administered Drug	$103,707	0.8%	6,116	$17	
25	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$100,183	0.8%	38	$2,636	
26	TRUVADA	HIV	$96,750	0.8%	77	$1,256	Y
27	FLOVENT HFA	Corticosteroids, Inhaled	$96,464	0.8%	539	$179	Y
28	Pemetrexed Injection	Physican Administered Drug	$94,257	0.8%	22	$4,284	
29	HUMALOG	Diabetes, Insulins	$90,132	0.7%	274	$329	Y
30	TRIUMEQ	HIV	$89,487	0.7%	35	$2,557	Y
31	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$89,458	0.7%	9	$9,940	Y
32	SYNAGIS*	STC 33 - Antivirals	$85,762	0.7%	64	$1,340	
33	Aflibercept Injection	Physican Administered Drug	$85,532	0.7%	166	$515	
34	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$85,408	0.7%	331	$258	Y
35	SPIRIVA	Anticholinergics, Inhaled	$85,399	0.7%	240	$356	Y
36	Etonogestrel Implant System	Physican Administered Drug	$78,306	0.6%	144	$544	
37	ONFI*	Antiepileptics (oral & rectal)	$78,112	0.6%	166	$471	N
38	NOVOLOG	Diabetes, Insulins	$74,777	0.6%	255	$293	Y
39	SABRIL	Antiepileptics (oral & rectal)	$74,691	0.6%	6	$12,449	N
40	HUMIRA*	Biologics for Autoimmune Conditions	$74,542	0.6%	25	$2,982	Y
		Top 40 Aggregate:	**$5,236,395**		**19,896**	**$6,270**	
		All FFS Drugs Totals:	**$12,559,609**		**219,434**	**$504**	

*** 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: April 25, 2018

ProDUR Report for January through March 2018

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	18	5	0	13	0.01%	27.78%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,758	418	1	1,335	1.47%	23.78%
DD (Drug/Drug Interaction)	Set alert/Pay claim	141	44	0	97	0.10%	31.21%
ER (Early Refill)	Set alert/Deny claim	79,582	16,612	134	62,824	68.87%	20.87%
ID (Ingredient Duplication)	Set alert/Pay claim	23,895	6,641	10	17,219	20.63%	27.79%
LD (Low Dose)	Set alert/Pay claim	777	185	0	590	0.60%	23.81%
LR (Late Refill/Underutilization)	Set alert/Pay claim	5	5	0	0	0.01%	100.00%
MC (Drug/Disease Interaction)	Set alert/Pay claim	979	300	0	677	0.80%	30.64%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	736	201	0	535	0.60%	27.31%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	58	41	0	17	0.03%	70.69%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,555	2,244	1	5,305	6.50%	29.70%
	Totals	**115,504**	**26,696**	**146**	**88,612**	**99.61%**	**23.11%**

ProDUR Report for January through March 2018

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,333	246	1,087	11,398	11.7%	18.5%
ER	Hydrocodone/APAP	52	18	34	4,029	1.3%	34.6%
ER	Oxycodone	69	30	39	2,429	2.8%	43.5%
ER	Oxycodone/APAP	21	9	12	1,318	1.6%	42.9%
ER	Tramadol	37	11	26	1,141	3.2%	29.7%
ER	Buspirone (Buspar)	1,841	305	1,536	22,411	8.2%	16.6%
ER	Lorazepam	562	144	418	13,650	4.1%	25.6%
ER	Alprazolam	445	86	359	9,946	4.5%	19.3%
ER	Diazepam	308	72	236	5,483	5.6%	23.4%
ER	Lamictal (Lamotrigine)	4,233	870	3,362	34,861	12.1%	20.6%
ER	Abilify (Aripiprazole)	2,701	536	2,164	20,768	13.0%	19.8%
ER	Seroquel (Quetiapine)	3,533	794	2,739	25,358	13.9%	22.5%
ER	Risperdal (Risperidone)	1,967	467	1,500	13,898	14.2%	23.7%
ER	Wellbutrin (Bupropion)	4,513	805	3,706	47,315	9.5%	17.8%
ER	Zoloft (Sertraline)	5,756	1,100	4,655	53,511	10.8%	19.1%
ER	Prozac (Fluoxetine)	4,058	756	3,302	42,206	9.6%	18.6%
ER	Celexa (Citalopram)	2,654	435	2,219	29,949	8.9%	16.4%

ProDUR Report for January through March 2018

Top Drugs in Early Refill

DUR Alert	1Q2018	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Totals =	12,368	514	676	3,090	21	8,067	0

Drug-Drug Interaction ProDUR

Overview: Drug to Drug Interaction triggers an alert if there is a major interaction between the drug being filled and another drug on the recipient's profile within 125 days from the current claim (this look back period can be changed). "Major" drug interaction parameters are provided by First Data Bank and loaded into the MMIS. Currently, there are >500 listed Major drug interactions.

Looking at the reports for the last few months there are not many times the alert is set (<50 times per month). A vast majority were with ziprasidone. Here are the major DD interactions listed for ziprasidone in the MMIS:

ADI Code	ADI Description	Active	DTE_BEGIN	DTE_END
1114	ZIPRASIDONE/SELECTED ANTIARRHYTHMICS	Y	20140524	22991231
1115	ZIPRASIDONE/PIMOZIDE; THIORIDAZINE	Y	20140524	22991231
1116	ZIPRASIDONE/MOXIFLOXACIN; SPARFLOXACIN	Y	20140524	22991231
1119	ZIPRASIDONE/SELECTED QT PROLONGING AGENTS	Y	20140524	22991231

Some of the most recently added major interactions include:

2877	ATORVASTATIN/OMBITASVIR-PARITAPREVIR-RITONAVIR	Y	20170706	22991231
2878	SELECT IMMUNOSUPPRESSANTS/OMBITASVIR-PARITAPREVIR-RITONAVIR	Y	20170706	22991231
2883	ROSUVASTATIN (> 5 MG)/SOFOSBUVIR-VELPATASVIR-VOXILAPREVIR	Y	20170807	22991231
2886	PRAVASTATIN (> 40 MG)/SOFOSBUVIR-VELPATASVIR-VOXILAPREVIR	Y	20170807	22991231
2890	GLECAPREVIR-PIBRENTASVIR/ATAZANAVIR	Y	20170906	22991231
2891	GLECAPREVIR-PIBRENTASVIR/RIFAMPIN	Y	20170906	22991231
2910	DROSPIRENONE-ETHINYL ESTRADIOL/ATAZANAVIR-COBICISTAT	Y	20171106	22991231
2912	ROSUVASTATIN (> 20 MG)/DARUNAVIR-COBICISTAT	Y	20171106	22991231
2918	ATORVASTATIN (> 20 MG)/ELVITEG-COBIC-EMTRICIT-TENOFOVIR DF	Y	20171106	22991231
2936	RASAGILINE (> 0.5 MG)/SELECTED CYP1A2 INHIBITORS	Y	20180108	22991231
2938	LETERMOVIR/PIMOZIDE	Y	20171206	22991231
2940	ATORVASTATIN (>20 MG)/LETERMOVIR	Y	20171206	22991231
2942	ERGOTAMINE DERIVATIVES/LETERMOVIR	Y	20171206	22991231
2989	DOFETILIDE/BICTEGRAVIR	Y	20180307	22991231
2990	BICTEGRAVIR/RIFAMPIN	Y	20180307	22991231
3000	S-ADENOSYLMETHIONINE (SAM-E)/TRANYLCYPROMINE	Y	20180307	22991231

Problem: 90% clients on CCO and their pharmacy claims history take several weeks to enter the MMIS, so interactions could be missed.

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified			740	
		Unique Patients Identified			1100	
		Prescriptions Changed to Recommended Within 3 Months of Intervention			211	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention			$7,007	
	Lamotrigine ER to IR	Unique Prescribers Identified	324			
		Unique Patients Identified	645			
		Prescriptions Changed to Recommended Within 3 Months of Intervention	120			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$41,685			
	QVAR to fluticasone	Unique Prescribers Identified	400			
		Unique Patients Identified	463			
		Prescriptions Changed to Recommended Within 3 Months of Intervention	57			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	($2,320)			
	Venlafaxine Tabs to Caps	Unique Prescribers Identified		585		
		Unique Patients Identified		807		
		Prescriptions Changed to Recommended Within 3 Months of Intervention		298		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$124,551		

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

Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	189	120	54	
		Total Faxes Successfully Sent	75	46	32	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	20	17	4	
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	13	6	3	
		Prescriptions Unchanged after 3 Months of Fax Sent	36	7		
		Safety Monitoring Profiles Identified	6	8		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$41,202	$33,640	$3,574	

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Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	49	25		
		Estimated Savings				
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	8	1		
		Estimated Savings				
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	49	27		
		Estimated Savings				
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5	4		
		Estimated Savings				
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed	7	13		
		Estimated Savings				
	Lock-In	RetroDUR_Profiles Reviewed	30	33	15	
		RetroDUR_Letters Sent To Providers	1	5	1	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
		Locked In	1	5	1	
		Estimated Savings				
	Polypharmacy	RetroDUR_Profiles Reviewed		60	30	
		RetroDUR_Letters Sent To Providers		9	2	
		Provider Responses		0	0	
		Provider Agreed / Found Info Useful		0	0	
		Estimated Savings		$1,500		

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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	25	23	10	
		Disqualified - Erroneous denial	25	23	10	
		Faxes Sent	5	3	3	
		Fax Sent - Controller	2	2		
		Fax Sent - SABA	3	1	1	
		Fax Sent - Combination Inhaler			1	
		No Subsequent Pulmonary Claims			1	

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What's New with Biologic Agents for Inflammatory Diseases?

By Deanna Moretz, PharmD, BCPS, *Drug Use Research and Management, Oregon State University College of Pharmacy*

Biological response modifiers have proven to be efficacious in treating a wide spectrum of autoimmune diseases including rheumatoid arthritis (RA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC) and Crohn's disease (CD). Approaches to treating rheumatic diseases with biologic agents include interference with cytokine function, inhibition of T-cell activation, or depletion of B cells. In the past few years substantial information about specific agents within this class of drugs has been published due to expanded indications including new pediatric approvals. In addition, several new therapeutic agents including biosimilar products for infliximab, etanercept and adalimumab have received U.S. Food and Drug Administration (FDA) approval, adding to the complexity of this drug class. **Table 1** summarizes the various biologic agents for the most common indications. The purpose of this newsletter is to summarize significant evidence published for biologic agents within the past 2 years for indications that may impact the Oregon Medicaid population.

Table 1. Common Indications for FDA-Approved Biologics

Ankylosing Spondylitis		
Adalimumab (HUMIRA) and biosimilars	Certolizumab pegol (CIMZIA)	Etanercept (ENBREL) and biosimilars
Golimumab (SIMPONI)	Infliximab (REMICADE) and biosimilars	Secukinumab (COSENTYX)
Crohn's Disease		
Adalimumab (HUMIRA)† and biosimilars	Certolizumab pegol (CIMZIA)	Infliximab (REMICADE)† and biosimilars†
Natalizumab (TYSABRI)	Ustekinumab (STELARA)	Vedolizumab (ENTYVIO)
Juvenile Idiopathic Arthritis		
Abatacept (ORENCIA)*	Adalimumab (HUMIRA)* and biosimilars‡	Canakinumab (ILARIS)*
Etanercept (ENBREL)* and biosimilars*	Tocilizumab (ACTEMRA)*	
Plaque Psoriasis		
Adalimumab (HUMIRA) and biosimilars	Brodalumab (SILIQ)	Etanercept (ENBREL)‡ and biosimilars
Guselkumab (TREMFYA)	Infliximab (REMICADE) and biosimilars	Ixekizumab (TALTZ)
Secukinumab (COSENTYX)	Ustekinumab (STELARA) ^	
Psoriatic Arthritis		
Abatacept (ORENCIA)	Adalimumab (HUMIRA) and biosimilars	Apremilast (OTEZLA)
Certolizumab pegol (CIMZIA)	Etanercept (ENBREL) and biosimilars	Golimumab (SIMPONI)
Infliximab (REMICADE) and biosimilars	Ixekizumab (TALTZ)	Secukinumab (COSENTYX)
Ustekinumab (STELARA)		
Rheumatoid Arthritis		
Abatacept (ORENCIA)*	Adalimumab (HUMIRA)* and biosimilars‡	Anakinra (KINERET)
Certolizumab pegol (CIMZIA)	Etanercept (ENBREL) and biosimilars	Golimumab (SIMPONI)
Infliximab (REMICADE) and biosimilars	Rituximab (RITUXAN)	Sarilumab (KEVZARA)
Tocilizumab (ACTEMRA)		
Ulcerative Colitis		
Adalimumab (HUMIRA) and biosimilars	Golimumab (SIMPONI)	Infliximab (REMICADE) and biosimilars

Indications are for adults 18 years and older unless indicated.
Key: * ≥ 2 years old, ‡ ≥ 4 years old, † ≥ 6 years old, ^ ≥ 12 years old

Expanded Indications

Abatacept

The approved age for which subcutaneous (SC) abatacept (Orencia®) can be administered was lowered from 6 years to 2 years for patients with polyarticular juvenile idiopathic arthritis (JIA) in March 2017. Abatacept is a T-lymphocyte inhibitor which is also FDA approved for management of adults with PsA and RA. The intravenous (IV) formulation of abatacept is indicated in pediatric patients 6 years and older. Abatacept also received an expanded FDA indication for treatment of PsA in adults in June 2017. This approval was based on two randomized, double-blind, placebo-controlled studies in adult patients with active PsA despite prior disease modifying treatment.[1,2]

Adalimumab

Adalimumab (Humira®), a tumor necrosis factor (TNF) blocker, was originally approved for the treatment of rheumatoid arthritis (RA) in 2002. In 2016 adalimumab received FDA approval for treatment of non-infectious uveitis in adult patients. The approval was based on a Phase 3 randomized controlled trial (RCT) conducted at 62 study sites in 21 countries.[3] Adults with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by 10–35 mg/day of prednisone were randomly assigned to receive either subcutaneous adalimumab or placebo, with a mandatory prednisone taper from week 2.[3] The primary efficacy endpoint was time to treatment failure. Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.[3] Time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (>18 months vs 8.3 months; hazard ratio (HR) 0.57, 95% CI 0·39–0·84; p=0.004).[3] Adalimumab significantly lowered the risk of uveitic flare or loss of visual acuity upon corticosteroid withdrawal in patients with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by systemic corticosteroids.[3]

Etanercept

Etanercept (Enbrel®), a TNF blocker, arrived on the U.S. market in 1998 for the management of adult RA. It is also indicated for adult PsA, PsO, AS, and JIA. In 2016, the FDA approved etanercept to treat pediatric patients 4 years and older with chronic moderate-to-severe PsO who are candidates for systemic therapy or phototherapy. Dosing of etanercept varies by indication and is administered via SC injection.

Ixekizumab

Ixekizumab (Taltz®), an IL-17 inhibitor, is a recent addition to the biologic agent class. It first received approval to treat adult PsO in 2016 and received an expanded indication for the treatment of adults with active PsA in December 2017. Dosing of ixekizumab varies by indication and is administered via SC injection. Ixekizumab was studied in two phase 3 randomized controlled trials (RCTs) in adult patients with PsA naïve to biologic therapy and in patients with inadequate response to TNF inhibitors.[4,5] The primary endpoint in both trials was the percentage of patients achieving at least 20% improvement in American College of Rheumatology (ACR20) response criteria at week 24. In both studies, patients treated with ixekizumab demonstrated a greater clinical response compared to placebo. In the SPIRIT-P1 trial, significantly more patients naïve to biologic therapy and treated with ixekizumab achieved an ACR20 response with ixekizumab 80 mg every 4 weeks (57.9%) than placebo (30.2%; p≤0.001).[4] In the SPIRIT-P2 trial, a higher proportion of patients who had not responded to TNF inhibitor therapy attained ACR20 with ixekizumab every 4 weeks (53%) than did placebo-treated patients (20%; 95% CI 22.4 to 45.2; p<0.0001).[5]

Biologic agents with pediatric indications include abatacept, adalimumab, canakinumab, etanercept, infliximab, and ustekinumab.

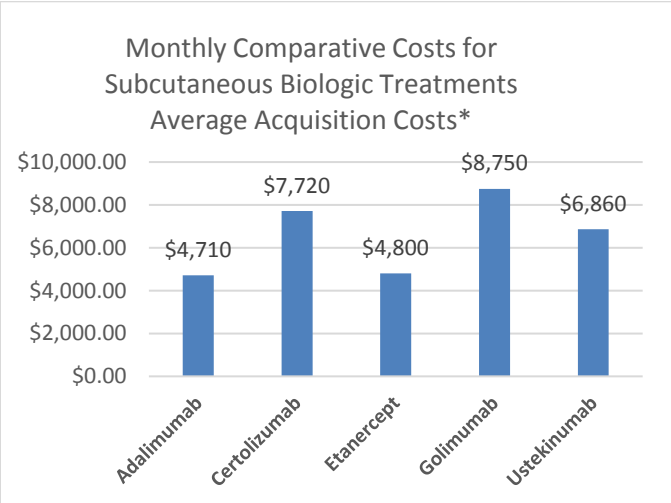
Tocilizumab

Tocilizumab (Actemra®), an IL-6 receptor inhibitor, first was received FDA approval to manage RA via IV infusion in 2010. In May 2017, tocilizumab was approved for the treatment of adult patients with giant cell arteritis (GCA) via subcutaneous injection. This approval was based on a randomized, double-blind, multicenter study in which patients with active GCA were randomized to either tocilizumab 162 mg every week, tocilizumab a 162 mg every other week, or two different placebo groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks).[6] The primary outcome was the rate of sustained glucocorticoid-free remission at week 52. The proportion of patients achieving the primary efficacy endpoint of sustained remission for those treated with tocilizumab weekly was 56.0%, for those treated with tocilizumab every other week was 53.1%, placebo-treated with 26-week prednisone taper was 14.0% and 18% for patients in the placebo group with the 52-week prednisone taper ($p<0.001$ for comparisons of either active treatment with placebo).5 The FDA approved dose of tocilizumab for GCA is 162 mg SC given once a week in combination with a glucocorticoid taper.[7]

Ustekinumab

Ustekinumab (Stelara®), an interleukin (IL)-12/23 inhibitor, was originally approved by the FDA to manage adult patients with moderate to severe PsO when given by SC administration in 2009. Ustekinumab was also approved for the treatment of adults with moderate to severe CD in patients who have failed other treatments in late 2016. Induction dosing for CD begins with a single weight-based IV infusion followed by maintenance dosing of ustekinumab 90 mg SC every 8 weeks.[8] In October 2017, ustekinumab was approved for treatment of adolescent patients aged 12-17 years with PsO.[8] This approval was based on a phase 3 RCT trial of 110 adolescent patients randomized to either placebo or weight-based ustekinumab with a minimum body surface (BSA) involvement of 10%, Psoriasis Area and Severity Index (PASI) score >12, and a Physician's Global Assessment (PGA) score >3 whose disease was inadequately controlled by topical therapy.[9] A greater proportion of ustekinumab-treated patients compared to placebo-treated patients achieved a PGA score of cleared or minimal (69.4% vs. 5.4%; $p<0.001$), PASI 75 (80.6% vs. 10.8%; $p<0.001$), and PASI 90 (61.6% vs. 5.4%; $p<0.001$) at week 12.[9] The only other biologic agent with FDA approval for treatment of PsO in pediatric patients is etanercept.

Table 2: Comparative Costs of Biologic Agents



*Based on commonly prescribed maintenance doses as of January 2018

Newly approved biologics, belimumab, sarilumab, and guselkumab, will be included in a follow-up newsletter to be published later this year.

Preferred biologic agents for Medicaid Fee-For-Service include etanercept and adalimumab.

Conclusion

In the past 2 years adalimumab, ixekizumab, tocilizumab, and ustekinumab have received expanded indications beyond their initial FDA approvals. Etanercept and ustekinumab have received approval for use in pediatric patients with PsO older than 4 and 12 years, respectively. Abatacept is now approved for SC administration in pediatric patients with JIA and is approved to treat PsA.

The biologic agents are available for patients with Medicaid Fee-For-Service insurance through the Oregon Health Plan (OHP). All of the biologic agents require prior authorization but adalimumab and etanercept are preferred agents. Trial and failure of adalimumab and etanercept may be required before advancing to other therapies for AS, PsO, RA or PsA.

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

Peer Reviewed By: Pascale Schwab, MD, Associate Professor of Medicine, Division of Arthritis and Rheumatic Diseases School of Medicine at OHSU and Cong-Qiu Chu, MD, Ph.D, Associate Professor of Medicine, Division of Arthritis and Rheumatic Diseases School of Medicine at OHSU

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AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
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Second Generation Antipsychotic Use in Major Depressive Disorder

Pearce Engelder, PharmD and Kathy Sentena, PharmD, both from Drug Use Research and Management, Oregon State University College of Pharmacy

Background

In the United States, major depressive disorder (MDD) is a chief contributor to disability and the tenth leading cause of death.[1-3] MDD is defined as a history of one or more major depressive episodes (characterized by 2 or more consecutive weeks with depressed mood or loss of interest alongside other depressive symptoms) without previous mania. Annually, about 7% of U.S. adults report at least 2 weeks of depressed mood or loss of pleasure in daily activities.[4,5] The annual rate is higher in adults treated in rural and urban primary care clinics (estimates range from 10%-29%).[4] About two-thirds of these episodes are accompanied by severe impairment that interferes with daily activities and interpersonal relationships.[5] The increasing incidence of MDD is also associated with a rising number of patients being prescribed second generation antipsychotics (SGA) as part of a treatment regimen for MDD. SGAs reduce symptoms of anxiety and personality disorders that are often concomitant with MDD. This newsletter will review the evidence for the use of SGAs as adjunctive therapy for MDD.

When cognitive therapy alone is unable to improve symptoms of depression, initiation of pharmacotherapy is recommended.[1] Second generation antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]), are recommended first-line based on similar efficacy and improved adverse effect profiles over first generation antidepressants.[2] According to the American Psychiatry Association (APA), the goals of antidepressant treatment are to achieve remission (defined as ≥3 weeks with the absence of both sad mood and reduced interest and ≤3 remaining symptoms of the major depressive episode), improve functionality, and increase quality of life.[3]

It is estimated that one-third to one-half of patients fail initial antidepressant therapy.[4] Patients who are nonresponsive to initial therapy should be considered for the following: optimization of the dose of current treatment, depression-focused psychotherapy or switch to a different antidepressant.[3] A trial that examined a sequential approach to antidepressant treatment failure found about two-thirds of patients failed initial treatment and required either a change to a different antidepressant or addition of adjunctive therapy.[6] Therapy changes continued based on failure of response, up to a fourth treatment stage.[7] After one year, two-thirds of patients were in remission; however, the rate of remission decreased each time therapy was changed.[6,7]

Augmentation Therapy

There is limited evidence to guide optimal adjunctive treatment; however, augmentation therapy is considered appropriate for patients with two or more treatment failures.[2] The APA MDD guidelines describe several different strategies for patients who require adjunctive therapy, including the addition of another antidepressant (from a different pharmacological class) or non-antidepressant such as lithium, thyroid hormone or a SGA.[3] Guideline recommendations from the Veterans Administration (VA) suggest that SGAs should be considered only after failure of other treatment options due to significant potential for adverse events.[8]

Four SGAs have Food and Drug Administration (FDA) approval for MDD and two are used off-label. Cost comparisons of treatment options used for augmentation therapy are presented in Table 1.[3,9]

Table 1. Cost of SGAs used as Augmentation Therapy for MDD[3,9]

Medication[3]	Daily Dose	30 Day Supply
Risperidone*	2 mg	$1
Buspirone*	15 mg	$2
Mirtazapine	30 mg	$2
Lithium*	300 mg	$3
Quetiapine	200 mg	$3
Trazodone	150 mg	$3
Bupropion SR	150 mg	$11
Ziprasidone*	60 mg	$12
Aripiprazole	15 mg	$16
Quetiapine ER	200 mg	$30
Olanzapine/ Fluoxetine (Symbyax™)	6 mg/50 mg	$401
Olanzapine + fluoxetine	5 mg + 40 mg	$4
Brexpiprazole (Rexulti®)	2 mg	$974
Cariprazine (Vraylar®)	3 mg	$1,155

Oregon Health Authority Average Actual Acquisition Costs (2/13/18)
* Treatments used off-label for MDD

Evidence for Augmentation with SGAs

A high quality systematic review and meta-analysis done by the Agency for Healthcare Research and Quality (AHRQ) identified 26 trials lasting 4-9 weeks that evaluated off-label uses of atypical antipsychotics for use in MDD.[10] There was insufficient evidence on direct comparisons of SGAs used for MDD.

- There was moderate quality evidence of efficacy, compared to placebo, for aripiprazole, quetiapine and risperidone when used adjunctively with SRRIs or SNRIs for the treatment of MDD (Table 2).
- Quetiapine extended release (ER) monotherapy demonstrated moderate evidence of efficacy in MDD based on Montgomery-Åsberg Depression Rating Scale (MADRS) remission rates (relative risk [RR] 1.43; 95% CI, 1.07 – 1.91; number needed to treat [NNT] 13) and MADRS response rates (RR 1.49; 95% CI, 1.23 to 1.81; NNT 6).[10]
- Active treatment comparisons found that the addition of an SGA to SSRI or SNRI resulted in improvement in symptoms compared to either a SSRI or SNRI alone. Combinations that were studied were: olanzapine/fluoxetine, ziprasidone/sertraline, quetiapine/paroxetine or quetiapine/venlafaxine.[10]

Table 2. SGA Augmentation in MDD[10]

Antipsychotic	Remission	Response
Aripiprazole*	RR 1.57 (95% CI: 1.24-2.00)/ NNT NP	RR 1.66 (95% CI: 1.37-2.01) / NNT 7
Quetiapine†	RR 2.76 (95% CI: 1.21-6.28) / NNT 5	RR 2.30 (95% CI: 1.35-3.92) / NNT 3
Risperidone†	RR 2.10 (95% CI: 1.43-3.09) / NNT 8	RR 1.50 (95% CI: 1.20-1.87) / NNT 7

Abbreviations: CI – confidence interval, NNT – number needed to treat, NP – not provided, RR – relative risk
*Key: * Based on MADRS scale , † Based on HAM-D Scale*

New SGAs for MDD Augmentation

Brexpiprazole – Brexpiprazole is the most recently FDA-approved SGA indicated for adjunctive treatment of MDD. Approval was based on two, phase 3, 6-week, double-blind studies in adult patients with a history of inadequate response to 1-3 previous antidepressants.[11,12] Both studies were funded by industry. In the first study, 379 patients were randomized to brexpiprazole 2 mg/day plus an antidepressant or placebo plus an antidepressant (36% SNRIs and 64% SSRIs).[11] Results are most applicable to patients similar to trial participants with the following characteristics: mean MADRS score of 27 (moderate depression), mean age 45 years, 70% women, 87% Caucasian.

The MADRS scale has 10 items associated with major depression with a range of 0-6 points for each item. Response is often defined as a 50% or greater decrease in MADRS from baseline and remission is a MADRS score of 10 or less.[13]

Study findings did not demonstrate a clinically relevant improvement for the primary outcome of reduction in MADRS total score. There was a mean reduction of -8.36 with brexpiprazole and –5.15.[11] With a mean MADRS score at baseline of 27, a decrease of around 8 points is unlikely to be clinically meaningful.

In the second study, patients (n=677) were given brexpiprazole 3mg/day, brexpiprazole 1 mg/day or placebo in addition to an assigned antidepressant (47% SNRIs and 53% SSRIs).[12] Included patients had a mean MADRS score of 26.5 (moderate depression), mean age of 47 years and 68% of patients were women. The brexpiprazole 3 mg/day group was found to lower MADRS scores more than placebo, but not to a clinically significant degree (95% CI, -3.39 to -0.51).[12] Changes for brexpiprazole 1 mg were not statistically different from placebo (-7.64 vs. -6.33), respectively.

With such a small effect on MADRS scores, it is unlikely that brexpiprazole has a clinical impact on depression symptoms. Common adverse events in both studies were weight gain and akathisia.

Cariprazine – Cariprazine is an SGA approved by the FDA in 2015 for schizophrenia and bipolar I disorder that has also been studied off-label for MDD. Cariprazine was studied in a randomized, placebo-controlled, double-blind trial lasting only 8-weeks in adult patients (n=808) with MDD and inadequate antidepressant response (baseline mean MADRS total score of 29).[14] Patients were a mean age of 46 years, 71% were women and 87% were Caucasian. Cariprazine 1-2 mg/day or 2-4.5 mg/day was given as an adjunct to SSRI or SNRI therapy and compared with placebo added to SSRI or SNRI treatment.

Results from augmentation with doses of 1-2 mg/day cariprazine were not statisttically significantly different from placebo. Response rates for cariprazine, based on changes in MADRS scores, were not clinically significantly different.[14] Adverse events occurring in greater than or equal to 10% of patients treated with cariprazine were akathisia, insomnia and nausea.

Overall, the evidence suggests that these new SGAs are not effective as adjunctive therapy in MDD. Both treatments are limited by small, short-term studies in patients with moderate depression.

Adverse Events

Common adverse events associated with all SGAs are weight gain, fatigue, sedation, akathisia and extrapyramidal symptoms. Additionally, specific SGAs are associated with a higher incidence of certain adverse reactions (Table 3).

Table 3. Select SGA Adverse Events [10,15]

Antipsychotic	Major Side Effect	NNH
Aripiprazole	Akathesia/Parkinsonism	7
Olanzapine	Weight gain	3
Quetiapine	Sedation	11
Risperidone	Increased risk of stroke in elderly	53
All SGAs (pooled)	Increased risk of death in elderly	87

Abbreviations: NNH – number needed to harm, SGA – second generation antipsychotic

Conclusions

- Aripiprazole, quetiapine and risperidone, when used for augmentation with SSRIs or SNRIs, have demonstrated the strongest evidence as augmentation therapy in patients with MDD who have failed other treatments. **Risperidone and quetiapine are both preferred treatments for Oregon Health Plans fee-for-service patients.**
- Newer SGAs are costlier and offer no efficacy advantage over generic options. There is insufficient long-term evidence for second generation antipsychotics as augmentation therapy for MDD.
- Second generation antipsychotics can have significant adverse events not associated with second generation anti-depressants.

For these reasons, SGAs should be considered for MDD augmentation only after exploring other treatment options.

Peer Reviewed By: William Nunley, MD, MPH and Cydreese Aebi PhD, RPh., Clinical Pharmacy Coordinator, Oregon State Hospital, Salem, Oregon

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New Drug Evaluation: Belimumab Injection, Intravenous and Subcutaneous

Date of Review: May 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 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.	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% Key Inclusion Criteria: -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 Key Exclusion Criteria: -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	ITT: 1.288 2.290 3.287 PP: 1.240 2.241 3.226 Attrition: 1. 48 (16.6%) 2. 49 (16.8%) 3. 61 (21.3%)	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%) Secondary Endpoints: ≥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%) 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%) 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	7%/15 14%/8 7%/15 12%/9 NS 8%/13 10%/10 11%/9	AE: 1.264 (92%) 2.266 (92%) 3.263 (92%) SAE: 1.47 (16%) 2.41 (14%) 3.36 (13%) Discontinuation due to SAE: 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 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 prednisone (>7.5mg/day) was higher in Latin America. 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: 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. Reporting Bias: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline. GSK also assisted in drafting the article and interpreting data. **Applicability**: Patient: 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. Intervention: 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%). Comparator: Placebo appropriate to determine efficacy on background SOC. 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.

				3. 199 (69%)				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: 7.5y -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) -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	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: ≥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%) 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%) 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) 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 10%/10 NS 11%/9 NS 9%/11 NS 10%/10 NS 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	**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%)

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	Demographics: -Mean age: 39 years -Female 94% -Hispanic or Latino: 29% -Mean SELENA-SLEDAI score ≥10: 60% -Mean PGA: 1.5 -Disease duration: 4 years Key Inclusion Criteria: -Age ≥18 y -SLE (SELENA-SLEDAI score ≥8 -Stable SLE medication regimen 30 days prior to study enrollment Key Exclusion Criteria: -Active lupus nephritis or CNS lupus	ITT: 1.556 2.280 PP: 1. 463 2. 214 Attrition: 1. 93 (16.7%) 2. 66 (23.6%)	Primary Endpoint: 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) Secondary Endpoint: 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): Selection Bias: UNCLEAR. Randomized 2:1, not clear how randomization was completed. Subjects stratified according to SELENA-SLEDAI score, complement level, and race. Performance Bias: UNCLEAR. Not clear how investigators were blinded and if protocol was standardized. Detection Bias: UNCLEAR. Blinding of outcome assessors was by the GSK physicians. Attrition Bias: HIGH. Higher attrition rate in placebo arm vs drug arms (23.6% vs 16.7%) Reporting Bias: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline Applicability: Patient: Patients had more severe disease as assessed by SELENA-SLEDAI score ≥ 8 than BLISS trials (≥ 6). Intervention: 200 mg once per week selected to achieve AUC similar to 10 mg/kg IV every 4 weeks Comparator: Placebo Outcomes: Composite SRI index with limitation as noted above Setting: 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) pharmacy and physician administered claims

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active lupus nephritis or severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
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*

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Drug Class Update with New Drug Evaluation: Fluoroquinolones

Date of Review: May 2018
Generic Name: delafloxacin

End Date of Literature Search: 12/30/2017
Brand Name (Manufacturer): Baxdela™ (Melinta Therapeutics, Inc)
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.

Author: K. Choi, PharmD Candidate, Megan Herink, PharmD

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, *Streptococci*, 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 2. 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.[16,17] 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 one 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.

In the second noninferiority study (study 303), with high risk of bias, 423 patients were randomized to delafloxacin and 427 patients were randomized to vancomycin plus aztreonam.[16] 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%). Overall, 19 (2.2%) patients had bacteremia at baseline and gram-negative pathogens were identified in 20.7%.

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 3**).

Table 3. 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 4**). 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 4. 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 5. 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/lesion size)
2) Investigator-assessed cure at follow up (complete or near resolution of signs and symptoms, with no further antibiotics needed)

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Pullman et al. (Study 302)[17] 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 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	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 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. O' Riordan et al. (Study 303)[16] 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), S. aureus identified (57.5%) 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 compromised immune system, liver disease, CrCl < 15ml/min, peripheral neuropathy, > 200 kg, other severe underlying comorbidities	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: 1. 16/417 (3.8%) 2. 17/425 (4.0%)	NS NS	**Risk of Bias (low/high/unclear)**: High Selection Bias: UNCLEAR; No information on method of randomization or allocation concealment. Higher rates of MRSA detected in delafloxacin group than placebo (24% vs. 18.1%). 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: LOW. ITT analysis performed for efficacy. Overall attrition was 13.6% but similar between groups. (13.5% in DFX and 13.8% in VANC/AZT) Reporting Bias: HIGH. 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. 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 (inpatient or outpatient) in 16 countries in North America, Latin America, Eastern Europe, and Asia. 46.8% were from North America.

*Systemic signs of infectionincluded lymph node enlargement, elevated C-reactive protein (>10x upper limit of normal), elevated white blood cell count (≥10,000 cell/µL), fever (≥38°C), purulent drainage, 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).

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: Medications for *Clostridium difficile* Infection

Date of Review: May 2018
Generic Name: Bezlotoxumab Infusion
PDL Class: Clostridium Difficile Antibiotics

Date of Last Review: May 2015
Literature Search: 01/01/2015 – 03/14/18
Brand Name (Manufacturer): Zinplava (Merck)
AMCP Dossier Received: Yes

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

Purpose for Class Update:
Review a new therapy, bezlotoxumab, targeted against *Clostridium difficile* toxin B to reduce the incidence of recurrent *Clostridium difficile* infection (CDI). In addition, any new comparative evidence for existing agents in this class will be reviewed and summarized.

Research Questions:
1. What is the comparative efficacy or effectiveness of metronidazole, vancomycin and fidaxomicin in treating patients with CDI?
2. What are the comparative harms of metronidazole, vancomycin and fidaxomicin when used for CDI treatment?
3. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status, type of pain, or comorbidities) for which one antibiotic is more effective or associated with more harm than other antibiotics?

Conclusions:
- Since the last literature scan on antibiotics for CDI, two new systematic reviews were published.[1,2] The Agency for Healthcare Research and Quality (AHRQ) evaluated recent comparative evidence for vancomycin, metronidazole and fidoxamicin.[1] Moderate quality evidence found vancomycin to be more effective than metronidazole for initial cure of CDI in adults.[1] In the prevention of recurrent CDI, moderate quality evidence supported the superior effectiveness of fidaxomicin over vancomycin.[1] A second systematic review from Cochrane reinforced the findings of the AHRQ report. The Cochrane review pooled date from four trials of moderate quality to support vancomycin superiority over metronidazole for achieving resolution of mild to moderate CDI with no relapse.[2] In the pooled analysis, 72% of metronidazole patients achieved symptomatic cure compared to 79% of vancomycin patients (RR 0.90, 95% Confidence Interval (CI) 0.84 to 0.97).[2] Two large studies of moderate quality found fidaxomicin superior to vancomycin in resolving symptoms of CDI.[2] In the Cochrane pooled analysis, 71% of fidaxomicin patients achieved symptomatic cure compared to 61% of vancomycin patients (relative risk [RR] 1.17, 95% CI 1.04 to 1.31).[2]
- The Infectious Disease Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) 2017 guideline updates recommend using oral vancomycin or fidaxomicin for an initial CDI episode.[3] Metronidazole is no longer recommended as a first line agent, except in circumstances where access to

vancomycin or fidaxomicin is limited or in initial cases of non-severe CDI.[3] The recommendations for treating recurrent CDI suggest trying an alternative antibiotic (vancomycin or fidaxomicin) than the medication that was used for the first episode of CDI.[3] Metronidazole is not recommended for treatment of recurrent CDI.[3] Although the comparative effectiveness of metronidazole and vancomycin in pediatric CDI is insufficient, either weight-based oral metronidazole or vancomycin are recommended for an initial episode or first recurrence of CDI in children.[3] Fidaxomicin is not FDA-approved for use in children less than 18 years of age, so it is not included in the IDSA/SHEA pediatric recommendations.[3]

- Two phase 3 trials (MODIFY I and MODIFY II) of moderate quality were conducted to evaluate the safety and efficacy of bezlotoxumab, a human monoclonal antibody, in reducing the incidence of recurrent CDI.[4] In both MODIFY I and MODIFY II, the rate of CDI recurrence through week 12 was significantly lower in the bezlotoxumab arms compared to the placebo arms (MODIFY I: 17% vs. 28%; 95% CI, -15.9 to -4.3; p <0.001; MODIFY II: 16% vs 26%; 95% CI, -15.5 to -4.3; p < 0.001).[4] Bezlotoxumab is not indicated for the treatment of CDI and is only approved for use in combination with antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg infusion.[5]
- During the 2 clinical trials, the most common adverse reactions occurring with bezlotoxumab within 4 weeks of infusion with a frequency greater than placebo included nausea (7% vs 5%), pyrexia (5% vs 3%) and headache (4% vs 3%).[4] In bezlotoxumab-treated patients, 10% experienced one or more infusion specific adverse reactions compared to 8% of placebo-treated patients.[4] In patients with a history of congestive heart failure [CHF], 12.7% of bezlotoxumab-treated patients and 4.8% of placebo-treated patients had the serious adverse reaction of heart failure exacerbation during the 12-week study period.[4] Additionally, in patients with a history of CHF, there were more deaths in bezlotoxumab-treated patients (19.5%) than in placebo-treated patients (12.5%).[4]

Recommendations:

- No further review or research needed at this time.
- Designate bezlotoxumab as a non-preferred drug subject to Prior Authorization.
- Modify fidaxomicin PA criteria to remove metronidazole as a prerequisite to fidaxomicin in patients with recurrent CDI.
- Review comparative drug costs in the executive session.

Previous Conclusions:

- There is moderate strength of evidence oral vancomycin is superior to oral metronidazole for clinical cure of first episode of mild to moderate *Clostridium difficile* infection. There is moderate strength of evidence of no difference between oral vancomycin and oral fidaxomicin in clinical cure rate of first episode of CDI. There is insufficient evidence to compare efficacy between metronidazole and fidaxomicin.
- There is high strength evidence that oral vancomycin is superior to oral metronidazole in severe or complicated CDI but there is insufficient evidence to support the use of fidaxomicin alone for complicated or fulminant CDI.
- There is moderate strength of evidence to repeat the initial antibiotic course for first recurrence of CDI, though moderate quality evidence suggests a course of fidaxomicin is superior to a course of oral vancomycin at preventing further recurrences of CDI. However, following a full-dose course of vancomycin with a slow taper or pulsed dosing over several weeks may also decrease recurrent cases of CDI.
- There is high quality evidence for 10 days of CDI treatment with insufficient evidence to support longer duration of therapy; the exception being pulsed or tapered vancomycin in cases of multiple recurrent CDI that may be given for several weeks after a full dose 10-day course is completed.
- There is insufficient evidence to support the combination of two orally administered antibiotics. Anecdotal evidence, however, suggests intravenous metronidazole or rectal enema administration of vancomycin may be helpful as adjunctive therapy in complicated or fulminant CDI, but never as monotherapy.

Previous Recommendations:

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

Background:

CDI has become the most common cause of health care–associated infections in American hospitals, and the additional annual health care costs related to CDI are estimated to be as much as $5.9 billion.[6] The Centers for Disease Control and Prevention (CDC) has identified CDI as a global public health threat due to the emerging prevalence of more virulent *C.difficile* strains and increasing mortality rates due to resistant strains of the bacteria.[7] Community associated CDI is also on the rise and is estimated to occur in one third of all CDI cases.[8] The frequency of recurrent CDI is about 21%.[9] Antibiotic exposure, in particular clindamycin, cephalosporins, and fluoroquinolones increase the risk of developing CDI.[10] All fluoroquinolone antibiotics carry a warning regarding CDI development. Broad spectrum antibiotics reduce normal gut flora which results in *C.difficile* overgrowth in the colon. Other risk factors for CDI include older age, recent hospitalization, inflammatory bowel disease, immunodeficiency, chemotherapy, chronic kidney disease, gastrointestinal surgical procedures, or use of a feeding tube. Toxigenic *C.difficile* bacteria produce both toxin A and toxin B or just toxin B. These toxins disrupt epithelial integrity, stimulate release of inflammatory mediators, and result in pseduomembrane formation.[11] Type 027 is a *C.difficile* strain that produces more types of toxins than other types of *C.difficile*; resulting in more severe CDI and possibly higher mortality rates.[12]

The diagnosis of CDI is based on clinical history and laboratory findings of *C.difficile* toxins in the stool. Symptoms include presence of diarrhea (defined as ≥ 3 unformed stools in 24 hours), cramps, fever, or lower abdominal pain. Laboratory testing cannot distinguish between colonization and infection. The gold standard for CDI diagnosis is lab verification of toxigenic *C.difficile* in stool along with histopathology showing psuedomembranes in patients with clinical symptoms.[11] Symptoms of CDI can range in severity from mild diarrhea to toxic megacolon, fulminant colitis, colonic perforation, multi-organ failure and death.[13] Treatment goals include resolution of diarrhea and reduction of CDI recurrence. Severe CDI may be accompanied by leukocytosis with a white blood cell count (WBC) greater than 15,000 cells/µL and elevated serum creatinine 1.5 times the patients' baseline value secondary to dehydration from extensive diarrhea. Some of the literature uses a Zar score to stratify patients with CDI into mild or severe groups. In the Zar severity scoring, one point each is assigned for age greater than 60 years, temperature greater then 38.3°C, albumin level less than 2.5 mg/dl or WBC greater than 15,000 cells/µl.[14] Patients that score greater than or equal to 2 points are considered to have severe CDI.[14] Severe, complicated CDI can result in shock, hypotension, ileus or megacolon. Recurrent CDI is defined by IDSA/SHEA as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.[15]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 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 and recent evidence-based 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:

Agency for Healthcare Research and Quality

In 2016 AHRQ published an updated systematic review on the early diagnosis, prevention, and treatment of CDI, which reviewed data from 2010 through April 2015.[1] Updated antibiotic comparative evidence comes from a RCT comparing fidaxomicin to vancomycin, [16] a 3-arm RCT comparing tolevamer (a non-antibiotic, toxin-binding resin not approved in the U.S.) to metronidazole and vancomycin, [17] and a 3-arm prospective cohort study comparing intravenous (IV) metronidazole to oral metronidazole and vancomycin.[18] The data from the prospective observational cohort study were not included in the AHRQ pooled analysis of RCTs. Data from the 2 recent RCTs were combined with studies from the original 2011 AHRQ report to assess the efficacy of each therapeutic intervention. A summary of all trials, findings and strength of evidence from the AHRQ reports to date is outlined in **Table 1**. Tolevamer does not have any antimicrobial activity, and its efficacy in treating CDI was inferior to metronidazole and vancomycin.[1] Therefore, it was excluded from the pooled data. The finding that vancomycin is more effective than metronidazole for initial cure of CDI in adults was new to the 2016 update.[1] New evidence for the superior effectiveness of fidaxomicin over vancomycin for the prevention of recurrent CDI was also included in the update.[1] No new evidence supports the use of nitazoxanide or rifaximin in preventing recurrent CDI.[1]

Table 1: Summary of standard treatment findings using pooled RCT data from original 2011 AHRQ report and 2016 update[1]

Intervention	Study Information	Findings	Strength of Evidence
Vancomycin vs. metronidazole	4 RCTs N=872	Initial Cure: favors vancomycin over metronidazole (83.9% vs. 75.7%) RR 1.08, 95% CI 1.02 to 1.15	High
	N=705	Recurrent CDI: not significantly different (16.5% vs. 18.7%) RR 0.89, 95% CI 0.65 to 1.23	Moderate
Fidaxomicin vs. vancomycin	2 RCTs N=1,111	Initial Cure: not significantly different (87.6% vs. 85.6%) RR 1.02, 95% CI 0.98 to 1.07	Moderate
	N=962	Recurrent CDI: favors fidaxomicin over vancomycin (14.1% vs. 26.1%) RR 0.55, 95% CI 0.42 to 0.71	High
Abbreviations: CDI = *Clostridium difficile* infection; CI = confidence interval; RCT = randomized controlled trial; RR = relative risk			

Cochrane Collaboration

A 2017 Cochrane systematic review evaluated evidence through January 2017 that studied antibiotic treatment for CDI in adults.[2] Twenty-two studies including 3215 subjects were included in the review. Most of the studies evaluated patients with mild to moderate CDI taking oral antibiotics 4 weeks after completion of therapy. Sixteen studies excluded patients with severe CDI and the other 6 studies had relatively few patients with severe CDI. Twelve different antibiotics were studied: vancomycin, metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin, cadazolid, LFF517, surtomycin and fidaxomicin. The studies that evaluated metronidazole, vancomycin and fidaxomicin were of moderate quality.[2] For the other nine antibiotics, the evidence was rated as having a high risk of bias due to small study size and substantial patient drop-out before study completion.[2] Four trials provided moderate quality evidence to support vancomycin superiority over metronidazole for achieving resolution of mild to moderate CDI with no relapse.[2] In the pooled analysis, 72% (318/444) of metronidazole patients achieved symptomatic cure compared to 79% (339/428) of vancomycin patients (RR 0.90, 95% CI 0.84 to 0.97).[2] Two large studies of moderate quality found fidaxomicin superior to vancomycin in resolving symptoms of CDI.[2] In the pooled analysis, 71% (407/572) of fidaxomicin patients achieved

symptomatic cure compared to 61% (361/592) of vancomycin patients (RR 1.17, 95% CI 1.07 to 1.27).[2] The differences in effectiveness between these antibiotics were not too large and the advantage of metronidazole is its far lower cost compared to the other two antibiotics.[2] There were no head-to-head trials of fidaxomicin and metronidazole. No firm conclusions can be drawn regarding the efficacy of antibiotic treatment in severe CDI as most studies excluded patients with severe disease.[2]

New Guidelines:

Infectious Disease Society of America/Society for Healthcare Epidemiology of America

Infectious Disease Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) 2017 guideline updates were published February 2018.[3] The literature search for the updated guidelines was conducted from 2009 through 2016 for evidence in adult and pediatric patients.[2] The time frame for the literature search did not include bezlotoxumab evidence, therefore bezlotoxumab was not included in the updated guidelines. The most recent treatment guidelines recommend using oral vancomycin or fidaxomicin for an initial CDI episode.[3] Oral fidaxomicin has been associated with a lower recurrence rate than oral vancomycin but is more costly.[3] Metronidazole is no longer recommended as a first line agent, except in circumstances where access to vancomycin or fidaxomicin is limited or in initial cases of non-severe CDI.[3] Non-severe CDI is characterized by a white blood cell count (WBC) less than or equal to 15,000 and serum creatinine less than 1.5 mg/dl.[3] In severe CDI, WBC greater than or equal to 15,000 and serum creatinine greater than 1.5 mg/dl are observed.[3] The initial treatment recommendations for CDI are based on the same evidence evaluated by recent systematic reviews compiled by AHRQ and the Cochrane Collaboration. Severe, complicated CDI is now referred to a fulminant CDI in the IDSA/SHEA guidelines.[3] Higher doses of oral vancomycin are recommended for patients with fulminant CDI symptoms, which has not changed from the original 2010 IDSA/SHEA guidance. If ileus is present, rectal vancomycin and intravenous metronidazole are recommended to achieve significant levels in the inflamed gastrointestinal tract.[3] The recommendations for treating recurrent CDI suggest trying an alternative antibiotic (vancomycin or fidaxomicin) than the medication that was used for the first episode.[3] If vancomycin was used for the first CDI episode, modifying the subsequent vancomycin dose to a tapered and pulsed regimen for recurrent CDI is another strategy to manage recurrent CDI.[3] Metronidazole is not recommended for treatment of recurrent CDI.[3] Patients who have failed to resolve recurrent CDI despite repeated antibiotic treatments may be candidates for fecal microbiota transplantation (FMT).[3] **Table 2** summarizes recommended IDSA/SHEA treatments for various presentations of CDI in adults.

Robust data assessing the optimal approach for treating CDI in children are limited.[3] Although the comparative effectiveness of metronidazole and vancomycin in pediatric CDI is insufficient, either weight-based oral metronidazole or vancomycin are recommended for an initial episode or first recurrence of CDI in children.[3] For second CDI recurrences, vancomycin is recommended over metronidazole in pediatric patients.[3] Fidaxomicin is not FDA approved for use in children less than 18 years of age, so it is not included in the IDSA/SHEA pediatric recommendations.[3] **Table 3** summarizes treatment recommendations for CDI in children.

Table 2. IDSA/SHEA Recommendations for the Treatment of *Clostridium difficile* Infection in Adults[3]

Clinical Definition	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	• Vancomycin 125 mg given 4 times daily for 10 days, OR	Strong/High
	• Fidaxomicin 200 mg given twice daily for 10 days	Strong/High

Clinical Definition	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
	• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days[a]	Weak/High
Initial episode, severe[b]	• Vancomycin 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
	• Fidaxomicin 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	• Vancomycin 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present.	Strong/Moderate (oral vancomycin); Weak/Low (rectal vancomycin); Strong/Moderate (intravenous metronidazole)
First recurrence	• Vancomycin 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
	• Use a prolonged tapered and pulsed vancomycin regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
	• Fidaxomicin 200 mg given twice daily for 10 days if vancomycin was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	• Vancomycin in a tapered and pulsed regimen, OR	Weak/Low
	• Fidaxomicin 200 mg given twice daily for 10 days, OR	Weak/Low
	• Fecal microbiota transplantation[c]	Strong/Moderate

a. All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.
b. The criteria proposed for defining severe or fulminant CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

c. The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

Table 3. IDSA/SHEA Recommendations for the Treatment of *Clostridium difficile* Infection in Children

Clinical Definition	Recommended Treatment	Pediatric Dose	Maximum Dose	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low Weak/Low
Initial episode, severe/ fulminant	• Vancomycin × 10 days (PO or PR) with or without metronidazole × 10 days (IV)[a]	• 10 mg/kg/dose qid • 10 mg/kg/dose tid	• 500 mg qid • 500 mg tid	Strong/Moderate Weak/Low
First recurrence, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low
Second or subsequent recurrence	• Vancomycin in a tapered and pulsed regimen[b], OR • Fecal microbiota transplantation	• 10 mg/kg/dose qid • Vancomycin: 10 mg/kg/dose qid;	• 125 mg qid • Vancomycin: 500 mg qid	Weak/Low Weak/Very low

Abbreviations: IV, intravenous; PO, oral; PR, rectal; qid, 4 times daily; tid, 3 times daily.

a.In cases of severe or fulminant CDI associated with critical illness, consider addition of intravenous metronidazole to oral vancomycin.
b. Tapered and pulsed regimen: vancomycin 10 mg/kg with max of 125 mg 4 times per day for 10–14 days, then 10 mg/kg with max of 125 mg 2 times per day for a week, then 10 mg/kg with max of 125 mg once per day for a week, and then 10 mg/kg with max of 125 mg every 2 or 3 days for 2–8 weeks.

National Institute for Health and Care Excellence

National Institute for Health and Care Excellence (NICE) prepared an evidence summary of bezlotoxumab for preventing recurrent CDI.[12] The report provides an analysis of the Phase 3 trials (MODIFY I and MODIFY II) which evaluated the safety and efficacy of bezlotoxumab in preventing recurrence of CDI in patients taking standard-of-care antibiotics. NICE guidance for utilization of bezlotoxumab is expected to be published late May of 2018.

New Formulations:
None identified.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 72 citations were manually reviewed from the initial literature search. After further review, all 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: Bezlotoxumab Infusion

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:
Bezlotoxumab is a human monoclonal immunoglobulin antibody that binds to and neutralizes *C. difficile* toxin B. Bezlotoxumab received Food and Drug Administration (FDA) approval in October 2016 for reduction of CDI recurrence in conjunction with antibacterial treatment in adults at high risk for CDI recurrence.[5] Bezlotoxumab does not have antibacterial properties and is not indicated as monotherapy for CDI treatment; therefore bezlotoxumab should only be used in combination with antibiotic therapy proven to treat CDI. The recommended dose is a single dose of 10mg/kg administered as an intravenous infusion over 60 minutes during antibacterial treatment for CDI.[5] A trial evaluating the safety and efficacy of bezlotoxumab in children with CDI (MODIFY III) is currently recruiting patients.[19]

Two multi-centered, phase 3, double-blind studies (MODIFY I and II) were conducted to evaluate the safety and efficacy of bezlotoxumab in patients receiving standard-of-care antibiotics for primary or recurrent CDI.[4] Bezlotoxumab either alone or in combination with actoxumab (a human monoclonal antibody that neutralizes *C difficile* toxin A), was compared to placebo to assess the primary efficacy endpoint of rate of recurrent CDI during the 12 weeks after infusion of the study drug.[4] Actoxumab was included in the MODIFY trials to meet FDA recommendations that evaluations of therapies neutralizing toxin A and toxin B be studied separately. Standard-of-care antibiotics included vancomycin, metronidazole or fidaxomicin. The study drug was administered at some point during the 10 to 14 day course of standard-of-care antibiotics at the discretion of the health care provider. The studies were conducted in both hospital and outpatient settings. Enrolled patients were 18 years of age or older and had a confirmed diagnosis of CDI, which was defined as diarrhea (passage of 3 or more loose bowel movements in 24 or fewer hours) and a positive stool test for toxigenic *C. difficile* from a stool sample collected no more than 7 days before study entry.[4]

In the MODIFY I study, patients were randomized 1:1:1:1 to receive a single, one-time infusion of 10 mg/kg of either bezlotoxumab, actoxumab, the combination of bezlotoxumab and actoxumab, or placebo.[4] CDI recurrence was defined as the development of a new episode of diarrhea associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the presenting CDI episode.[4] Patients were assessed for clinical cure of the presenting CDI episode, defined as no diarrhea for 2 consecutive days, following the completion of a 14 day antibiotic regimen.[4] Patients who achieved clinical cure were then assessed for recurrence of CDI through 12 weeks following administration of the study drug.[4] A secondary endpoint, sustained clinical response, was defined as clinical cure of the

presenting CDI episode and no CDI recurrence through 12 weeks after infusion.[4] MODIFY II had similar inclusion and exclusion criteria and similar definitions of clinical endpoints as the MODIFY I trial.[4]

The interim analysis of the MODIFY I trial showed the rate of recurrent infection was significantly higher in the actoxumab group than in the actoxumab–bezlotoxumab group (p=0.02), and more deaths and serious adverse events were found to have occurred in the actoxumab group than in the placebo group.[4] Actoxumab was not efficacious when given alone, so enrollment in the actoxumab monotherapy group was stopped. In the MODIFY II study, the monotherapy actoxumab arm was excluded and patients receiving standard antibiotics for CDI were randomized 1:1:1 to receive a single, one-time, 10 mg/kg infusion of either bezlotoxumab, bezlotoxumab and actoxumab, or placebo.[4]

In both MODIFY I and MODIFY II, the rate of CDI recurrence through week 12 was significantly lower in the bezlotoxumab arms compared to the placebo arms (MODIFY I: 17.4% vs. 27.6%; 95% CI, 15.9 to 4.3; p =0.0003; Absolute Risk Reduction (ARR) 10; NNT 10 and MODIFY II: 15.7% vs. 25.7%; 95% CI 15.5 to 4.3; p = 0.0003, ARR 10; NNT 10).[4] For the secondary endpoint, sustained clinical cure, there was a statistically significant difference between bezlotoxumab and placebo in MODIFY II (66.8% vs. 52.1%; 95% CI 7.7 to 21.4; p <0.0001) but not in MODIFY I (60.1% vs. 55.2%; 95% CI -2.1 to 11.7; p=0.17).[4] However, in the pooled dataset from both trials, the sustained clinical cure rate observed with bezlotoxumab was 63.5% compared to 53.7% with placebo (95% CI 4.8 to 14.5; p=0.0001).[4]

Limitations:
In the MODIFY trials, a similar proportion of patients received oral metronidazole (48%) or oral vancomycin (48%) while 4% of the patients received oral fidaxomicin as the standard-of-care antibiotic.[4] Because only 4% of participants were taking fidaxomicin in the trials, so it is unclear what benefits bezlotoxumab has in patients who received fidaxomicin. Although it is not specifically licensed for this indication, there is some evidence that fidaxomicin reduces recurrence of CDI compared with vancomycin, and it is not known whether bezlotoxumab offers any benefits over fidaxomicin alone.[12] The duration of benefit of bezlotoxumab beyond a 12 week follow-up is unknown. In addition, the optimal timing of bezlotoxumab administration in conjunction with standard-of-care antibiotics is not clear since bezlotoxumab was administered at variable times based on provider discretion.

Which patient populations are likely to derive the greatest benefit from bezlotoxumab administration is not clear as it was administered to patients with first and recurrent episodes of CDI. Many participants in the trials did not have severe CDI or risk factors for developing severe or recurrent infection. For example, about 65% did not have a previous history of CDI, about 70% of participants were aged less than 75 years, and about 80% of the participants had a Zar score below 2, indicating less severe infection.[12] Low numbers of participants with immunosuppression, elevated temperature or white blood cell count, impaired renal or hepatic function or other serious conditions, (such as pseudomembranous colitis or toxic megacolon) were included in the phase 3 trials.[12]

The FDA noted a number of significant challenges in interpreting the data from the two MODIFY trials. The pre-specified primary endpoint in both trials was the proportion of subjects with CDI recurrence during the 12-week follow-up period after infusion of study drug.[20] The FDA had raised concerns about the CDI recurrence endpoint prior to the commencement of the second trial while the first trial was still ongoing.[20] The concern with the CDI recurrence endpoint is that it ignores the potential impact of the investigational drug on initial clinical cure and counts patients who do not have initial clinical cure of their presenting CDI episode as successes (i.e. not having a recurrence).[20] The FDA had noted that if an imbalance in the initial cure rates is seen, the effect of the study drug on recurrence can be very difficult to interpret.[20] The Agency recommended that the manufacturer use a primary endpoint of global cure (sustained clinical response) defined as clinical cure of the initial CDI episode and absence of CDI recurrence.[20] However, the manufacturer did not modify the trial design after receiving FDA guidance.

In both Phase 3 trials, recurrence rates in the 12-week follow up period were lower in patients who received bezlotoxumab compared to those who received placebo.[20] However, the imbalance in initial cure rates, especially the lower cure rates seen in the bezlotoxumab arm in MODIFY I, make it difficult to interpret the efficacy of bezlotoxumab using recurrence rate as the primary endpoint.[20] Global cure or sustained clinical response is a valid measure of the efficacy of bezlotoxumab and is the more interpretable endpoint because it considers both initial cure of the CDI episode and absence of recurrence.[20] To be a success, a patient needs to achieve clinical cure of the CDI episode and not have a recurrence. While in both trials, there was favorable treatment effect with bezlotoxumab for the pre-specified primary endpoint of reducing recurrences, in both trials there was an imbalance in the initial cure rate (one in favor of bezlotoxumab, the other against bezlotoxumab).[20] While sustained clinical response was not the manufacturer's pre-specified primary endpoint, in the setting of an imbalance in the initial cure rate, the recurrence endpoint is difficult to interpret making it reasonable to evaluate the trials using sustained clinical response as the primary endpoint.[20]

Clinical Safety:

The most common adverse reactions occurring with bezlotoxumab within 4 weeks of infusion with a frequency greater than 4% are outlined in **Table 4**. In patients with a history of CHF, 12.7% (15/118) of bezlotoxumab-treated patients and 4.8% (5/104) of placebo-treated patients had the serious adverse reaction of heart failure exacerbation during the 12-week study period.[5] Additionally, in patients with a history of CHF, there were more deaths in bezlotoxumab-treated patients (19.5%) than in placebo-treated patients (12.5%).[5] The causes of death varied, and included cardiac failure, infections, and respiratory failure.

Table 4. Adverse Reactions Reported with Bezlotxoumab[5]

Adverse Reaction	Bezlotoxumab (n = 786)	Placebo (N=781)
Nausea	7%	5%
Pyrexia	5%	3%
Headache	4%	3%
Infusion Related Reactions	10%	8%

Table 5 summarizes the pharmacology and pharmacokinetic properties of bezlotoxumab. **Table 6** summarizes the characteristics of the MODIFY I and II trials.

Table 5. Pharmacology and Pharmacokinetic Properties

Parameter	
Mechanism of Action	Human monoclonal antibody that binds to *C.difficile* toxin B and neutralizes its effects
Distribution and Protein Binding	Volume of distribution: 7.33 liters
Elimination	N/A
Half-Life	19 days
Metabolism	Protein Catabolism

Abbreviations: NA = not applicable

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Recurrent CDI in subpopulations at risk for recurrence (age > 65 yo, Prior CDI within past 6 months, immunocompromised)
2) Proportion of patients with global cure
3) Proportion of patients with initial clinical cure
4) Serious adverse events
5) Discontinuations due to adverse events

Primary Study Endpoint:

1) Proportion of patients with recurrent CDI at 12 weeks

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Wilcox MH, et al.[21] DB, PC, MC, RCT 2 Phase 3 trials [MODIFY I (n = 1452; 158 sites in 19 countries) and MODIFY II (n= 1203; 171 sites in 17 countries)]	1. Actoxumab + Bezlotoxumab x1 dose (10 mg/kg each) 2. Actoxumab x1 dose (10 mg/kg) 3. Bezlotoxumab x1 dose (10 mg/kg) 4. Placebo	Demographics: -Median age: 65 y -White: 86% -Inpatient: 68% -Female: 56% -Age ≥65 y: 53% - ≥1 CDI episode in past 6 mos: 28% - ≥2 previous CDIs: 14% -Antibiotics: Metronidazole: 49% Vancomycin: 47% Fidaxomicin: 4% Key Inclusion Criteria: -Adults ≥ 18 years with CDI receiving SOC therapy. (CDI defined as ≥ 3 unformed stools in 24 hours with positive stool test for toxigenic *C.difficile*.)	ITT: 1.773 2.232 3.781 4.773 Attrition: 1.114 (15%) 2.34 (15%) 3.111 (14%) 4.126 (16%)	Primary Endpoint: Proportion of patients with recurrent CDI at 12 weeks MODIFY I: Bezlotoxumab: 17.4% (67/386) Placebo: 27.6% (109/395) Adjusted Difference: 10.1% (95% CI, 15.9 to 4.3; p=0.0003) MODIFY II: Bezlotoxumab: 15.7% (62/395) Placebo: 25.7% (97/378) Adjusted Difference: 9.9% (95% CI, 15.5 to 4.2; p=0.0003) Secondary Endpoints: Sustained cure: initial CDI cure and no CDI recurrence through week 12 MODIFY I 3.60.1% (232/386) 4.55.2% (218/395) Adjusted Difference: 4.8% (95% CI, -2.1 to 11.7; p=0.1722) MODIFY II 3.66.8% (264/395) 4. 52.1% (197/378) Adjusted Difference: 14.6% (95% CI, 7.7 to 21.4; p=0.0001)	10.1 /10 9.9 /10 NS 14.6/ 7	AE (4 weeks after infusion) 1.59% 2.67% 3.62% 4.61% SEA: 1.16% 2.28% 3.20% 4.21% Death: 1.4% 2.6.0% 3.4% 4.4% Nausea: 1. 6% 2. 12% 3. 6% 4. 5% Infusion Site Reactions: 1. 8% 2. 11% 3. 10% 4. 8%	NA NA NA NA NA	**Study: Moderate Quality** **Risk of Bias (low/high/unclear)**: Selection Bias: **Unclear**. Randomized 1:1:1:1 after stratification into 2 groups based on SOC therapy and hospitalization status (inpatient vs. outpatient). Details of randomization process not included in protocol. Performance Bias**: Low**. Unblinded pharmacist prepared the infusion, but not involved in patient assessment. All other investigators were blinded. SOC therapy determined by prescribing physician. Detection Bias: **Low**. Data assessors were blinded. Data from 2 trials pooled to enhance statistical assessment. Attrition Bias: **Low**. Attrition rates were similar across all 4 arms. Analysis completed in ITT population. Reporting Bias: **Low**. All authors reviewed and edited manuscript. Funded by Merck. **Applicability**: Patient: Primarily used in an inpatient setting in older patients – no differentiation between initial or recurrent CDI patients. Intervention: Bezlotoxumab studied as a one-time 10 mg/kg dose only. Actoxumab arm stopped early due to interim analysis showing no benefit and possible harm. No information available about re-dosing

		Key Exclusion Criteria: -UC or Crohn's Disease -Receipt of cholestyramine, rifaximin, or nitazoxanide within 14 days prior to study dose or during the 12 week study		(Pooled data Modify I and II) 3. 63.5% 4. 53.7% Adjusted difference 9.7% (95% CI, 4.8 to 14.5%; p=0.0001)	9.7/ 11	Headache: 1. 4% 2. 6% 3. 5% 4. 3%	NA	bezlotoxumab –only studied as a one-time infusion in conjunction with antibiotic therapy. Comparator: Placebo appropriate as no other therapies are approved to prevent CDI recurrence in combination with SOC. Outcomes: Global cure would have been a better primary endpoint. Longer follow-up needed to determine durability of bezlotoxumab or if re-dosing is needed. Setting: 322 sites in 30 countries with 60% of sites represented outside of U.S.

Abbreviations: AE = Adverse effect; CDI = *Clostridium difficile* infection; CI = confidence interval; DB = double blind; ITT = intention to treat; MC = multi center; Mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; RCT = randomized controlled trial; SAE = serious adverse effect; SOC = standard of care (metronidazole, vancomycin, or fidaxomicin); UC = ulcerative colitis; Y = Years

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAVEN	VIAL	VANCOMYCIN HCL	VANCOMYCIN HCL	Y
ORAL	CAPSULE	VANCOCIN HCL	VANCOMYCIN HCL	Y
ORAL	CAPSULE	VANCOMYCIN HCL	VANCOMYCIN HCL	Y
ORAL	CAPSULE	FLAGYL	METRONIDAZOLE	Y
ORAL	CAPSULE	METRONIDAZOLE	METRONIDAZOLE	Y
ORAL	TABLET	FLAGYL	METRONIDAZOLE	Y
ORAL	TABLET	METRONIDAZOLE	METRONIDAZOLE	Y
ORAL	TABLET ER	FLAGYL ER	METRONIDAZOLE	Y
ORAL	TABLET	DIFICID	FIDAXOMICIN	N
IV	VIAL	ZINPLAVA	BEZLOTOXUMAB	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 3 2017

1 exp Clostridium difficile/	*11358*
2 vancomycin.mp. Or exp Vancomycin/	*23770*
3 metronidazole.mp. or exp Metronidazole/	*16817*
4 fidaxomicin.mp.	*249*
5 bezlotoxumab	*30*
6 2 or 3 or 4 or 5	*39462*
7 1 and 6	*2010*
8 limit 7 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase IV or comparative study or controlled clinical trial or meta-analysis or practice Guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews	*357*
9 limit 8 to English language and humans and yrs. =2015-current	*72*

ZINPLAVA- bezlotoxumab injection, solution
Merck Sharp & Dohme Corp.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZINPLAVA™ (bezlotoxumab) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

ZINPLAVA is a human monoclonal antibody that binds to Clostridium difficile toxin B, indicated to reduce recurrence of Clostridium difficile infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence. (1)

Limitation of Use:

ZINPLAVA is not indicated for the treatment of CDI. ZINPLAVA is not an antibacterial drug. ZINPLAVA should only be used in conjunction with antibacterial drug treatment of CDI. (1)

DOSAGE AND ADMINISTRATION

- Administer ZINPLAVA during antibacterial drug treatment for CDI. (2.1)
- The recommended dose is a single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes. (2.2)
- Dilute prior to intravenous infusion. Administer via a low-protein binding 0.2 micron to 5 micron in-line or add-on filter. See Full Prescribing Information for dilution and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 1,000 mg/40 mL (25 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Heart Failure: Was reported more commonly in ZINPLAVA-treated patients with a history of congestive heart failure (CHF) in the two Phase 3 clinical trials. In patients with a history of CHF, ZINPLAVA should be reserved for use when the benefit outweighs the risk. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (reported in ≥4% of patients) included nausea, pyrexia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 10/2016

Fidaxomicin (Dificid®)

Goal(s):

- To optimize appropriate treatment of *Clostridium difficile*-associated infection.

Length of Authorization:

10 days

Requires PA:

- Fidaxomicin

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 *Clostridium difficile*-associated infection (CDI)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Will the prescriber consider changing to a preferred antibiotic? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Does the patient have at least one documented trial of or contraindication to appropriate therapy with vancomycin ~~or metronidazole for a first recurrence or contraindication to therapy~~?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have severe, complicated CDI (life-threatening or fulminant infection or toxic megacolon)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 10 days

P&T / DUR Review: *5/18 (DM); 5/15; 4/12*
Implementation: *TBD; 7/1/15; 7/12*

Bezlotoxumab (Zinplava™)

Goal(s):

- To optimize appropriate prevention of recurrent *Clostridium difficile*-associated infection.

Length of Authorization:

- One time infusion

Requires PA:

- Bezlotoxumab (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. Does the patient have a diagnosis of **recurrent** *Clostridium difficile*-associated infection (CDI)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient currently receiving metronidazole, vancomycin or fidaxomicin?	**Yes**: Approve for one dose	**No**: Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *5/18(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: Botulinum Toxins

Date of Review: May 2018 **Date of Last Review:** May 2014

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

Purpose for Class Update:
Review evidence for uses of botulinum toxin and funding for these indications under the Oregon Health Plan (OHP) Prioritized List of Health Services.

Research Questions:
1. Are there differences in efficacy/effectiveness between botulinum toxin (BoNT) therapy to support choosing a specific BoNT based on indication?
2. Are there differences in harms between BoNT therapy to support restricting use of a specific BoNT based on indication?
3. Are there subpopulations based on demographic characteristics (i.e., age, gender, comorbid conditions) in which certain BoNT therapies may be more effective or safer than others?

Conclusions:
- Six new high quality systematic reviews of BoNT treatment for conditions funded under the OHP were identified. These reviews focused on the efficacy of BoNT treatment for limb spasticity, symptomatic benign prostatic hyperplasia (BPH), strabismus, and cervical dystonia. The American Academy of Neurology (AAN) also published a practice guideline update on BoNT treatment for blepharospasm, cervical dystonia, adult spasticity, and headache.
- A systematic review with meta-analyses evaluated efficacy of BoNT type A (BoNTA) treatment on improving 'ease of care' for patients the upper and lower limb spasticity. A meta-analysis of BoNTA for 4 to 12 weeks for treatment of upper limb spasticity demonstrated a statistically significant effect for all outcomes in favor of BoNTA based moderate quality evidence (standardized mean difference [SMD] 0.80; 95% confidence interval [CI], 0.55 to 1.06; p<0.001).[9] The relative risk for the global assessment of benefit measures was 2.21 (95% CI, 1.67 to 2.93; p<0.0001, number needed to treat [NNT]=5) if rated by patients and 2.51 (95% CI, 1.21 to 5.20, p=0.01, NNT=6) if rated by the clinician.[9] A meta-analysis of upper limb outcomes for 12 to 24 weeks demonstrated a continued statistically significant effect in favor of BoNTA for individual outcomes (SMD 0.48; 95% CI, 0.34 to 0.62; p<0.001).[9] For lower limb studies, both the patient- and clinician-rated scores failed to demonstrate a significant effect and were rated as low to insufficient evidence.[9]
- Another systematic review examined the efficacy of BoNTA on improving activity restriction (i.e., active function) of the upper and lower limbs and quality of life in patients with spasticity. Active range of motion in the upper limb was examined in 8 studies using stroke patients but nearly all of them found no statistically significant difference between BoNTA and placebo.[10] Only one of 3 studies found statistically significant improvement of active range of motion in lower limbs.[10] No statistically significant differences were found in 7 studies that evaluated timed walk tests.[10] Overall evidence for these

outcomes was insufficient to low quality primarily due to lack of study directness and small sample sizes.[10] Data were insufficient to assess effect of BoNTA on quality of life.[10]

- A systematic review was performed to assess the overall treatment efficacy and safety of BoNTA for benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS). The pooled overall SMD in the mean change in International Prostate Symptom Score (IPSS) from baseline for BoNTA versus the placebo group was −1.02 (95% CI −1.97, −0.07).[11] Overall, there is low quality evidence that BoNTA for BPH with LUTS is not more efficacious than placebo and that there are no differences in adverse events.[11]
- The Cochrane collaboration examined the efficacy of BoNT in the treatment of strabismus. The systematic review with meta-analyses found insufficient evidence for effect of BoNT on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and BoNT are combined.[12] High quality trials using robust methodologies are required to compare the clinical efficacy of various formulations of BoNT, to compare BoNT with and without adjuvant solutions, and to compare BoNT to alternative surgical interventions in strabismus cases with and without potential for binocular vision.[12]
- The Cochrane collaboration updated a 2003 review that compared efficacy of BoNTA versus BoNT type B (BoNTB) for cervical dystonia.[13] All trials evaluated the effect of a single BoNT treatment session, and not repeated treatment sessions, using doses from 100 units to 250 units of BoNTA (all onabotulinumtoxinA [onaBoNTA] formulations) and 5,000 units to 10,000 units of BoNTB (rimabotulinumtoxinB [rimaBoNTB]).[13] The meta-analysis found no difference between the 2 types of BoNT in terms of overall efficacy, with a mean difference of -1.44 (95% CI -3.58 to 0.70) points lower on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for BoNTB-treated participants, measured at 2 to 4 weeks after injection. The proportion of patients with adverse events was also not different between BoNTA and BoNTB (BoNTB vs. BoNTA: RR 1.40; 95% CI 1.00 to 1.96). Overall, they found low quality evidence that a single treatment of onaBoNTA and a single treatment of rimaBoNTB are equally effective and safe in the treatment of adults with certain types of cervical dystonia.[13]
- Based on evidence reviewed by the AAN, either onaBoNTA or incobotulinumtoxinA (incoBoNTA) are recommended (Level B), and abobotulinumtoxinA (aboBoNTA) may be considered (Level C), as treatment options for blepharospasm; onaBoNTA should be offered as a treatment option to patients with chronic migraine to increase the number of headache-free days (Level A) and should be considered to reduce headache impact on health-related quality-of-life (Level B); aboBoNTA and rimaBoNTB should be offered (Level A), and onaBoNTA and incoBoNTA should be considered (Level B), as options for the treatment of cervical dystonia; for focal manifestations of adult spasticity involving the upper limb, aboBoNTA, incoBoNTA, and onaBoNTA should be offered (Level A), and rimaBoNTB should be considered (Level B), as treatment options; and for focal manifestations of adult spasticity involving the lower limb that warrant treatment, onaBoNTA and aboBoNTA should be offered (Level A) as treatment options.[16]
- IncoBoNTA (Xeomin) received an indication in December 2015 for the improvement of adult patients with upper limb spasticity.[17]
- AboBoNTA (Dysport) received an indication in July 2016 for the treatment of lower limb spasticity in pediatric patients 2 years of age and older and an indication in June 2017 for treatment of lower limb spasticity in adult patients.[1]

Recommendations:

- Update current clinical prior authorization criteria to reflect current coverage and guidelines in the OHA Prioritized List of Health Services.

Previous Conclusions:

- There is moderate quality evidence that BoNTA is recommended first-line for cervical dystonias due to increased efficacy compared to standard therapies. BoNTB is recommended for BoNTA-resistant dystonias. There is low quality evidence of no difference between aboBoNTA and onaBoNT in the treatment of cervical dystonia.
- There is low quality evidence demonstrating efficacy of BoNTA for the treatment of blepharospasm. However, open-label studies have demonstrated a significant effect size and clinical practice guidelines recommend BoNT as a treatment option for blepharospasm. There is low quality evidence of no difference between aboBoNTA and onaBoNTA and no difference between aboBoNTA and incoBoNTA in the treatment of blepharospasm.
- There is moderate quality evidence that aboBoNTA, onaBoNTA and rimaBoNTB reduces muscle tone and improves passive function for upper limb spasticity and low-quality evidence for lower limb spasticity. There is insufficient evidence for an effect on active function.
- There is low quality evidence that unspecified BoNTA products may be associated with benefit in the prophylaxis of chronic migraine headaches (≥15 days a month), but results are inconsistent. In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headaches per month. There is moderate quality evidence of no benefit of prophylaxis with BoNTA in patients with intermittent migraine attacks (less than 15 headache days per month) or chronic tension type headache.
- There is high quality evidence of no difference between BoNT injections and placebo in neck pain. There is insufficient evidence to support the use of BoNT injections to improve pain or function in patients with lower back pain.
- There is low quality and inconsistent evidence for the use of BoNT for increasing healing of anal fissure and appears less effective than sphincterotomy.
- In the treatment of strabismus, there is low quality evidence that BoNT may be as effective as surgery for retreatment of acquired or infantile esotropia but does not appear effective for acute 6th nerve palsy or adult horizontal strabismus.
- There is low quality evidence of clinical efficacy of BoNT in the treatment of axillary hyperhidrosis and palmar hyperhidrosis. There is insufficient comparative evidence. Aluminum chloride preparations are the most widely used first-line agents.
- There is moderate quality evidence that BoNTA injections in the detrusor are the most effective minimally invasive treatment to reduce urinary incontinence in patients with neurogenic detrusor over activity that is unresponsive to more conservative therapies.
- There is moderate to high quality evidence that pneumatic dilation and surgical myotomy are more effective on long term remission that BoNT for the treatment of achalasia. BoNT is effective short term, but response diminishes at 2 years. It is a reasonable treatment approach for patients who are not candidates for surgical therapy.
- There is insufficient evidence to make conclusions on the use of BoNT to treat neurogenic dysphagia. A recent systematic review identified no randomized controlled trials that met inclusions criteria and an overall lack of evidence to demonstrate efficacy.
- There is insufficient evidence demonstrating long term efficacy of BoNT for the treatment of laryngeal dysphonia or spasmotic dysphonia.

Previous Recommendations:

- Implement prior authorization criteria to limit use to diagnoses supported by evidence.

Background:

Acetylcholine is an important neurotransmitter in the parasympathetic, and to some degree, in the sympathetic autonomic nervous system.[2] Several autonomic disorders arise from over-activity of acetylcholine. For example, cholinergic over-activity occurs at the neuromuscular junction in overactive bladder or at the neurosecretory junction in hypersecretory disorders.[2] The ability of BoNTs to block release of acetylcholine at neuromuscular junctions accounts for

its therapeutic action to relieve dystonia, spasticity, and other related disorders.[3] Both the direct and indirect actions of the toxin are largely or completely reversible.[3]

BoNT drugs are comprised of the botulinum toxin component, formed by botulinum neurotoxin and non-toxic complexing proteins, and excipients.[4] When BoNT is injected into tissue, it binds with high affinity to glycoprotein structures located on the cholinergic nerve terminal.[4] BoNT inhibits release of acetylcholine at presynaptic cholinergic nerve terminals of the peripheral nervous system and at ganglionic nerve terminals of the autonomic nervous system.[5] Muscle tissue is unable to contract with disruption of neurotransmission of acetylcholine, causing paralysis.[5] Depending on the target tissue, BoNT can block the cholinergic neuromuscular transmission, but also the cholinergic autonomic innervation of sweat, tear and salivary glands and smooth muscles.[5] Recovery of neuromuscular activity occurs through regeneration of axonal sprouts and motor end plates which limits the duration of activity of BoNT to a few months.[5] In general, the effects of BoNT are first observed after 2 to 3 days, with maximal effect after about 2 weeks, and prolonged effects for 2 to 3 months before the effect begins to wear off.[4] The time course of this effect is remarkably reproducible over time without evidence of tachyphylaxis.[4]

Adverse effects associated BoNT generally fall into 3 broad categories. First, diffusion of the toxin from the intended sites of action can lead to unwanted inhibition of transmission at neighboring nerve endings.[3] Second, sustained blockade of transmission can produce effects similar to anatomic denervation, including muscle atrophy.[3] Third, neutralizing antibodies can be formed against all the foreign protein within the BoNT which can result in therapy failure.[3]

Currently, there are 3 BoNTA products (aboBoNTA [Dysport®]; incoBoNTA (Xeomin®); onaBoNTA (Botox®; Botox® Cosmetic) and one BoNTB product (rimaBoNTB [Myobloc®]) available commercially in the United States. Indications and off-label uses for each of these products are listed in **Tables 1 and 2**. These preparations are not interchangeable; assay methods used to determine potency of botulinum toxins are specific to each individual manufacturer and formulation.[6]

Table 1. Indications for Botulinum Toxins Approved by the U.S. Food and Drug Administration.

Botulinum toxin type A:

- AbobotulinumtoxinA (DYSPORT):
  - The treatment of adults with cervical dystonia
  - The temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients <65 years of age
  - The treatment of spasticity in adults
  - The treatment of lower limb spasticity in pediatric patients ≥2 years of age
- IncobotulinumtoxinA (XEOMIN):
  - Upper limb spasticity in adults
  - Cervical dystonia in adults
  - Blepharospasm in adults with prior treatment of onabotulinumtoxinA (Botox®)
  - Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults
- OnabotulinumtoxinA (BOTOX; BOTOX COSMETIC):
  - Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
  - Treatment of urinary incontinence due to detrusor over-activity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication

- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer)
- Treatment of spasticity in adult patients
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age
- Treatment of strabismus in patients ≥12 years of age

Botulinum toxin type B:

* RimabotulinumtoxinB (MYOBLOC):
  - Management of cervical dystonia (spasmodic torticollis) to decrease severity of associated abnormal head position and neck pain in adults

Table 2. Off-label Clinical Uses of Botulinum Toxins.[4]

Ophthalmology

- Protective ptosis *(a procedure to close the upper eyelid to facilitate healing of severe corneal infections)*
- Entropion *(inversion of the lower eyelid producing painful corneal irritation)*

Neurology

- Dystonias
  - Focal: oromandibular dystonia, lingual dystonia, Meige syndrome (blepharospasm with oromandibular and lingual dystonia), tardive dystonia, bruxism (forceful closure of jaws), occupational dystonias (writer's cramp, musician's cramp)
  - Segmental dystonia
  - Hemidystonia
  - Axial dystonia
  - Generalized dystonia
  - Symptomatic dystonias: Hallervorden-Spatz syndrome, etc.
- Spasticity
  - Focal; leg
  - Non-focal: hemispasticity (arm and leg), paraspasticity (both legs), tetraspasticity (high spinal/supraspinal processes)
- Hemifacial spasm (synchronous unilateral muscles contractions innervated by facial nerve)

Urology

- Detrusor sphincter dyssynergia (dyscoordination of the detrusor and the sphincter bladder muscles that result in UTIs from residual urine)
- Urinary retention
- Bladder pain syndrome
- Pelvic floor spasms
- Benign prostate hyperplasia
- Anal fissures

Otorhinolaryngology

- Laryngeal dystonia (spasmodic dysphonia)
- Pharyngeal dystonia
- Gustatory sweating (sweating while eating)
- Crocodile's tears (uncontrolled flow of tears during eating in patients with facial nerve impairment)
- Chronic rhinitis

Pediatrics

- Infantile cerebral palsy (produces complex movement disorders with paresis, spasticity, ataxia and apraxia)

Gastroenterology

- Achalasia (aperistalsis and reduced relaxation of the lower esophageal sphincter)

• Reinnervation synkinesias (involuntary facial contractions producing eyelid closure when perioral movements are intended, and perioral movements when eyelid closure is intended)
• Tics (involuntary muscle contractions results in disinhibited movement of any body region, but usually of the face or shoulder muscles)
• Cerebral palsy
• Hyperhidrosis (excessive sweating)
  ○ Focal: palmar, plantar
  ○ Diffuse
• Sialorrhea (drooling, typically from Parkinsonian syndromes, motor neuron disease)
• Tremor (mostly of the neck)
• Muscular Pain
  ○ Muscular dystonia, spasticity, piriformis syndrome, thoracic outlet syndrome, epicondylitis lateralis (tennis elbow)
• Raynaud phenomenon
• Untreatable focal seizures
	• Cricipharyngeal achalasia (upper esophageal sphincter affected)
	• Unspecific esophageal spasms
	• Gastroparesis
	• Sphincter Oddi spasms

BoNT has been studied and used for several different hypersecretory disorders.[2] Primary focal hyperhidrosis is a chronic idiopathic disorder of excessive sweating which most often affects the axillae, palms, soles, and forehead.[2] Drooling may be a disabling problem in parkinsonian syndromes, amyotrophic lateral sclerosis (ALS), and cerebral palsy.[2] Of these conditions, BoNT is established as safe and effective for the treatment of axillary hyperhidrosis and is probably safe and effective for palmar hyperhidrosis and in drooling in patients with Parkinson's Disease.[2] There is insufficient evidence to support the effectiveness of BoNT in hyperlacrimation. There are no head-to-head studies that have compared BoNT with other treatment options in hyperhidrosis or drooling, but BoNT is typically reserved until other treatments have been exhausted.[2] In neurodegenerative disorders such as ALS, BoNT should be used with caution as dysphagia or worsening weakness may occur.[2]

BoNT has been studied and used for some neurologic disorders. Patients with neurogenic bladder suffer from detrusor over-activity (detrusor hyperreflexia), which may be combined with detrusor sphincter dyssynergia (DSD; uncoordinated voiding).[2] Both conditions cause high intravesical pressure and can lead to upper urinary tract damage.[2] Treatment for both DSD and detrusor over-activity include pharmacologic therapy, catheterization or surgery.[2] BoNT is established as safe and effective for the treatment of neurogenic detrusor over-activity in adults, but evidence for management of DSD is conflicting.[2] BoNT is probably safe and effective for the treatment of DSD in patients with spinal cord injury but lacks benefit for the treatment of DSD in patients with MS.[2]

BoNT has been extensively studied for migraine headache.[2] BoNT has not shown to be effective for episodic migraine based on available studies.[2] Chronic daily headache (CDH) is a headache that occurs more than 15 days out of a month, and it may be a migraine or tension headache.[2] The primary outcome measure for all CDH studies was the mean change in headache-free days per month.[2] Based on inconsistent results from studies, there is insufficient evidence to support or refute a benefit of BoNT for the treatment of chronic daily headache.[2] BoNT injection is probably ineffective for patients with chronic tension-type headaches based available study results.[2]

BoNT is effective for treatment of adult spasticity of the upper or lower limb by reducing muscle tone and improving passive function.[3] Treatment aims to increase range of motion (passive and/or active), reduce pain, or achieve other functional goals (e.g., hygiene/ease of dressing).[7] However, there is lack of consensus on what constitutes meaningful functional gain following treatment for spasticity. There is insufficient evidence in controlled trials to support use of BoNT in adults to improve active (voluntary) function.[3] There are no controlled studies comparing BoNT to other treatment modalities for adult spasticity.

BoNT is now standard clinical practice for the treatment of many disorders of excess motor activity, including numerous forms of dystonia and spasticity.[3] However, treatment response varies widely within and among indications.[3] Future studies should investigate factors that predict which patient subgroups have optimal response.[3] A major limitation in published clinical trials of BoNT is the lack of standardized rating tools for many clinical indications (e.g., spasticity or focal hand dystonia).[3] Furthermore, there is often disagreement among investigators, clinicians, patients, and regulatory agencies as to what constitutes functional improvement.[3] Future studies would benefit from the development of validated scales applicable across the spectrum of tasks eliciting the abnormal movements and sensitive to changes with focal treatment such as BoNT.[3]

Cerebral palsy is a movement and posture disorder that appears in early childhood. Muscle hypertonia can lead to fixed contractures, torsional deformities of long bones, and joint instability as the child grows.[3] Treatment options for childhood cerebral palsy include physical and occupational therapy, splinting/casting, surgical approaches, and BoNT.[3] As in adult spasticity, there is lack of consensus on what constitutes meaningful functional gain following treatment for spasticity.[3] Nonetheless, BoNT injection of the gastrocnemius-soleus muscles is established as effective in the treatment of spastic equinus in patients with cerebral palsy.[3] In patients with adductor spasticity, BoNT is probably effective in improving adductor spasticity and range of motion, as well as postoperative pain in children undergoing adductor muscle lengthening surgery.[3] In patients with upper extremity symptoms, BoNT is probably effective in improving spasticity and range of motion.[3] BoNT of the calf muscles should be offered as a treatment option for equinus varus deformity in children with cerebral palsy.[3] BoNT should be considered as a treatment option for treatment of adductor spasticity and for pain control in children undergoing adductor-lengthening surgery.[3] BoNT should be considered as a treatment option in children with upper extremity spasticity.[3]

Blepharospasm is a focal dystonia characterized by involuntary contraction of orbicularis oculi, causing involuntary closure of the eye.[8] Blepharospasm was one of the first indications studied for BoNT treatment. The evidence supporting BoNT use in blepharospasm is limited. The large magnitude of benefits in the initial open label studies and the lack of other effective therapy likely have discouraged efforts to study BoNT in larger and more properly controlled clinical trials.[8] OnaBoNTA received an FDA indication for blepharospasms in 1989, although incoBoNTA also has an indication and likely has similar efficacy.[8]

Hemifacial spasm is characterized by a combination of unilateral clonic and tonic spasms of the muscles innervated by the facial nerve. Treatment options include carbamazepine, baclofen, or a benzodiazepine, with limited efficacy, or microvascular decompression of the facial nerve.[8] BoNT injection can also be considered as a treatment option, but evidence is limited to 2 studies which showed possible effectiveness with aboBoNTA and onaBoNTA. It is not known how BoNT compares to standard oral drug treatments.

Spasmodic torticollis, more commonly known as cervical dystonia, is a focal dystonia causing involuntary activation of the muscles of the neck and shoulders resulting in abnormal, sustained, and painful posturing of the head, neck, and shoulders.[8] BoNT has longstanding and widespread use in the treatment of cervical dystonia as there are no effective alternative medical therapies. [8] There are no data to compare BoNT with surgical treatment of cervical dystonia.

BoNT is probably effective for the treatment of focal upper extremity limb dystonia. Focal hand dystonia is a common form, which usually refers to “writer’s cramp” and other occupational hand dystonias.[8] For these conditions, BoNT presents risk for causing excessive muscle weakness.[8] The pattern of limb dystonia varies widely among patients, and there are currently no effective alternative medical or well-established surgical therapies for these conditions.[8]

Laryngeal dystonia (spasmodic dysphonia) generally presents as adductor type (ADSD) and less frequently as abductor type of spasmodic dysphonia (ABSD).[8] ADSD is characterized by a “strain-strangle” voice, while ABSD produces a breathy and hypophonic voice.[8] There are no effective alternative medical or surgical therapies for spasmodic dysphonia.[8] However, BoNT is probably effective for the treatment of ADSD, although evidence to support its use in ADSD is limited.[8] There is insufficient evidence to support use of BoNT in ABSD.[8]

Tics are relatively brief, intermittent movements (motor tics) or sounds (vocal or phonic tics), usually associated with Tourette syndrome.[8] Oral anti-dopaminergic drugs (e.g., second-generation antipsychotics) are often used to treat troublesome multifocal tics.[8] BoNT is possibly effective for the treatment of motor tics based off of a single study, but there is insufficient data to use BoNT in phonic tics.[8] There are no studies to compare the efficacy of BoNT and oral agents in the treatment of tic disorders.

Oral agents and deep brain stimulation are alternative treatments for essential tremor.[8] BoNT is probably effective at reducing the tremor amplitude in patients with essential hand tremor and should be considered as a treatment in those patients who fail treatment with oral agents.[8] However, evidence is insufficient to draw conclusions regarding BoNT for treatment of head and voice tremor.[8] No studies have compared the efficacy of BoNT to oral agents or deep brain stimulation.[8] The benefits must be considered in conjunction with the common adverse effect of muscle weakness associated with BoNT injection.[8]

The Health Evidence Review Commission (HERC) Prioritized List of Health Services funds treatment of BoNT for following conditions:[9]

- Chemodenervation with BoNT (CPT 64642-64647) is funded on line 292 for treatment of upper and lower limb spasticity (ICD-10-CM codes G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83).
- Chemodenervation with BoNT (CPT 67345) is funded on lines 351 and 393 for the treatment of strabismus due to other neurological disorders (ICD-10 H50.89).
- Chemodenervation with BoNT (CPT 64612, 64616) is funded on line 362 only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD-10-CM G24.9).
- Chemodenervation with BoNT (CPT 43201) is funded on line 378 for treatment of achalasia (ICD-10 K22.0).

Chemodenervation with BoNT (CPT 64650, 64653) is not funded for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61) because these conditions fall below the funding line on line 515.[9]

The HERC updated treatment guidelines within the Prioritized List of Health Services for use of chemodenervation for chronic migraine and for over-active bladder.[9] Specifically, the guideline notes address continuing funding only for positive response from BoNT therapy for these conditions. Details are highlighted below:

GUIDELINE NOTE 42, CHEMODENERVATION FOR CHRONIC MIGRAINE [9]
Line 409
Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:

1. have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine;
2. has not responded to or have contraindications to at least 3 prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, anticonvulsant or tricyclic antidepressant); and
3. treatment is administered in consultation with a neurologist or headache specialist.

Treatment is limited to 2 injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.

GUIDELINE NOTE 45, CHEMODENERVATION OF THE BLADDER [9]
Line 327
Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least 2 urinary incontinence antimuscarinic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.

In addition, Guideline Note 37 does not permit use of BoNT for conditions of the back and spine due to lack of evidence of effectiveness for the treatment of conditions on lines 346 and 527, including cervical, thoracic, lumbar and sacral conditions.[9]

Prior authorization criteria for botulinum toxins was first approved by the Oregon Pharmacy & Therapeutics Committee in September 2014.

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 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:

Limb Spasticity: Ease of Care

A systematic review evaluated efficacy of BoNTA on improving ease of care in patients with upper and lower limb spasticity.[10] Tasks performed for the patient by a caregiver or by the patient's unaffected limb are often referred to as passive function or self-care activities.[10] Limitation to passive function or self-care activities can lead to increased caregiver burden, complications of spasticity, and soft tissue changes, such as skin breakdown, malodor, and difficulty washing and dressing the limb.[10] Studies were included in the review if they were RCTs, included the use of BoNTA versus a placebo control group, on either upper or lower limb in adult inpatients or outpatients, with outcome measures relating to ease of care.[10] Muscle spasticity of any origin was considered. The outcomes considered were passive range of movement, global assessment of benefit scales (also called clinical global impression, global assessment scale), disability assessment scale, caregiver burden scales and goals/goal attainment scale.[10] Evidence quality was assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[10]

In the upper limb, 14 trials looked at passive range of movement, 4 at the disability assessment scale, 9 at the global assessment of benefit, 6 at caregiver burden scales and 6 at goal-setting. The majority of trials used stroke patients with a few including acquired brain injury or using mixed neurological diagnoses.[10] The Disability Assessment Scale was the most consistently applied tool.[10] Goal-setting in particular was often poorly explained, making it difficult to ascertain the nature of the goals.[10] Only 2 studies used the validated Goal Attainment Scale.[10] Statistically significant improvement for treatment groups was found for all studies using the global assessment of benefit and the disability assessment scale, in 8 trials that used passive range of movement, and 3 trials that used caregiver burden scales.[10] Both trials using the Goal Attainment Scale found statistically significant improvements with BoNTA.[10]

In the lower limb, 5 trials examined passive range of movement, 7 trials measured global assessment of benefit, 2 trials looked at caregiver burden with the hygiene score and only one trial set goals.[10] Treatment was either aimed at the hip adductors or the triceps.[10] Results were less notable for the treatment groups in the lower limb: 2 trials found improvements in passive range of movement but failed to reach significance, and 4 trials found statistically significant improvements in global assessment of benefit.[10]

A meta-analysis of the upper limb results for weeks 4 to 12 demonstrated a statistically significant effect for all outcomes in favor of BoNTA with moderate quality evidence (SMD 0.80; 95% CI, 0.55 to 1.06; $p<0.001$).[10] The relative risk for the global assessment of benefit measures was 2.21 (95% CI, 1.67 to 2.93; $p<0.0001$, NNT=5) if patient-rated, and was 2.51 (95% CI, 1.21 to 5.20, $p=0.01$, NNT=6) if clinician-rated.[10] A meta-analysis of upper limb outcomes for weeks 12 to 24 demonstrated a continued significant effect in favor of BoNT for individual outcomes (SMD 0.48; 95% CI, 0.34 to 0.62; $p<0.001$).[10] For lower limb studies, both the patient- and clinician-rated scores failed to demonstrate a significant effect and were rated as low and very low quality evidence, respectively.[10]

Limb Spasticity: Activity Restriction and Quality of Life

A systematic review examined the efficacy of BoNTA on improving activity restriction (i.e., active function) of the upper and lower limbs and quality of life using the GRADE system in patients with spasticity.[11] Studies were eligible for inclusion if they were RCTs, included the use of BoNTA versus placebo or control group on either the upper or lower limb in adult inpatients or outpatients, and evaluated outcomes measures related to active function or quality of life.[11] Studies were chosen for meta-analysis if they provided sufficient data as a group in either dichotomous form (when data allowed results to be divided into improved versus no change/worse) or as means and standard deviations. Data were used from between 1 and 6 months post-intervention; results were then analyzed for 4 to 12 weeks (to analyze the effect over the active time for BoNTA) and for 12 to 24 weeks (to gauge any significant lasting effects of treatment). Dichotomous data were analyzed using the Mantel-Haenszel method to provide risk ratios (RR). Continuous data were analyzed using the inverse-variance

method to give a weighted mean difference for individual outcome measures where possible. The standardized mean difference was used to pool the results of all outcome measures together as it allows for a variety of measurement methods. Random effects models were used in the presence of significant unexplained heterogeneity. Twenty-five studies were included: 18 on the upper limb, 6 on the lower limb and one on both the upper and lower limb. Eight studies used quality of life outcome measures and 22 measured active function outcomes.[11]

In general, all studies used varied measuring techniques, which were not always fully described or objective.[11] The level of function in subjects also varied greatly with only one study stipulating appropriate inclusion criteria for existing active function. In addition, quality of life issues were not stipulated in the inclusion criteria for any study.[11] Additional methodological weaknesses for the studies using quality of life measures were the lack of proven specificity and sensitivity of the scales for problems caused by spasticity. Active range of motion in the upper limb was examined in 8 studies using stroke patients, but nearly all studies found no statistically significant difference between placebo and treatment groups.[11] Only one of 3 studies found statistically significant improvement of active range of motion in lower limb studies.[11] All 3 studies that used the Action Research Arm Test, which assesses changes in limb function in patients with history of stroke resulting in hemiplegia, found significant improvements in scores for the treatment groups; however, the one study that examined stroke only found a statistically significant improvement in a subgroup of patients who had no arm function at the start of the study.[11] Seven studies used the Barthel Index, which is a generic global scale rating 10 items of activities of daily living and mobility.[11] All but one study evaluated stroke patients. Two of 6 studies that performed gait analysis found a significant difference in favor of BoNTA.[11] No statistically significant differences were found in 7 studies that evaluated timed walk tests (5 studies used a 10-minute walk test; one a 6-minute walk test, and one a 2-minute walk test).[11] Overall evidence for these outcomes was insufficient to low quality primarily due to lack of study directness and small sample sizes.[11] Data were insufficient to assess effect of BoNTA on quality of life.[11]

Benign Prostatic Hyerplasia

Benign prostatic hyperplasia (BPH) with LUTS is a common clinical complaint in adult men, and the risk of developing BPH increases with age. A systematic review was performed to assess the overall treatment efficacy and safety of BoNTA compared with placebo.[12] This meta-analysis was guided by the standard PRISMA protocol (preferred reporting items for systematic reviews and meta-analyses) and methods proposed by the Cochrane Collaboration.[12] Randomized controlled trials with intention-to-treat (ITT) analysis of patients diagnosed with BPH and LUTS were included.[12] Diagnostic tools included the International Prostate Symptom Score (IPSS), maximal urinary flow rate (Qmax), post-void residual volume (PVR), rectal examination, and ultrasonography-confirmed prostate volume (PV) increase.[12] The experimental group received BoNT-A 200 units injection, and the control group received placebo injection.[12] No other doses were included because of insufficient data for doses other than 200 units.[12] Outcome measures included changes in IPSS, Qmax, PV, and PVR from baseline in patients receiving BoNT-A versus placebo.[12] The primary outcome was change in IPSS.[12] Statistical heterogeneity was assessed by the Cochran's Q test and the I^2 statistic.[12] Either the Cochran's Q statistic ($p<0.1$) or I^2 statistic (>50%) indicated the existence of significant heterogeneity between studies.[12]

Only 3 studies from 55 citations met inclusion criteria, which included 531 patients (265 patients in the BoNTA group and 266 patients in the placebo group).[12] The duration of treatment ranged from 8 to 24 weeks.[12] The route of administration was transperineal and transrectal, and the injection sites were the transition zone and lobe of the gland.[12] The pooled overall SMD in the mean change in IPSS from baseline for the BoNTA group versus the placebo group was −1.02 (95% CI −1.97, −0.07).[12] Heterogeneity test produced a $p<0.01$, and the I^2 was 94.5%.[12] No statistically significant results were found with the secondary endpoints: the pooled overall SMD in the mean change in Qmax from baseline for the BoNTA group versus the placebo group was 0.78 (95% CI −0.13, 1.69); the pooled overall SMD in the mean change in PV from baseline for the BoNTA group versus the placebo group was −0.76 (95% CI −1.69, 0.18); and the pooled overall SMD in the mean change in PVR from baseline for the BoNTA group versus the placebo group was −0.63 (95% CI −1.54, 0.28).[12] The most frequent adverse events were hematuria (11.3% and 9.8%) and hematospermia (7.2% and 8.6%) in the BoNTA and placebo groups, respectively.[12] There was

no significant difference in all reported adverse events between the 2 groups.[12] The investigators concluded from the meta-analysis that BoNTA injection for BPH with LUTS is not more efficacious than placebo and that there are no differences in procedure-related adverse events.[12]

Strabismus

The use of BoNT as a treatment modality for strabismus is well reported, but it is unclear how effective it is in compared to other treatment options for strabismus. The primary objective of a Cochrane review was to examine the efficacy of BoNT in the treatment of strabismus, focused on types of strabismus that particularly benefit from BoNT (such as small angle strabismus or strabismus with binocular potential, i.e. the potential to use both eyes together as a pair), compared with alternative conservative or surgical treatment options.[13]

Six RCTs evaluating use of BoNT for treatment of strabismus were eligible for inclusion. The studies were judged to be a mixture of low, unclear and high risk of bias; however, none of the studies had low risk of bias for all domains.[13] Two trials conducted in Spain (102 patients, number of eyes not specified) compared BoNT with surgery in children that required retreatment for acquired or infantile esotropia.[13] These two studies provided low-quality evidence that children who received BoNT may have a similar or slightly reduced chance of achieving ocular alignment (RR 0.91, 95% CI 0.71 to 1.16), binocular single vision (RR 0.88, 95% CI 0.63 to 1.23), sensory fusion (RR 0.88, 95% CI 0.63 to 1.23) and stereopsis (RR 0.86, 95% CI 0.59 to 1.25) compared with children who received surgery.[13] One trial from Canada compared BoNT with surgery in 30 adult patients (30 eyes) with horizontal strabismus and reported a reduced chance of ocular alignment with BoNT (RR 0.38, 95% CI 0.17 to 0.85; low-quality evidence).[13] One trial in the UK (n=47) suggested that BoNT may result in a similar or slightly improved chance of ocular alignment in patients with acute onset sixth nerve palsy compared with observation (RR 1.19, 95% CI 0.96 to 1.48; low-quality evidence).[13] Low-quality evidence from one trial from Brazil (n=23) was not able to show that adjuvant BoNT in strabismus surgery increases the chances of ocular alignment compared with strabismus surgery alone (RR 1.83, 95% CI 0.41 to 8.11).[13] One trial from China (47 patients; 94 eyes) suggested that patients receiving BoNT combined with sodium hyaluronate may have a similar or slightly reduced chance of achieving ocular alignment compared with BoNT alone (RR 0.81, 95% CI 0.36 to 1.82; low-quality evidence).[13] Reported complications in people given BoNT in the included trials included ptosis (range 9% to 42%) and vertical deviation (range 8% to 19%).[13] Ptosis occurred less frequently in patients treated with BoNT combined with sodium hyaluronate compared to BoNT alone.[13] The authors concluded there is a lack of evidence for effect of BoNT on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and BoNT are combined.[13] High quality trials using robust methodologies are required to compare the clinical efficacy of various formulations of BoNT, to compare BoNT with and without adjuvant solutions, and to compare BoNT to alternative surgical interventions in strabismus cases with and without potential for binocular vision.[13]

Cervical Dystonia

The Cochrane Collaboration updated a 2003 review that compared efficacy of BoNTA versus BoNTB for cervical dystonia.[14] Cervical dystonia is the most common form of focal dystonia and is a disabling disorder characterized by painful involuntary head posturing.[14] Although BoNTA is considered the first-line therapy for cervical dystonia and BoNTB is considered an alternative option, there is no compelling theoretical reason to consider BoNTB less effective than BoNTA. Of note, a separate Cochrane review found that BoNTB is associated with statistically significant and clinically relevant reduction in cervical dystonia impairment including severity, disability and pain, and is well tolerated, when compared to placebo.[15] For this review, double-blind, parallel, placebo-controlled RCTs that compared BoNTA versus BoNTB in adults with cervical dystonia were included.[14] Two independent authors identified and selected eligible studies, extracted data, and evaluated the risk of bias. Meta-analyses were performed using the random-effects model to compare BoNTA versus BoNTB to estimate pooled effects and corresponding 95% CI. The primary efficacy outcome was improvement on any validated symptomatic rating scale (e.g., Tsui scale,

Toronto Western Spasmodic Torticollis Rating Scale, and Cervical Dystonia Severity Scale), measured between weeks 3 and 6 post-injection.[14] The primary safety endpoint was the proportion of participants with any adverse event, measured at any point during study follow-up.[14]

Since the 2003 review was published, 3 additional RCTs were identified. Two studies exclusively enrolled participants with a known positive response to BoNTA treatment. The Cochrane investigators were concerned that may result in bias by population enrichment, with a higher probability of participants who benefit from BoNTA treatment.[14] In addition, the Cochrane investigators found that none of the trials were free of for-profit bias, nor did they provide information regarding registered study protocols.[14] All trials evaluated the effect of a single BoNT treatment session, and not repeated treatment sessions, using doses from 100 units to 250 units of BoNTA (all onaBoNTA formulations) and 5,000 units to 10,000 units of BoNTB (rimaBoNTB). The investigators found no difference between the two types of BoNT in terms of overall efficacy, with a mean difference of -1.44 (95% CI -3.58 to 0.70) points lower on the Toronto Western Spasmodic Torticollis Rating Scale (assess severity of spasm, disability and pain; range 0-85) for BoNTB-treated patients, measured at 2 to 4 weeks after injection. The proportion of patients with adverse events was also not different between BoNTA and BoNTB (BoNTB vs. BoNTA: RR 1.40; 95% CI 1.00 to 1.96). However, BoNTB was associated with an increased risk of treatment-related sore throat/dry mouth (BoNTB 46.7% vs. BoNTA 10.5%: RR 4.39; 95% CI 2.43 to 7.91). Treatment-related dysphagia (swallowing difficulties) was not different between BoNTA and BoNTB (RR 2.89; 95% CI 0.80 to 10.41). According to the investigators, the two types of BoNT were otherwise clinically non-distinguishable in all the remaining outcomes.[14] Overall, they found low quality evidence that a single treatment of onaBoNTA and a single treatment of rimaBoNTB are equally effective and safe in the treatment of adults with certain types of cervical dystonia. Treatment with BoNTB appears to present an increased risk of sore throat/dry mouth, but overall, there is no clinical evidence to support or contest the preferential use of one form of BoNT over the other.[14]

Lateral Epicondylitis
A systematic review recently assessed the effectiveness of BoNT compared with non-surgical treatments in patients with lateral epicondylitis (tennis elbow); however, the study will not be further reviewed here because this condition is not funded under the OHP.[16]

New Guidelines:
American Academy of Neurology
The American Academy of Neurology (AAN) published a practice guideline update on BoNT for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache.[17] In 2008, the AAN published their original guideline for use of BoNT. Since then, new research on use of BoNT for these indications prompted the update.

The guideline panel was comprised of specialists with experience in the therapeutic use of BoNT for the indications under consideration or with expertise in guideline methodology.[17] The AAN claims to be committed to producing independent and critical clinical practice guidelines.[17] According to the AAN, significant efforts are made to minimize the potential for conflicts of interest to influence recommendations.[17] To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the guidelines and the developers of the guidelines.[17] Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to the project.[17] The AAN forbids commercial participation in, or funding of, guideline projects.[17] Drafts of the guideline were reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields.[17] Detailed methods to AAN guideline development are available online.[18] The articles were classified as Class I (e.g., high quality RCT) through Class IV (non-controlled study or case report) using the AAN guideline process.[18] Please see http://tools.aan.com/globals/axon/assets/9023.pdf for more information on guideline methodology and classification of evidence.

Blepharospasm

BoNT is considered the first-line treatment of blepharospasm by most movement disorder specialists.[17] The 2008 guideline concluded that BoNT as a class is probably safe and effective for treatment of blepharospasm on the basis of 2 studies comparing onaBoNTA with placebo, one study comparing onaBoNTA with aboBoNTA, and one study comparing onaBoNTA with incoBoNTA.[8] The AAN concluded from the evidence that onaBoNTA and incoBoNTA are probably safe and effective, and aboBoNTA is possibly effective, for treating blepharospasm.[8]

Since the 2008 AAN guideline reviewed the evidence of BoNT for blepharospasm,[8] one class I double-blinded RCT found that incoBoNTA (doses of up to 50 units/eye) was superior to placebo; a class II placebo-controlled RCT found that aboBoNT (40 units, 80 units or 120 units) improved disability in a dose-related manner based on the Blepharospasm Disability Index (minimum clinically important difference [MCID] was not identified); and a class I double-blinded RCT and class II double-blinded RCT both found comparable magnitude and duration of benefit between onaBoNTA and incoBoNTA.[17] Commonly reported adverse events with BoNT injections included periorbital hematoma (25%), ptosis (range of risk differences [RDs] 13%– 54%), dry eyes (range of RDs 7.1%–13%), and blurred vision (RD 42%).[17] Four class IV observational studies reported long-term outcomes, which showed sustained benefit from aboBoNTA or onaBoNTA for at least 15 years and incoBoNTA for at least 5 years.[17]

The AAN concluded onaBoNTA (2 class II studies from 2008 guideline) and incoBoNTA (1 class I study) are probably safe and effective, and aboBoNTA (1 Ccass II study) is possibly effective, for treating blepharospasm.[17] There is insufficient evidence to determine the efficacy of rimaBoNTB.[17] In addition, incoBoNTA and onaBoNTA (1 class I comparative effectiveness study from the 2008 guideline and 2 more recent comparative effectiveness studies [class I and class II]) are equivalent in efficacy for treating blepharospasm.[17] AboBoNTA and onaBoNTA (1 class II study from the 2008 guideline) are possibly equivalent for treating blepharospasm.[17] Based on these conclusions, the AAN recommends either onaBoNTA or incoBoNTA be considered (Level B), and aboBoNTA may be considered (Level C), as treatment options for blepharospasm.[17]

Cervical Dystonia

BoNT is accepted as first-line treatment for cervical dystonia.[17] The 2008 guideline concluded that BoNT is established as safe and effective for treatment of cervical dystonia on the basis of one class I trial of onaBoNTA, 2 class I trials of aboBoNTA, and 3 class I trials of rimaBoNTB.[8] In addition, on the basis of a single class I study that compared aboBoNTA with trihexyphenidyl, the guideline concluded that BoNT is probably more efficacious and better tolerated than trihexyphenidyl for cervical dystonia.[8]

Since the 2008 AAN guideline reviewed the evidence of BoNT for cervical dystonia,[8] a placebo-controlled class I RCT found that incoBoNTA (120 units and 240 units) significantly improved Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total scores (and severity, disability and pain subscores) from baseline to week 4.[17] A 12-point change is the minimal clinically important change after treatment using TWSTRS as endpoint for an average trial population.[19] A second placebo-controlled class II RCT found onaBoNTA produced greater improvements in the Cervical Dystonia Severity Scale and Global Assessment Scale.[17] The studies found rhinitis and treatment-related dysphagia were more frequent with onaBoNTA than placebo.[17] Five studies compared different formulations of BoNT: 2 class I studies found similar TWSTRS scores at 4 weeks between onaBoNTA (150-250 units) or rimaBoNTB (10,000 units); one class I study found onaBoNTA (70-240 units) resulted in similar Tsui scores at 4 weeks compared to aboBoNTA (240-720 units); a double-blind class II, non-inferiority, cross-over RCT also found similar Tsui scores from baseline to 4 weeks after injection, as well as similar TWSTRS, global impression and frequency of adverse effects from baseline to 4 weeks after injection, when aboBoNTA was compared to onaBoNTA (2.5:1 dose ratio); and a class II double-blind, crossover RCT of onaBoNTA versus aboBoNTA (1:3 dosing ratio) showed similar benefit at week 4, but there was a significant shorter duration and lower efficacy of onaBoNTA at

week 12 as assessed by reduction in TWSTRS total score, suggesting the 1:3 dose ratio is suboptimal for dose conversions.[17] Three long-term, prospective, open-label studies (class IV) evaluated the clinical response of repeated injections of onaBoNTA and found persistent benefit for up to 2 years.[17]

The AAN concluded aboBoNTA (2 class I studies reviewed in the 2008 guideline) and rimaBoNTB (3 class I studies reviewed in the 2008 guideline) are established as safe and effective for the treatment of cervical dystonia; onaBoNTA (one class I study reviewed in the 2008 guideline, one more recent class II study) and incoBoNTA (one more recent class I study) are probably safe and effective for the treatment of cervical dystonia; and rimaBoNTB and onaBoNTA (2 class I comparative effectiveness studies) are equivalent in efficacy for treating cervical dystonia.[17] AboBoNTA and onaBoNTA (1 class I study) are probably equivalent for treating cervical dystonia.[17] Based on these conclusions, the AAN recommends aboBoNTA and rimaBoNTB be offered (Level A), and onaBoNTA and incoBoNTA should be considered (Level B), as options for the treatment of cervical dystonia.[17]

Adult Spasticity

The 2008 guideline concluded BoNT is established as effective in the treatment of adult spasticity in the upper extremity on the basis of 6 class I studies of aboBoNTA, 4 class I studies of onaBoNTA, and one class I study of rimaBoNTB.[3] The guideline also concluded that BoNT is effective in treating lower limb spasticity on the basis of 2 class I studies of aboBoNTA and 1 class I study of onaBoNTA. Studies demonstrated that BoNT is effective for reducing muscle tone and improving passive function (e.g., improved range of motion) and is probably effective for improving active function (1 class I study of aboBoNTA).[3]

Since the 2008 AAN guideline reviewed the evidence of BoNT for upper limb spasticity,[3] 4 new class I trials investigating aboBoNTA demonstrated significant reductions in upper limb tone as measured by the modified Ashworth scale (MCID not established); 4 studies (3 class I, 1 class II) demonstrated consistent efficacy in tone reduction in the upper limb from onaBoNTA; one class I comparative study found onaBoNTA was superior to tizanidine for improving wrist and finger flexor tone, whereas tizanidine showed no benefit over placebo but was associated with significant adverse effects; 2 new class I trials showed significant improvement in tone reduction with incoBoNTA; and one class I study did not find a significant difference between rimaBoNTB and placebo in improvement in upper elbow extension as measured by the Modified Frenchay Scale.[17]

The guideline concluded from the overall evidence for these agents in upper limb spasticity that aboBoNTA, incoBoNTA, and onaBoNTA are established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple class I studies for all preparations).[17] RimaBoNTB is probably safe and effective for the reduction of adult upper limb spasticity (1 class I study).[17] In addition, onaBoNTA is probably superior to tizanidine for reducing upper extremity tone in adult spasticity.[17] Data are inadequate to determine the efficacy of aboBoNTA, onaBoNTA, incoBoNTA, or rimaBoNTB for improvement of active function associated with adult upper limb spasticity (class I studies, inconsistent results dependent on active functional outcome).[17] Based on these conclusions, the AAN recommends for focal manifestations of adult spasticity involving the upper limb, aboBoNTA, incoBoNTA, and onaBoNTA should be offered (Level A), and rimaBoNTB should be considered (Level B), as treatment options.[17] OnaBoNTA should be considered before tizanidine for treatment of upper extremity spasticity (Level B).[17]

Since the 2008 AAN guideline reviewed the evidence of BoNT for lower limb spasticity,[3] one placebo-controlled class I trial evaluated aboBoNTA use in multiple sclerosis with reduced pain in both legs in patients randomized to aboBoNTA.[17] Three class I studies of onaBoNTA in the treatment of adult lower limb spasticity demonstrated significant reduction in tone but found inconsistent results in regard to functional measures.[17] No studies met inclusion criteria addressing the efficacy of incoBoNT-A or rimaBoNTB for adult lower limb spasticity.[17]

The guideline concluded from the overall evidence for these agents in lower limb spasticity that aboBoNTA and onaBoNTA are established as safe and effective for the reduction of adult lower limb spasticity (multiple class I studies); data are inadequate to determine the efficacy of incoBoNTA or rimaBoNTB for improvement of active function in adult lower limb spasticity; and data are inadequate to determine the efficacy of aboBoNTA, onaBoNTA, incoBoNTA, or rimaBoNTB for improvement of active function associated with adult lower-limb spasticity (no studies available or inconsistent results dependent on specific outcome from multiple class I studies).[17] Based on these conclusions, the AAN recommends for focal manifestations of adult spasticity involving the lower limb that warrant treatment, onaBoNTA and aboBoNTA should be offered (Level A) as treatment options.[2] There is insufficient evidence to support or refute a benefit of incoBoNTA or rimaBoNTB for treatment of adult lower limb spasticity.[17]

Headache

Chronic migraine refers to migraine attacks that occur 15 days or more per month for at least 3 months, with attacks lasting 4 hours or more.[17] The 2008 guideline found inconsistent results from 4 class II studies that compared onaBoNTA with placebo, resulting in insufficient evidence for use of BoNT for treatment of chronic migraine.[2] Since then, 2 class I placebo-controlled studies have been published that met inclusion criteria for the 2016 guideline. In one study, onaBoNTA was ineffective at reducing total headache episodes (the primary endpoint) but was effective at reducing total headache days/28 days by a mean difference of 1.4 days (95% CI, -2.4 to -0.40).[17] In the second study, onaBoNTA reduced headache days/28 days from baseline to weeks 21-24 posttreatment by 9 days versus 6.7 fewer headache days with placebo (indicating a high placebo response).[17] The guideline also identified a class III study which showed similar efficacy between onaBoNTA and topiramate in chronic migraine.[17] The magnitude of benefit onaBoNTA demonstrated from these 2 studies was small (1.7 and 2.4 more headache-free days).[17] Pooled analysis from the 2 studies also showed improvement in health-related quality of life after 24 weeks with onaBoNT-A.[17]

The AAN guideline concluded from the overall evidence that onaBoNTA is established as safe and effective at reducing the number of headache days in patients from chronic migraine (2 class I studies) and probably effective at improving health-related quality-of-life (1 class I study).[17] Based on these conclusions, the AAN recommends onaBoNTA should be offered as a treatment option to patients with chronic migraine to increase the number of headache-free days (Level A) and should be considered to reduce headache impact on health-related quality-of-life (Level B).

OnaBoNTA is ineffective for the treatment of episodic migraines based on evidence from 3 class I studies and should not be offered as a treatment option for this type of migraine (Level A).[17]

New Formulations or Indications:

IncoBoNTA (Xeomin) received an indication in December 2015 for the improvement of adult patients with upper limb spasticity.[20] The efficacy of incoBoNTA for this indication is based on two placebo-controlled, double-blind, multi-centered RCTs in patients with post-stroke spasticity of the upper limb.[20] Study 1 (n=317) included the main 12-week double-blinded phase followed by three 12-week open-label extension treatment cycles (total duration 48 weeks).[20] Patients received incoBoNTA 400 units or placebo administered intramuscularly during the main phase and incoBoNTA 400 units every 12 weeks for the extension study.[20] In Study 1, one co-primary efficacy variable was the change from baseline in Ashworth Scale (AS) score of the primary target clinical pattern determined by the investigator at the week 4 visit.[20] The AS is a clinical measure (scores range from 0-4; MCID not established) of the severity of spasticity by judging resistance to passive movement.[20] The spasticity of the elbow flexors, wrist flexors, finger flexors, and thumb muscles as well as the forearm pronators was assessed on the 0 to 4-point AS at each visit.[20] At week 4, mean AS scores decreased by -0.9 points for incoBoNTA and -0.5 points for placebo based on last observation carried forward for the intention-to-treat population.[20] This difference was statistically significant. The other co-primary efficacy variable of Study 1 was the Investigator's Global Impression of Change Scales (GICS) after 4 Weeks of treatment with incoBoNTA or placebo.[20] The GICS is a global

measure of a subject's functional improvement.[20] Investigators were asked to evaluate the subject's global change in spasticity of the upper limb due to treatment, compared to symptoms before the last injection.[20] The response was assessed using a 7-point Likert scale that ranges from -3 (very much worse) to +3 (very much improved).[20] A greater percentage of incoBoNTA-treated subjects (40%) than placebo-treated subjects (22%) reported 'much improved' in their spasticity.[20] Only 4 patients reported 'very much improved' (3 with incoBoNTA and 1 with placebo).[20] The efficacy of incoBoNTA based from the second study is not described.

AboBoNTA (Dysport) received an indication in July 2016 for the treatment of lower limb spasticity in pediatric patients 2 years of age and older.[1] The efficacy of aboBoNTA for this indication is based from one double-blind, placebo-controlled multi-centered trial in patients 2 to 17 years of age with lower limb spasticity because of cerebral palsy resulting in dynamic equinus foot deformity.[1] Pediatric patients (n=235) with a Modified Ashworth Score (MAS) score 2 or higher (score 0-4, with higher scores indicating increase muscle tone and rigidity) at the ankle plantar flexor were enrolled to aboBoNTA 10 units/kg/leg, 15 units/kg/leg or placebo injected into the gastrocnemius and soleus muscles.[1] The co-primary endpoints were the mean change from baseline in MAS in ankle plantar flexor at week 4 and the mean Physician's Global Assessment (PGA) score at week 4.[1] At week 4, least square mean MAS scores decreased by -1.0, -0.9 and -0.5 points for aboBoNTA 15 units/kg/leg, aboBoNTA 10 units/kg/leg and placebo, respectively.[1] The MAS differences between either dose of aboBoNTA and placebo were statistically significant.[1] Least square mean PGA response to treatment increased by 1.5, 1.5 and 0.7 points for aboBoNTA 15 units/kg/leg, aboBoNTA 10 units/kg/leg and placebo, respectively.[1] The PGA differences between either dose of aboBoNTA and placebo were statistically significant.[1]

AboBoNTA (Dysport) received an indication in June 2017 for the treatment of lower limb spasticity in adult patients.[1] The efficacy of aboBoNTA for this indication is based on one double-blind, placebo-controlled, multi-center trial in patients with lower limb spasticity who were at least 6 months post-stroke or post-traumatic brain injury.[1] Patients (n=381) had a Modified Ashworth Scale (MAS) score of 2 or higher in the affected ankle joint for toxin naïve patients or MAS score of 3 or greater in affected ankle joint for toxin non-naïve patients.[1] The primary endpoint was muscle tone as assessed by the MAS at the ankle joint at week 4.[1] At week 4, the least square mean MAS scores decreased by 0.6, 0.8, and 0.5 points for aboBoNTA 1000 units, aboBoNTA 1500 units, and placebo, respectively.[1] The MAS difference between aboBoNTA 1500 units and placebo was statistically significant but the difference between the aboBoNTA 1000 unit dose and placebo was not.[1]

OnaBoNTA (Botox Cosmetic) received an indication in October 2017 for temporary improvement in the appearance of moderate to severe forehead lines associated with frontalis muscle activity.[21] This indication is not funded by the OHP.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 224 citations were manually reviewed from the initial literature search. After further review, all 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, not funded under OHP).

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Appendix 1: Current Preferred Drug List

GENERIC NAME	BRAND NAME	FORM	PDL STATUS
ABOBOTULINUMTOXINA	DYSPORT	VIAL	
INCOBOTULINUMTOXINA	XEOMIN	VIAL	
ONABOTULINUMTOXINA	BOTOX	VIAL	
ONABOTULINUMTOXINA	BOTOX COSMETIC	VIAL	
RIMABOTULINUMTOXINB	MYOBLOC	VIAL	

Botulinum Toxins

Goal(s):
- Approve botulinum toxins for funded OHP conditions supported by evidence of benefit.
- Require positive response to therapy for use in chronic migraine headaches or overactive bladder.

Length of Authorization:
- From 90 days to 12 months

Requires PA:
- Use of botulinum toxins without associated dystonia or neurological disease diagnosis in last 12 months.

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

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor over-activity (e.g., overactive bladder)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is botulinum toxin treatment for any of the following? a. Upper or lower limb spasticity (G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83); b. Strabismus due to a neurological disorder (H50.89); c. Blepharospasm (G24.5); d. Spasmodic torticollis (G24.3); e. Torsion dystonia (G24.9); or f. Achalasia (K22.0).	**Yes:** Approve for up to 12 months	**No:** Go to #4

Approval Criteria		
~~3. Does patient have diagnosis of neurological-induced dystonia or spasticity in which a botulinum toxin is a first-line treatment option?~~ ~~Examples:~~ ~~• Genetic torsion dystonia (G241);~~ ~~• Acquired torsion dystonia (G803; G2402; G248);~~ ~~• Blepharospasm (G245);~~ ~~• Spasmodic torticollis (G243);~~ ~~• Other fragments of torsion dystonia (G249);~~ ~~• Paralysis associated with CVD (I69931-I69969);~~ ~~• Multiple sclerosis (G35);~~ ~~• Neuromyelitis optica (G360);~~ ~~• Spastic hemiplegia, other specified hemiplegia (G8100-G8194);~~ ~~• Cerebral palsy (G800-G809);~~ ~~• Quadriplegia and quadraparesis (-G8250-G8254);~~ ~~• Paraplegia (G8220);~~ ~~• Diplegia of upper limbs (G830);~~ ~~• Monoplegia of lower limb (G8310-G8314);~~ ~~• Monoplegia of upper limb (G8320-G8324);~~ ~~• Unspecified monoplegia (G8330);~~ ~~• Other specified paralytic syndrome (G8381-G8389);~~ ~~• Muscular dystrophies (G710-G712); or~~ ~~• Strabismus in other neuromuscular disorders (H5089).~~	~~**Yes:** Approve for up to 12 months~~	~~**No:** Go to #4~~
4. ~~Does patient have a diagnosis of~~Is botulinum toxin treatment for chronic migraine, with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5	**No:** Go to #7
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Has the patient had an inadequate response, or has contraindications, to ≥1 drugs from ~~each~~ at least 3 of the following ~~3~~ drug classes? • Beta-blockers: (propranolol; metoprolol; atenolol; nadolol; or timolol) • Tricyclic antidepressants: (nortriptyline or amitriptyline) • Anticonvulsants: (divalproex sodium/valproic acid; carbamazepine; topiramate; or gabapentin) • Calcium channel blockers (diltiazem; verapamil; or nimodipine)	**Yes:** • Baseline headaches/month: _____. Approve no more than 2 injections~~treatments~~ given ≥3 months apart. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
7. ~~Does patient have a diagnosis~~Is botulinum toxin treatment for idiopathic or neurogenic detrusor over-activity ~~(eg, overactive bladder syndrome)~~ (ICD10-CM N32.81)?	**Yes:** Go to #8	**No:** Pass to RPh. Go to #9
8. Has the patient had an inadequate response to, or is intolerant of, ≥2 incontinence anti-muscarinic drugs (e.g., fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, or trospium)?	**Yes:** • Baseline urine frequency/day: _____. • Baseline urine incontinence episodes/day: _____. Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness.

9. RPh only: Medical literature with evidence for use in funded conditions must be submitted and determined to be appropriate for use before approval is granted.

Deny for the following conditions; not funded by the OHP
Axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61) Neurologic conditions with none or minimally effective treatment or treatment not necessary (G244; G2589; G2581; G2589; G259); Facial nerve disorders (G510-G519); Spastic dysphonia (J387); Anal fissure (K602); Disorders of sweat glands (e.g., focal hyperhidrosis) (L301; L740-L759; R61); Other disorders of cervical region (M436; M4802; M530; M531; M5382; M5402; M5412; M542; M6788); Acute and chronic disorders of the spine without neurologic impairment (M546; M545; M4327; M4328; M532X7; M532X8; M533; M438X9; M539; M5408; M545; M5430; M5414-M5417; M5489; M549); Disorders of soft tissue (M5410; M609; M790-M792; M797); Headaches (G44209; G44009; G44019; G44029; G44039; G44049; G44059; G44099; G44209; G44219; G44221; G44229; G44309; G44319; G44329; G4441; G4451-G4453; G4459; G4481-G4489; G441; R51); Gastroparesis (K3184) Lateral epicondylitis (tennis elbow)) (M7710-M7712)
Deny for medical appropriateness because evidence of benefit is insufficient

Dysphagia (R130; R1310-R1319);
Other extrapyramidal disease and abnormal movement disorders (G10; G230-GG238; G2401; G244; G250-G26);
Other disorders of binocular eye movements (e.g., esotropia, exotropia, mechanical strabismus, etc.) (H4900-H518);
Tics (F950-F952; F959);
Laryngeal spasm (J385);
Spinal stenosis in cervical region or brachial neuritis or radiculitis NOS (M4802; M5412-M5413);
Spasm of muscle in absence of neurological diagnoses (M6240-M62838);
Contracture of tendon (sheath) in absence of neurological diagnoses (M6240; M62838);
Amyotrophic sclerosis (G1221);
Clinically significant spinal deformity or disorders of spine with neurological impairment (M4800; M4804; M4806; M4808; M5414-M5417);
Essential tremor (G25.0)
Hemifacial spasm (G513)
Occupational dystonias (e.g., “Writer’s cramp”) (G248, G249)
Hyperplasia of the prostate (N400-403; N4283)
Conditions of the back and spine for the treatment of conditions on lines 346 and 527, including cervical, thoracic, lumbar and sacral conditions. See Guideline Note 37.

Renewal Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a reduction of ≥76 headache days per month compared to baseline headache frequency?	**Yes:** Approve no more than 2 injections given ≥3 months apart. ~~Approve for up to 12 months~~ Baseline:____ headaches/month Current:____ headaches/month	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved prior authorization for management of idiopathic or neurogenic detrusor over-activity?	**Yes:** Go to #4	**No:** Go to Approval Criteria
4. Is there a reduction of urinary frequency of ≥8 episodes per day or urinary incontinence of ≥2 episodes per day compared to baseline frequency?	**Yes:** Approve for up to 12 months • Baseline:____ urine frequency/day • Current:____ urine frequency/day -or- • Baseline:____ urine incontinence episodes/day • Current:____ urine incontinence episodes/day	**No:** Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *5/18 (AG); 11/15; 9/14; 7/14*
Implementation: *TBD; 10/13/16; 1/1/16*

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Drug Use Evaluation: Methadone

Research Questions:

- What are the characteristics of patients with fee-for-service (FFS) methadone claims before and after the removal of methadone from the Oregon Medicaid FFS preferred drug list (PDL)?
- How has utilization of methadone changed after its removal from the PDL?
- What is the incidence of hospitalization and ED visits due to methadone overdose before and after the removal of methadone from the PDL?
- What is the incidence of hospitalization and ED visits due to heroin overdose before and after removal of methadone from the PDL?

Conclusions:

- Utilization of methadone for pain management has decreased substantially since the removal of methadone from the PDL.
- Since the change in methadone PDL status, there has been a trend in decreased hospitalizations for methadone overdose and increased hospitalizations for heroin overdose.

Recommendations:

- Maintain status of methadone as a non-preferred agent on the Oregon Medicaid FFS PDL.

Background:

Opioid misuse in the United States (U.S.) has increased over the past two decades.[1] In 2012, Oregon had the highest rate of non-medical use of prescription pain medications in the U.S. [1] Data from the Oregon Prescription Drug Monitoring Program (PDMP) show that almost 25% of Oregonians received a prescription for opioid medications in 2012.[1] Increased opioid prescribing has led to a higher incidence of overdose. Between 2000 and 2012, about 322 people per year in Oregon died due to unintentional and undetermined drug overdose. [1] Methadone was associated with over 50% of prescription opioid-related deaths from 2000-2011 in Oregon.[1]

Methadone is indicated for chronic pain as well as for opioid use disorder through opioid treatment programs. It carries a FDA Black Box warning for increased risk of death and risk of abuse and misuse.[2] Its long duration of action and affordability may be reasons for its use for pain management. However, because of methadone's long half-life, variable pharmacokinetics, and delayed onset, it can can lead to accumulation with dose titration, resulting in respiratory depression or cardiac arrest.[3] Retail distribution of methadone more than doubled between 2000 and 2006; methadone-associated overdose deaths showed a similar increase.[1] In December 2006, the Food and Drug Administration (FDA) issued a Public Health Advisory to encourage reporting of death and life-threatening adverse events in patients receiving methadone. In 2012, the Centers for Disease Control and Prevention (CDC) recommended that insurance formularies should not list methadone as a preferred drug for the treatment for chronic non-cancer pain and be reserved for use in selected circumstances only (such as cancer pain or palliative care).[4] A retrospective analysis found that those receiving methadone for non-cancer pain relief had 46% increased risk of overdose dose compared to those receiving alternative therapy.[5] Therefore, the recommendation to remove methadone from the Oregon Medicaid FFS PDL was made in July 2013.

The CDC recently assessed state Medicaid PDL policies and their effect on methadone prescribing and methadone-related deaths.[6] Overall, there was a large decline in methadone-related overdose deaths between 2007 and 2014. However, rates of fatal and nonfatal methadone overdose in South Carolina, which did not include methadone on the PDL, was significantly lower than in North Carolina ($p<0.001$) and Florida ($p<0.001$), which still included methadone on the PDL. Rates of fatal and nonfatal methadone overdose were similar between North Carolina and Florida.[6] This analysis suggests that addition of methadone to the PDL is associated with increased rates of methadone overdose in Medicaid recipients.

While prescription opioid abuse remains a problem in the U.S., heroin use has also increased in the past decade. Heroin is readily available and is more affordable than prescription opioids, making it an attractive alternative in opioid dependent persons.[7] The Healthcare Cost and Utilization Project found that while emergency department (ED) and inpatient discharge rates for prescription opioid overdoses began to decline around 2010, discharge rates for heroin overdoses sharply increased around 2008.[8] One factor that contributes to heroin use is availability and affordability.[7] Heroin users often transition from prescription opioid use.[7] A study of intravenous (IV) drug users found a significant rate of users reported problematic prescription opioid use before starting heroin, including 47% of IV drug users in Portland, Oregon.[9] Furthermore, between 2008 and 2010, 82.6% of heroin users report using prescription opioids prior to heroin compared to 64.1% between 2002 and 2004.[10] With increased restriction on availability of oral prescription opioids such as methadone, use of heroin may continue to increase and result in increased hospitalizations for heroin overdose.

The goal of this report is to evaluate the impact of removal of methadone from Oregon Medicaid's PDL on methadone utilization and assess rate of overdoses resulting in hospital admissions or ED visits due to methadone or heroin.

Methods:

This is a retrospective pre/post cohort study to evaluate the impact of making methadone non-preferred. Utilization of methadone over time was evaluated by including FFS pharmacy claims from January 2011 through June 2017 and reported as claims per enrolled member per month x1000.

Patient demographics were reported on all patients with a paid FFS drug claim for methadone from January 1, 2013 to December 31, 2013 (pre policy group) and from January 1, 2014 to December 31, 2014 (post policy group). A year before and after the policy change was chosen since it is difficult to draw conclusions about an effect after a year. Patients were excluded if they had any of the following benefit packages which indicate Medicare part D coverage (benefit packages BMM, BMD, MND, CWM, SMF, SNB or MED). Patients were also excluded if they had a diagnosis of palliative care with a terminal diagnosis or with cancer-related pain at any time from a year prior to their first pharmacy claim to the end of their respective period (**ICD 10**: C690-C799; C800-C802 and **ICD 9**: V66.7, 799.3, 140-239, 338.3). Number of patients receiving more than 90 morphine milligram equivalent doses of methadone was also captured.

To capture the incidence of hospitalizations or ED visits due to methadone and heroin overdose, a separate cohort to analyze this research question was compiled. All Medicaid patients admitted to a hospital or presenting to an ED with an ICD code for methadone poisoning or heroin poisoning (**Table 1**) from January 2011 through June 2017 were included and depicted as a rate per enrolled member per month x10,000.

Table 1: ICD Codes for Methadone and Heroin Poisoning

Description	ICD-9 code	ICD-10 code
Poisoning by methadone	965.02, E850.1	T40.3X1A-4A
Poisoning by heroin	965.01	T40.1X1A-4A

Results:

Patient demographics are similar among patients receiving methadone for pain management before and after the change in methadone PDL status (**Table 2**). There was a 58% reduction of patients who had claims for methadone after the status change (197 patients in 2013 and 83 patients in 2014). The majority of patients both pre- and post-policy change were between the ages of 18 to 54 years, and over 65% were white. Similarly, in both cohorts, about half the patients received more than 90 morphine milligram equivalents per day.

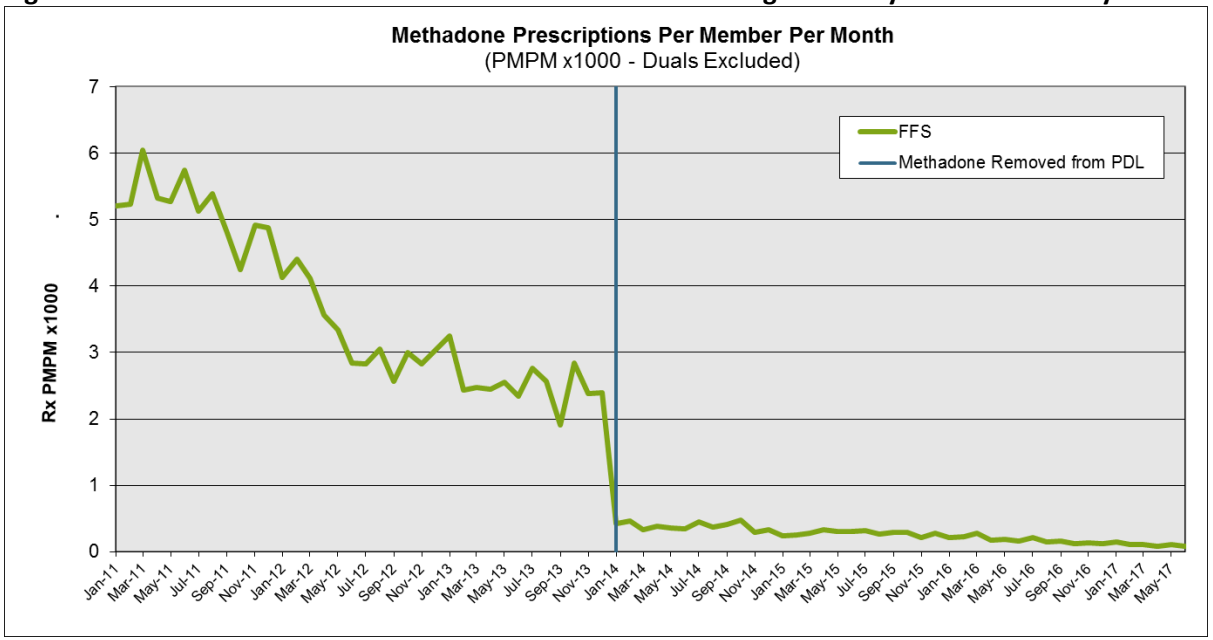
Table 2. Demographics of Patients with FFS Methadone Claims

Demographics	Pre Policy 2013 (n=197)	Post Policy 2014 (n=83)
Average age	45	47
Age (years)	n (%)	n (%)
0-17	5 (2.5)	1 (1.2)
18-54	139 (70.6)	57 (68.7)
55-64	50 (25.4)	24 (28.9)
65+	3 (1.5)	1 (1.2)
Female	121 (61.4)	44 (53)
White	131 (66.5)	57 (68.7)
Methadone dose >90 MME/day	94 (47.7)	47 (56.6)

Abbreviations: MME = morphine milligram equivalent

Figure 1 displays overall utilization (as methadone prescriptions per member per month x1000) over time from 2011 to 2017. Utilization sharply decreased around the time of the change in methadone PDL status, with 125 claims in December 2013 out of 52,106 members (2.4 PMPM x1000) to 48 claims in January 2014 out of 112,554 members (0.43 PMPM x1000). The number of claims was reduced after the change in methadone status even though the number of members increased by over 116% due to the Affordable Care Act (ACA) Medicaid expansion at that time. After 2014, utilization remained low with a downward trend.

Figure 1. FFS Methadone Utilization Before and After the Change in Policy Effective January 2014



Despite the decline in overall utilization, the absolute number of patients with hospitalizations for methadone or heroin overdose increased from 2013 to 2014 in both FFS and CCO patients as depicted in **Table 3.** However, the PMPM of methadone poisoning decreased in FFS patients from 2013 to 2014.

Table 3. Number of Patients with Hospitalizations or ED Visits for Methadone or Heroin Poisoning

Patient Hospitalizations/ED Visits	**Pre Policy 2013**		**Post Policy 2014**	
	n	PMPMx10,000	n	PMPMx10,000
Methadone Poisoning	n=86	1.38	n=134	1.41
FFS	19	2.45	29	2.09
CCO	67	1.23	107	1.32
Heroin Poisoning	n=145	2.33	n=432	4.54
FFS	27	3.48	102	7.36
CCO	118	2.16	337	4.14

Although there appears to be extensive variability in rates of hospitalization for both methadone and heroin poisoning (**Figures 2 and 3)**, the linear trend reveals an overall downward trend in hospitalizations/ED visits from methadone overdose and an upward trend in hospitalizations/ED visits from heroin overdose. For methadone poisoning, the decreasing trend was similar before and after methadone was removed from the PDL (**Figure 2**). However, for heroin poisoning, the rate of increase was higher after methadone was removed from the PDL (**Figure 3**).

Figure 2. Patients Hospitalized for Methadone Poisoning from 2011 to 2017 (Per-Member Per-Month x10,000)

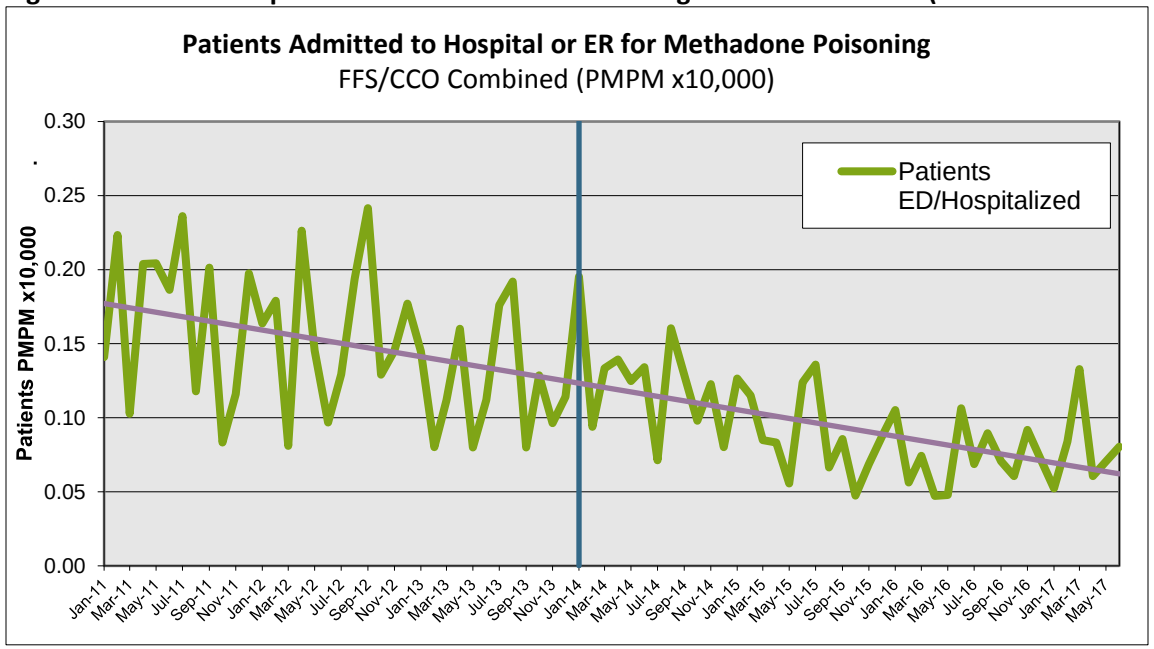
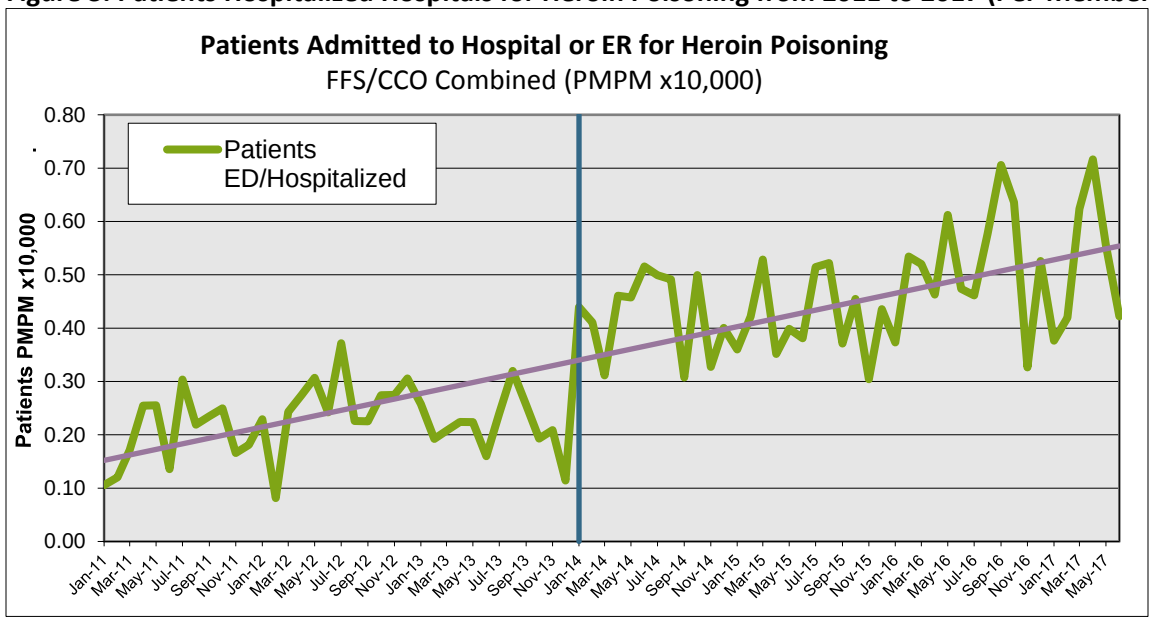


Figure 3. Patients Hospitalized Hospitals for Heroin Poisoning from 2011 to 2017 (Per-Member Per-Month x10,000)



Discussion

Patient demographics are similar among patients receiving methadone before and after the change in PDL status. Utilization of methadone sharply decreased at the start of 2014 when methadone was removed from the PDL. However, there did not seem to be a change in the number of patients receiving high dose methadone (≥ 90 morphine milligram equivalent [MME]). The CDC guidelines recommend avoiding daily doses ≥ 90 MME which significantly increase risk for motor vehicle accidents, opioid use disorder, and overdose.[4] There was already evidence of decrease in methadone utilization between 2011 and 2012, even before the change in PDL status. This may be due to CDC and FDA efforts in provider education leading up to the change in methadone PDL status. The ACA was enacted in 2014, which resulted in more Medicaid enrollees in Oregon around the time of this PDL change. The absolute number of methadone claims decreased in 2014 despite the significant increase in patients enrolled in Medicaid FFS, resulting in a significantly reduced proportion of patients with methadone claims.

Despite the decreased utilization, there did not appear to be a significant difference in the absolute number of hospitalizations due to methadone poisoning or heroin poisoning in 2013 and 2014. The impact of the change in PDL status of methadone on both methadone and heroin poisonings may not be evident because of the change in number of Medicaid enrollees due to the ACA. However, as shown in Figure 2 and 3, the amount of patients (per member per month x10,000) admitted for methadone poisonings has trended downward from 2011 to 2017 while the patients admitted for heroin poisonings has trended upwards. The rate of decrease in ED visits or hospitalizations from methadone poisoning was similar before and after the change in methadone's PDL status. However, the rate of increase in ED visits or hospitalizations for heroin poisoning was higher after methadone was removed from the PDL.

This increasing trend in heroin overdose may be influenced by reduced access to prescription opioids. While payers may restrict availability of methadone and other prescription opioids, they are unable to restrict the use of heroin as a substitute. However, no firm conclusions can be made as to whether the increased heroin hospitalizations are due to the removal of methadone from the PDL or due to other factors such as heroin cost or availability.

Limitations:

This evaluation is subject to the limitations of all claims-based retrospective analyses. This evaluation does not show if the hospitalizations were from repeat admissions of the same patient. It also does not capture overdoses that are reversed in the community. The percentage of overdoses captured is likely only a small proportion of all overdoses, and we are unable to capture deaths due to heroin or methadone overdose due to limitations in the data. Furthermore, this analysis did not capture any methadone prescriptions purchased with cash. It is possible that patients were paying out-of-pocket for their methadone prescription after the change in PDL status. Additionally, the ACA Medicaid expansion could result in differences between the two cohorts of patients compared in this analysis.

References:

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Long-acting Opioid Analgesics

Goals:

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

Length of Authorization:

90 days (except 12 months for end-of-life or cancer-related pain)

Covered Alternatives:

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

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.

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

Opioid	90 MME/day	Notes
Codeine	600 mg	Codeine is not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism placing certain populations at risk for overdose.)
Fentanyl (transdermal patch)	37.5 mcg/hr	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Morphine	90 mg	

Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

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

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

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day
OXYCONTIN	2 doses/day
TROXYCA ER	2 doses/day

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

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP.

3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for cancer-related pain (ICD10 G89.3) or under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed opioid analgesics by only a single prescribing practice or prescriber?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #9

9. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #10
10. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.**	**Yes:** Go to #12 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
12. Has the patient had a urinary drug screen (UDS) within the past 1 year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

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

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

Citation of the original publication:

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

Clinical Notes:

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

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

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

Symptoms and Treatment of Opioid Withdrawal.

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

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine

Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *3/17 (MH); 11/16; 05/16*

Implementation: *Phase implementation initiated 8/21/17*

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Drug Use Evaluation: Gabapentin Use in the FFS Population

Research Questions:

- How have gabapentin prescription claims and dosing patterns changed in relation to opioid claims following the release of the Center for Disease Control (CDC) 2016 guideline for chronic opioid use?
- Has there been an increase in emergency department visits, hospitalizations, or overdoses associated with gabapentin prescription claims since the release of the CDC guidelines?
- Is gabapentin being prescribed appropriately for FDA-approved indications (i.e. postherpetic neuropathy) in the Oregon Health Plan (OHP) fee-for-service (FFS) patient population?

Conclusions:

- Gabapentin utilization in the OHP FFS population has modestly increased by an average of 2 prescriptions per 1000 enrolled members per month over the past three years, which coincides with the publication of the CDC's 2016 Guidelines for chronic opioid use. Increased utilization is due to a 51% increase in new prescriptions, of which less than 15% exceed 90 days. Seventy-five percent of gabapentin claims are prescribed for an average daily dose of less than 1,800 mg/day, which is similar for claims before and after the publication of the CDC recommendations. Daily doses do not appear to be higher in patients with concurrent opioid use.
- There has been no increase in hospitalizations or emergency department (ED) visits associated with a gabapentin prescriptions, based on assessment of claims data. There were 8.9% and 35.6%, respectively, in the pre-cohort and 8.2% and 31.4%, respectively in the post cohort.
- Chronic musculoskeletal pain accounted for 50% of new gabapentin starts despite a lack of evidence for efficacy in this population. Some of this utilization may be related to overall decreases in opioid utilization in the OHP FFS population (32.5% decrease).

Recommendations:

- As there are no clear safety issues identified with this evaluation, no changes are recommended at this time.

Background:

Gabapentin currently has no restrictions or prior authorization (PA) criteria for use by OHP patients. The FDA-approved indications for gabapentin include treatment of partial onset seizures and postherpetic neuralgia. However, it is commonly prescribed for a number of off-label indications. According to a recent report, the volume of gabapentin prescriptions has increased from 2012 to 2016 in the United States (U.S.).[1] In 2016, gabapentin was the tenth most commonly prescribed medication in the U.S. with 64 million prescriptions (compared to 39 million in 2012).[1] This is concerning given increasing off-label use with poor quality evidence to support efficacy in pain management. A 2017 Cochrane meta-analysis examined 37 placebo-controlled trials of gabapentin in a variety of neuropathies (primarily postherpetic and diabetic neuropathy but also including spinal cord injury, phantom limb pain, complex regional pain syndrome, HIV-

associated neuropathy, and radicular leg pain).[2] Evidence was rated as moderate for use in diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) but very low in other neuropathic conditions due to limited data.[2] Small population size, short duration, and inconsistent outcome reporting limited the quality of these studies.[2] The authors concluded gabapentin was likely to provide pain relief at doses of 1,800-3,600 mg/day for postherpetic and diabetic neuropathies (number needed to treat [NNT] 6.9; 95% confidence interval [CI] 5.5 to 9.4 and NNT 6.9; 95% CI 4.6 to 8.3, respectively for 50% or greater reduction in pain relative to placebo).[2] This was limited by a higher rate of adverse events relative to placebo leading to withdrawal of therapy (11 vs. 8.2%, number needed to harm [NNH] 30; 95% CI 20 to 66).[2]

In addition to various off-label uses, increasing gabapentin utilization may be influenced in part by new PA restrictions implemented for opioids following the March 2016 publication of the Centers for Disease Control and Prevention (CDC) Opioid Use in Chronic Pain Guidelines.[3] These guidelines discuss the general lack of evidence for efficacy with chronic opioid use in conjunction with the clear risk of harm associated with higher morphine equivalent doses (MED).[3] As such, caution is recommended with MED greater than or equal to 50 mg/day while MED greater than or equal to 90 mg/day is not recommended.[3] Opioid and gabapentinoid use may be closely connected.[4] An analysis of PA restrictions on pregabalin use in Medicaid patients in two undisclosed states found decreasing pregabalin use associated with a subsequent increase in opioid utilization.[4]

An increase in gabapentin utilization is also concerning given case reports of gabapentin misuse – including but not limited to use of another person's medication, use by non-recommended route of administration, or use of a higher dose than prescribed – which may be increasing concurrently.[5,6] In one study, the estimated prevalence of gabapentin misuse was 1% among the general population and 15% to 22% in patients with a history of opioid abuse.[5] A national sample of law-enforcement and regulatory agencies also reported 407 drug diversion cases with increasing rates over time (from zero cases per 100,000 population in 2002 to 0.027 cases per 100,000 population in 2015).[6] Surveys of law enforcement personnel suggest gabapentin abuse is associated with prescription opioids and heroin abuse.[6] A systematic review published in 2016 gathered 11 epidemiologic studies and 23 case studies describing gabapentin misuse.[5] Over half of these studies identified current substance abuse or history of substance abuse in those misusing gabapentin.[5] In another study, gabapentin misuse was evident in 22% of patients presenting for inpatient opioid detoxification.[7]

Increasing utilization of gabapentin and pregabalin has prompted the publication of an advisory the National Health Service in the United Kingdom on the potential for misuse and abuse with these medications.[8] Concerns for misuse and lack of clinical studies demonstrating efficacy for low back pain of these agents led to a 2017 meta-analysis of gabapentinoid use in chronic back pain.[9] Three randomized controlled trials with an overall low evidence rating due to small sample sizes and a high risk of selection bias were reviewed.[9] Gabapentin was not found to differ from placebo in pain relief as measured by change in 1-10 numerical rating scale (very low level confidence in effect estimate).[9] Over 6 to 12 weeks of treatment, gabapentin was associated with increases in dizziness (NNH 7; 95% CI 4 to 30) and fatigue (NNH 8; 95% CI 4 to 44) when compared to placebo (very low level of confidence in effect estimate).[9] Gabapentin was also associated with a higher incidence of visual disturbance (NNH 6; 95% CI 4 to 13, moderate level of confidence in effect estimate) and difficulties with mentation (NNH 6; 95% CI 4 to 15, low level of confidence in effect estimate).[9]

Gabapentin has also been used off-label for management of postoperative pain.[10] The American Pain Society recommends gabapentin or pregabalin as part of a multimodal pain management strategy in patients undergoing surgery.[10] The evidence for the recommendation was rated as moderate quality based on decreased postoperative pain scores and opioid requirements.[10] Another recent randomized, controlled trial compared gabapentin to placebo and did not find

significant differences in time to pain cessation between the two groups but did see quicker cessation of opioid therapy in the gabapentin group (median 25 days [interquartile range (IQR) 8-53 days] vs. median 32 days [IQR 9-55 days]).[11] Treatment was started preoperatively and continued for 72 hours following surgery.[11]

An analysis completed in a commercial insurance population assessed the use of gabapentin alongside other drugs of abuse using a Lorenz curve from 2013 to 2015.[12] Lorenz curves stratify an amount of medication used or dispensed as a function of time or days covered and are a useful tool for identifying medications that are prone to overuse by a small proportion of the population.[13-16] In the gabapentin analysis, the top 1% of gabapentin utilizers accounted for 19% of use with a mean of 11,274 mg/day and median use of 9,534 mg/day.[12] When simultaneous gabapentin and opioid use was examined, abuse potential (defined as patients with three or more claims exceeding the dose threshold of either 50 MED/day or gabapentin 3,600 mg/day within the past 12 months) occurred in 24% of patients.[12] These findings are particularly concerning given the observations recently published in a case-control study of 1,256 patients with fatal opioid overdose.[17] When comparing these patients to 4,169 controls matched for age, duration on opioids, and disease risk index, gabapentin exposure was associated with an increased risk of death (odds ratio [OR] 1.49; 95% CI: 1.18-1.88) after adjusting for potential confounders.[17] Odds of death increased with doses ≥1,800 mg/day (OR 1.58; 95% CI: 1.09-2.27).[17]

This report aims to gather information on current patterns of gabapentin use in the OHP FFS population including indication, dose, duration of therapy, and risks for gabapentin overdose.

Methods:

To assess utilization and dosing trends, a cross-sectional design was developed to characterize chronic gabapentin use in OHP FFS members. In order to identify average use over a period of time following the publication of the CDC opioid guidelines (Post-CDC Cohort), members were chosen for inclusion on the basis of a paid FFS paid pharmacy claim for gabapentin from 7/1/2016 to 6/30/2017 to allow for a four month period of time for the CDC prescribing recommendations to impact prescribing practices. A historical control group from 2/1/15 to 1/31/16 was chosen prior to publication of the CDC guidelines (Pre-CDC Cohort), to establish trends in utilization and provide a basis for analysis in changes over time. In order to examine chronic gabapentin use, patients were included if they had at least 90 days of continuous gabapentin use during the cohort span (with no more than 14 days gap between the end of one claim and the start of the next claim). To ensure completeness of data, patients had to have at least 75% days of OHP eligibility from the month of their first claim to one month after the end of their last claim during the study period. Patients were excluded if they had any of the following benefit packages which indicate Medicare Part D coverage: benefit packages BMM, BMD, MND, CWM, SMF, SNB, or MED. Patients were also excluded if they had a seizure disorder diagnosis (**Appendices 1 and 2**) from one year prior to the cohort span or any time during the cohort span.

Baseline characteristics, including age, gender, and ethnicity, are presented in **Table 1**. Average daily dose (ADD) of gabapentin for each patient was calculated as (strength * quantity dispensed / day supply) for each claim, and averaged for each patient. Concurrent opioid use was determined on the basis of a paid FFS pharmacy claim for any prescription opioid listed in **Appendix 3** for at least 90 days concurrently with gabapentin claims. Average and median daily gabapentin dose was calculated for the patients in both cohorts which was further analyzed based on concomitant opioid use (presented in **Table 2**).

All-cause hospitalizations and ED visits within 30 days of a paid gabapentin claim were also recorded for these patients based on billing codes (**Appendix 4**). Comparisons were made between the two cohorts and included breakdowns based on daily gabapentin dose (greater than 1,800 mg to 2,400 mg, greater than 2,400 mg to 3,600 mg, and greater than 3,600 mg).

In order to assess changes in utilization over time, overall FFS gabapentin and opioid pharmacy utilization trends are shown in **Figure 1** from 2015 to the present, reported as unique utilizing members per enrolled member per month (PMPM).

To assess prescribing trends, patients starting gabapentin (new starts) were also compared during the same pre- and post-CDC guideline time periods described above. A new start is defined as a patient with a gabapentin claim and no other gabapentin claims in the previous 6 months. The first claim is called the index event. In order to be included for this analysis, patients had to have 75% OHP eligibility in the 6 months prior to the index date. As described previously, patients were excluded for having a seizure diagnosis or Medicare Part D coverage. Patients were also excluded if the gabapentin claim was for 15 days or less as these would likely be peri-procedural. Indications were identified within the six months prior to the index date. These were categorized as FDA approved, non-FDA approved but with evidence for use, non-FDA approved without evidence for use, and no indication found (**Table 3**). If an FDA-approved indication is identified, no further search for off-label indications were performed. Similarly, indications with evidence for use were chosen regardless of whether the patient had other indications that the gabapentin could have been prescribed for. A list of all ICD codes and characterizations appears in **Appendices 1 and 2**.

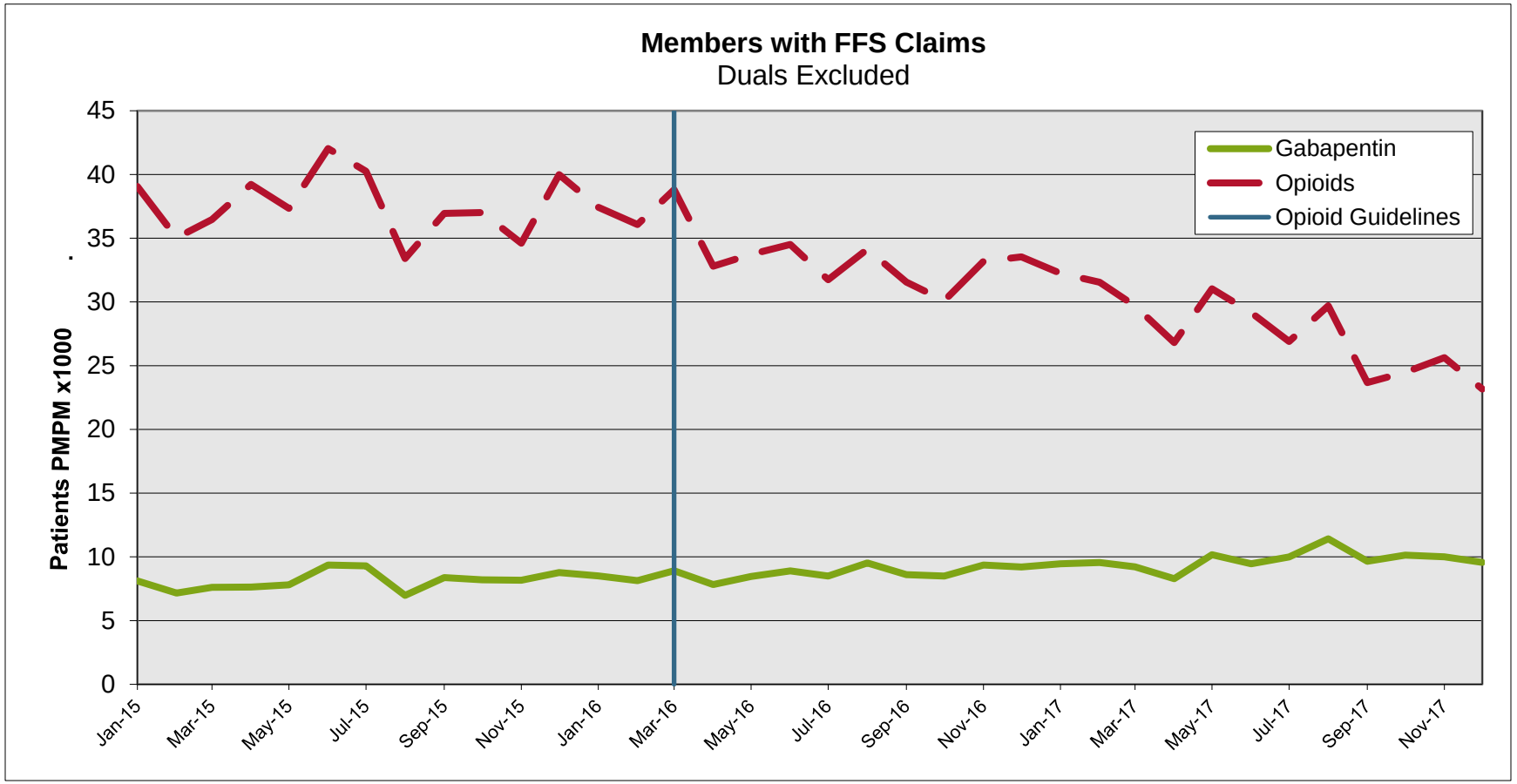
Results:

Table 1. Demographics of Chronic Gabapentin Users

	Pre Cohort		Post Cohort	
N=	828		894	
Average Age (min/max)	46	(6-75)	45	(8-75)
<19	15	1.8%	15	1.7%
19-64	808	97.6%	869	97.2%
>64	5	0.6%	10	1.1%
Female	567	68.5%	606	67.8%
White	457	55.2%	429	48.0%

Demographics of chronic gabapentin users in the OHP FFS population are presented in **Table 1**. Around two-thirds of the study population are female with 51.5% of them being Caucasian with an average age of 45-46 years.

Figure 1. Total Monthly Prescriptions for Gabapentin and Opioids from 1/1/15 to 8/30/17



Overall, gabapentin utilization in the FFS population increased an average of 2 claims x 1000 PMPM from January 2015 to December 2017. (**Figure 1**). During this same time period, opioid utilization decreased an average of 14 claims x 1000 PMPM.

Table 2. Chronic Gabapentin Dosing Pre- and Post-CDC Guideline Publication

	Pre Cohort						Post Cohort					
	Overall		With Opioid		Without Opioid		Overall		With Opioid		Without Opioid	
N=	828		203	24.5%	625	75.5%	894		174	19.5%	720	80.5%
Average Daily Dose	1,334		1,532		1,270		1,329		1,611		1,261	
Median Daily Dose	1,138		1,200		900		1,018		1,572		900	
By Max Dose												
>3600 mg/day	10	1.2%	4	2.0%	6	1.0%	7	0.8%	1	0.6%	6	0.8%
>2700 mg/day	58	7.0%	18	8.9%	40	6.4%	69	7.7%	19	10.9%	50	6.9%
>1800 mg/day	140	16.9%	42	20.7%	98	15.7%	143	16.0%	39	22.4%	104	14.4%
>900 mg/day	259	31.3%	69	34.0%	190	30.4%	277	31.0%	58	33.3%	219	30.4%
<=900 mg/day	361	43.6%	70	34.5%	291	46.6%	398	44.5%	57	32.8%	341	47.4%

There was more chronic gabapentin use in the post CDC-guideline cohort compared to the pre-CDC guideline cohort (894 vs. 828, respectively) (**Table 2**). The number of chronic gabapentin users co-prescribed an opioid decreased by 5% (from 24.5% to 19.5%); these patients received on average 300-400 mg higher daily doses of gabapentin than those without a concurrent opioid. Approximately 75% of patients received daily gabapentin doses of 1,800 mg or less with about 45% of patients receiving daily doses less than 900 mg. The gabapentin average daily dose between the two cohorts is largely unchanged.

Despite the increased utilization, gabapentin use associated with a hospitalization or ED visit was largely unchanged in chronic users. Percentage of chronic gabapentin users with a hospitalization or ED visit within 30 days following a paid gabapentin claim were 8.9% and 35.6%, respectively, in the pre-cohort and 8.2% and 31.4%, respectively, in the post-cohort. Hospitalization or ED visits occurred in 94 (out of 208) patients in the pre-cohort and 100 (out of 219) patients in the post-cohort with an average daily dose greater than 1,800 mg. Relative percentage of patients with a hospitalization or ED visit in the two cohorts was similar across different dosing thresholds.

Table 3. Gabapentin Users by Indication in 6 Months Prior to New Start

	Pre Cohort		Post Cohort	
N=	2,105		3,189	
FDA Approved	**32**	**1.5%**	**37**	**1.2%**
Postherpetic neuropathy	32	1.5%	37	1.2%
With diabetes	4	0.2%	4	0.1%
Non-FDA approved with evidence for use	**88**	**4.2%**	**7**	**0.2%**
Diabetic neuropathy	76	3.6%		0.0%
Neuropathy (painful polyneuropathy, phantom limb pain, chemotherapy-induced neuropathy, spinal cord injury pain)	12	0.6%	7	0.2%
With diabetes	78	3.7%	0	0.0%
Non-FDA approved without evidence for use	**1,167**	**55.4%**	**1,895**	**59.4%**
Neuropathy (HIV neuropathy, central post-stroke pain, trigeminal neuralgia)	722	34.3%	612	19.2%
Migraine headache prophylaxis	169	8.0%	255	8.0%
Chronic musculoskeletal pain	523	24.8%	1,416	44.4%
By Total Days Supply				
<= 30	343	65.6%	1,021	72.1%
>30 and <=90	115	22.0%	251	17.7%
>90	65	12.4%	144	10.2%
Fibromyalgia	247	11.7%	243	7.6%
With diabetes	187	8.9%	384	12.0%
Any of the Above	**1,287**	**61.1%**	**1,939**	**60.8%**
With diabetes	269	12.8%	388	12.2%
None of the Above	**818**	**38.9%**	**1,250**	**39.2%**
With diabetes	157	7.5%	281	8.8%

Table 4. Gabapentin New Starts by Total Day Supply in Cohort Span
Note: Patients with 15 days' supply or less were excluded

	Patient Count			
	Pre Cohort		Post Cohort	
N=	2,105		3,189	
Total days' supply				
<= 30	1,352	64.2%	2,234	70.1%
>30 and <=90	439	20.9%	596	18.7%
>90	314	14.9%	359	11.3%

The number of new patients starting on gabapentin between the two cohorts increased by 51% between 2/1/15-1/31/16 and 7/1/2016-6/30/2017 (**Table 3).** Fewer patients were identified in the post-cohort as having diabetic neuropathy compared to the pre-cohort. Conversely, more patients were identified as having some form of chronic musculoskeletal pain in the post-cohort (44.4%) compared to the pre-cohort (24.8%). However, the percentage of patients with a diagnosis of diabetes was largely unchanged between the two time periods (20.2% and 20.9% for the pre- and post-cohorts, respectively). Compelling indications for use were not readily apparent in a majority of patients in either the pre- or post-cohorts. Patients in the post-cohort, identified as having chronic musculoskeletal pain, used gabapentin for a shorter period of time compared to the pre-cohort, a trend that was observed in overall utilization by patients in the post-cohort (**Table 4**).

Discussion:

Overall, increased gabapentin utilization in the OHP FFS population following the publication of the 2016 CDC opioid guidelines has been modest. Based on FFS claims data more patients were initiated on gabapentin, but most patients only received a short-term supply of gabapentin, with few repeated claims indicating possible chronic use. However, much of this use seems to be for indications without compelling evidence for use, as a large percentage of patients appeared to receive gabapentin for chronic musculoskeletal pain (44%). Off-label use may be related in part to Guideline Note 60 on the OHP Prioritized List which restricts approval of opioid claims for back and spine conditions to acute use only. In addition, recent changes to the FFS opioid PA criteria that aims to decrease long-term use and restrict daily doses to 90 mg morphine equivalents/day or less may be encouraging providers to prescribe alternative medications for pain management.

Of note, many of the patients on chronic gabapentin do not seem to be receiving evidence-based doses (1,800 mg/day or higher). However, this is difficult to accurately assess as gabapentin requires renal dose adjustments and analysis of renal function cannot be calculated based on claims data. Based on the average age of the patients who received gabapentin (19-64), this is unlikely a factor. It is unclear from these data if short term utilization (less than 15% of prescriptions

were over 90 days in length) is related to discontinuation due to side effects of gabapentin versus a trial of use stopped prior to reaching a therapeutic dose. The lower doses observed in claims data may also reflect patients in the midst of titrating upwards on gabapentin therapy.

Between the pre- and post-cohorts, there was a decrease in the number of patients co-prescribed gabapentin and opioids (203 vs. 174 [24.5% vs. 19.5%], respectively) with an increase in the number of patients co-prescribed opioids (625 compared to 720 [75.5% vs. 80.5%], respectively). Much of this may be related to the changes in opioid management policies for OHP FFS patients that have placed larger restrictions on opioid prescribing. A difference in the relative number of patients reaching doses 1,800 mg/day or greater is not apparent between the pre- and post-cohorts. Patients with a concurrent opioid prescription claims were more likely to have higher gabapentin doses compared with patients not taking opioids, 21% compared to 15% for daily doses of 1,800 mg to less than 2,700 mg/day and 10% compared to 7% for daily doses 2,700 mg to less than 3,600 mg/day.

In summary, gabapentin use seems to be modestly increasing as opioid use decreases without an apparent increase in utilization of emergency services or hospitalization. In the FFS population, a large majority of utilization is for short durations of therapy and is prescribed for patients with diagnoses of musculoskeletal pain. There is insufficient evidence to support the use of gabapentin in musculoskeletal pain. Additionally, doses seen in Oregon Medicaid patients who use gabapentin chronically are lower than the therapeutic doses found to have efficacy in randomized, clinical trials (≥1800 mg/day). Given that more than two-thirds of OHP patients have received gabapentin for 30 days or less, it is possible that ineffectiveness or adverse effects were a factor that impacted duration of therapy. Currently there are no PA criteria for gabapentin and although use has increased, much of this seems to be as an alternative to opioid therapy. Creating a barrier to this use may drive prescribing back to opioids which have clear risks of harm, something that is not immediately apparent in these data with gabapentin. Future research exploring use in the Medicaid population managed by the Coordinated Care Organizations may reveal differences from this analysis as these insurers are more likely to retain patients longer than FFS.

Limitations:

These data are not without their limitations since examination of claims data is accompanied with a large number of assumptions. For one, just because a patient picked up a prescription for gabapentin does not mean they adhered to prescribing recommendations. Conversely, just because there is not a claim does not mean a patient did not pay cash or obtain gabapentin through some other means. There are also limitations evident in the stratification of gabapentin usage by disease state. Per data analysis of specific ICD9/10 codes for diabetic neuropathy, it appears gabapentin use has decreased, but when general ICD9/10 codes for diabetes as a whole were analyzed, both the pre- and post- cohort had a similar percentage of patients with a diagnosis of diabetes. This may be due to the differences in the complexity of the two coding systems and the wide array of available diagnoses that ICD10 offers. Similarly, an examination of hospitalization and ED visits can only be done through the correlation of claims data, making it difficult to conclude that gabapentin use is necessarily what drove the patient to seek that care.

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Appendix 1: ICD9 codes

Seizures
345 Epilepsy and recurrent seizures
Postherpetic neuropathy
053 Herpes zoster
Diabetic neuropathy
357.2 Polyneuropathy in diabetes
249.6 Secondary diabetes mellitus with neurological manifestations
250.6 Diabetes with neurological manifestations
Neuropathy with evidence for use (phantom limb pain, chemotherapy-induced neuropathy, spinal cord injury pain)
353.6 Phantom limb (syndrome)
357.3 Polyneuropathy in malignant disease
952 Spinal cord injury without evidence of spinal bone injury
Non-evidenced neuropathy (HIV neuropathy, central post-stroke pain, trigeminal neuralgia, other neuropathy)
350 Trigeminal nerve disorders
042 Human immunodeficiency virus [HIV] disease
430 Subarachnoid hemorrhage
431 Intracerebral hemorrhage
432 Other and unspecified intracranial hemorrhage
433 Occlusion and stenosis of precerebral arteries
434 Occlusion of cerebral arteries
435 Transient cerebral ischemia
436 Acute, but ill-defined, cerebrovascular disease
437 Other and ill-defined cerebrovascular disease
438 Late effects of cerebrovascular disease
953 Injury to nerve roots and spinal plexus
954 Injury to other nerve(s) of trunk excluding shoulder and pelvic girdles
955 Injury to peripheral nerve(s) of shoulder girdle and upper limb
956 Injury to peripheral nerve(s) of pelvic girdle and lower limb
957 Injury to other and unspecified nerves
729.2 Neuralgia, neuritis, and radiculitis, unspecified
338 Pain, not elsewhere classified
355 Mononeuritis of lower limb and unspecified site
356 Hereditary and idiopathic peripheral neuropathy
357.0 Acute infective polyneuritis
357.1 Polyneuropathy in collagen vascular disease
357.4 Polyneuropathy in other diseases classified elsewhere
357.5 Alcoholic polyneuropathy
357.6 Polyneuropathy due to drugs
357.7 Polyneuropathy due to other toxic agents
357.8 Other inflammatory and toxic neuropathy
357.81 Chronic inflammatory demyelinating polyneuritis
357.82 Critical illness polyneuropathy
357.89 Other inflammatory and toxic neuropathy
357.9 Unspecified inflammatory and toxic neuropathy
Migraine headache prophylaxis
346 Migraine
Chronic musculoskeletal pain
720 Ankylosing spondylitis and other inflammatory spondylopathies
721 Spondylosis and allied disorders
722 Intervertebral disc disorders
Fibromyalgia
729.1 Fibromyalgia
Diabetes
249.XXX-250.XXX

Appendix 2: ICD10 Codes

Seizures
G40 Epilepsy and recurrent seizures
Postherpetic neuropathy
B02 Zoster [herpes zoster]
Diabetic neuropathy
E08.40 Diabetes mellitus due to underlying condition with diabetic neuropathy, unspecified
E08.41 Diabetes mellitus due to underlying condition with diabetic mononeuropathy
E08.42 Diabetes mellitus due to underlying condition with diabetic polyneuropathy
E08.43 Diabetes mellitus due to underlying condition with diabetic autonomic (poly)neuropathy
E08.44 Diabetes mellitus due to underlying condition with diabetic amyotrophy
E08.49 Diabetes mellitus due to underlying condition with other diabetic neurological complication
E08.610 Diabetes mellitus due to underlying condition with diabetic neuropathic arthropathy
E09.40 Drug or chemical induced diabetes mellitus with neurological complications with diabetic neuropathy, unspecified
E09.41 Drug or chemical induced diabetes mellitus with neurological complications with diabetic mononeuropathy
E09.42 Drug or chemical induced diabetes mellitus with neurological complications with diabetic polyneuropathy
E09.43 Drug or chemical induced diabetes mellitus with neurological complications with diabetic autonomic (poly)neuropathy
E09.44 Drug or chemical induced diabetes mellitus with neurological complications with diabetic amyotrophy
E09.49 Drug or chemical induced diabetes mellitus with neurological complications with other diabetic neurological complication
E09.610 Drug or chemical induced diabetes mellitus with diabetic neuropathic arthropathy
E10.40 Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41 Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42 Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43 Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44 Type 1 diabetes mellitus with diabetic amyotrophy
E10.49 Type 1 diabetes mellitus with other diabetic neurological complication
E10.610 Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E11.40 Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41 Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42 Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43 Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44 Type 2 diabetes mellitus with diabetic amyotrophy
E11.49 Type 2 diabetes mellitus with other diabetic neurological complication
E11.610 Type 2 diabetes mellitus with diabetic neuropathic arthropathy
E13.40 Other specified diabetes mellitus with diabetic neuropathy, unspecified
E13.41 Other specified diabetes mellitus with diabetic mononeuropathy
E13.42 Other specified diabetes mellitus with diabetic polyneuropathy
E13.43 Other specified diabetes mellitus with diabetic autonomic (poly)neuropathy
E13.44 Other specified diabetes mellitus with diabetic amyotrophy
E13.49 Other specified diabetes mellitus with other diabetic neurological complication
E13.610 Other specified diabetes mellitus with diabetic neuropathic arthropathy
Neuropathy with evidence for use (phantom limb pain, chemotherapy-induced neuropathy, spinal cord injury pain)
G54.6 Phantom limb syndrome with pain
G13.0 Paraneoplastic neuromyopathy and neuropathy
S34 Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level
Non-evidenced neuropathy (HIV neuropathy, central post-stroke pain, trigeminal neuralgia, other neuropathy)
G50 Disorders of trigeminal nerve
B20 Human immunodeficiency virus [HIV] disease
I60 Nontraumatic subarachnoid hemorrhage
I61 Nontraumatic intracerebral hemorrhage
I62 Other and unspecified nontraumatic intracranial hemorrhage
I63 Cerebral Infarction
I67 Other cerebrovascular diseases
I69 Sequelae of cerebrovascular disease
B26.84 Mumps polyneuropathy
G13.1 Other systemic atrophy primarily affecting central nervous system in neoplastic disease
G50.1 Atypical facial pain
G51.0 Bell's palsy
G51.1 Geniculate ganglionitis
G51.2 Melkersson's syndrome
G51.3 Clonic hemifacial spasm
G51.4 Facial myokymia
G51.8 Other disorders of facial nerve
G51.9 Disorder of facial nerve, unspecified
G52.0 Disorders of olfactory nerve
G52.1 Disorders of glossopharyngeal nerve
G52.2 Disorders of vagus nerve
G52.3 Disorders of hypoglossal nerve
G52.7 Disorders of multiple cranial nerves
G52.8 Disorders of other specified cranial nerves
G52.9 Cranial nerve disorder, unspecified
G53 Cranial nerve disorders in diseases classified elsewhere
G54.0 Brachial plexus disorders
G54.1 Lumbosacral plexus disorders
G54.2 Cervical root disorders, not elsewhere classified
G54.3 Thoracic root disorders, not elsewhere classified
G54.4 Lumbosacral root disorders, not elsewhere classified
G54.5 Neuralgic amyotrophy
G54.8 Other nerve root and plexus disorders
G54.9 Nerve root and plexus disorder, unspecified
G55 Nerve root and plexus compressions in diseases classified elsewhere

G56.00 Carpal tunnel syndrome, unspecified upper limb
G56.01 Carpal tunnel syndrome, right upper limb
G56.02 Carpal tunnel syndrome, left upper limb
G56.03 Carpal tunnel syndrome, bilateral upper limbs
G56.10 Other lesions of median nerve, unspecified upper limb
G56.11 Other lesions of median nerve, right upper limb
G56.12 Other lesions of median nerve, left upper limb
G56.13 Other lesions of median nerve, bilateral upper limbs
G56.20 Lesion of ulnar nerve, unspecified upper limb
G56.21 Lesion of ulnar nerve, right upper limb
G56.22 Lesion of ulnar nerve, left upper limb
G56.23 Lesion of ulnar nerve, bilateral upper limbs
G56.30 Lesion of radial nerve, unspecified upper limb
G56.31 Lesion of radial nerve, right upper limb
G56.32 Lesion of radial nerve, left upper limb
G56.33 Lesion of radial nerve, bilateral upper limbs
G56.40 Causalgia of unspecified upper limb
G56.41 Causalgia of right upper limb
G56.42 Causalgia of left upper limb
G56.43 Causalgia of bilateral upper limbs
G56.80 Other specified mononeuropathies of unspecified upper limb
G56.81 Other specified mononeuropathies of right upper limb
G56.82 Other specified mononeuropathies of left upper limb
G56.83 Other specified mononeuropathies of bilateral upper limbs
G56.90 Unspecified mononeuropathy of unspecified upper limb
G56.91 Unspecified mononeuropathy of right upper limb
G56.92 Unspecified mononeuropathy of left upper limb
G56.93 Unspecified mononeuropathy of bilateral upper limbs
G57.00 Lesion of sciatic nerve, unspecified lower limb
G57.01 Lesion of sciatic nerve, right lower limb
G57.02 Lesion of sciatic nerve, left lower limb
G57.03 Lesion of sciatic nerve, bilateral lower limbs
G57.10 Meralgia paresthetica, unspecified lower limb
G57.11 Meralgia paresthetica, right lower limb
G57.12 Meralgia paresthetica, left lower limb
G57.13 Meralgia paresthetica, bilateral lower limbs
G57.20 Lesion of femoral nerve, unspecified lower limb
G57.21 Lesion of femoral nerve, right lower limb
G57.22 Lesion of femoral nerve, left lower limb
G57.23 Lesion of femoral nerve, bilateral lower limbs
G57.30 Lesion of lateral popliteal nerve, unspecified lower limb
G57.31 Lesion of lateral popliteal nerve, right lower limb
G57.32 Lesion of lateral popliteal nerve, left lower limb
G57.33 Lesion of lateral popliteal nerve, bilateral lower limbs
G57.40 Lesion of medial popliteal nerve, unspecified lower limb
G57.41 Lesion of medial popliteal nerve, right lower limb
G57.42 Lesion of medial popliteal nerve, left lower limb
G57.43 Lesion of medial popliteal nerve, bilateral lower limbs
G57.50 Tarsal tunnel syndrome, unspecified lower limb
G57.51 Tarsal tunnel syndrome, right lower limb
G57.52 Tarsal tunnel syndrome, left lower limb
G57.53 Tarsal tunnel syndrome, bilateral lower limbs
G57.60 Lesion of plantar nerve, unspecified lower limb
G57.61 Lesion of plantar nerve, right lower limb
G57.62 Lesion of plantar nerve, left lower limb
G57.63 Lesion of plantar nerve, bilateral lower limbs
G57.70 Causalgia of unspecified lower limb
G57.71 Causalgia of right lower limb
G57.72 Causalgia of left lower limb
G57.73 Causalgia of bilateral lower limbs
G57.80 Other specified mononeuropathies of unspecified lower limb
G57.81 Other specified mononeuropathies of right lower limb
G57.82 Other specified mononeuropathies of left lower limb
G57.83 Other specified mononeuropathies of bilateral lower limbs
G57.90 Unspecified mononeuropathy of unspecified lower limb
G57.91 Unspecified mononeuropathy of right lower limb
G57.92 Unspecified mononeuropathy of left lower limb
G57.93 Unspecified mononeuropathy of bilateral lower limbs
G58.0 Intercostal neuropathy
G58.7 Mononeuritis multiplex
G58.8 Other specified mononeuropathies
G58.9 Mononeuropathy, unspecified
G59 Mononeuropathy in diseases classified elsewhere
G60.0 Hereditary motor and sensory neuropathy
G60.2 Neuropathy in association with hereditary ataxia
G60.3 Idiopathic progressive neuropathy
G60.8 Other hereditary and idiopathic neuropathies
G60.9 Hereditary and idiopathic neuropathy, unspecified
G61.1 Serum neuropathy
G61.81 Chronic inflammatory demyelinating polyneuritis
G61.82 Multifocal motor neuropathy
G61.89 Other inflammatory polyneuropathies
G61.9 Inflammatory polyneuropathy, unspecified
G62.0 Drug-induced polyneuropathy
G62.1 Alcoholic polyneuropathy
G62.2 Polyneuropathy due to other toxic agents
G62.81 Critical illness polyneuropathy
G62.82 Radiation-induced polyneuropathy
G62.89 Other specified polyneuropathies
G62.9 Polyneuropathy, unspecified
G63 Polyneuropathy in diseases classified elsewhere
G64 Other disorders of peripheral nervous system
G65.0 Sequelae of Guillain-Barré syndrome
G65.1 Sequelae of other inflammatory polyneuropathy
G65.2 Sequelae of toxic polyneuropathy
G70.1 Toxic myoneural disorders
G70.2 Congenital and developmental myasthenia
G70.89 Other specified myoneural disorders
G70.9 Myoneural disorder, unspecified
G83.4 Cauda equina syndrome
G90.01 Carotid sinus syncope

G90.09 Other idiopathic peripheral autonomic neuropathy
G90.2 Horner's syndrome
G90.4 Autonomic dysreflexia
G90.50 Complex regional pain syndrome I, unspecified
G90.511 Complex regional pain syndrome I of right upper limb
G90.512 Complex regional pain syndrome I of left upper limb
G90.513 Complex regional pain syndrome I of upper limb, bilateral
G90.519 Complex regional pain syndrome I of unspecified upper limb
G90.521 Complex regional pain syndrome I of right lower limb
G90.522 Complex regional pain syndrome I of left lower limb
G90.523 Complex regional pain syndrome I of lower limb, bilateral
G90.529 Complex regional pain syndrome I of unspecified lower limb
G90.59 Complex regional pain syndrome I of other specified site
G90.8 Other disorders of autonomic nervous system
G90.9 Disorder of the autonomic nervous system, unspecified
G99.0 Autonomic neuropathy in diseases classified elsewhere

M21.331 Wrist drop, right wrist
M21.332 Wrist drop, left wrist
M21.339 Wrist drop, unspecified wrist
M21.511 Acquired clawhand, right hand
M21.512 Acquired clawhand, left hand
M21.519 Acquired clawhand, unspecified hand
M21.521 Acquired clubhand, right hand
M21.522 Acquired clubhand, left hand
M21.529 Acquired clubhand, unspecified hand
M21.531 Acquired clawfoot, right foot
M21.532 Acquired clawfoot, left foot
M21.539 Acquired clawfoot, unspecified foot
M34.83 Systemic sclerosis with polyneuropathy
M79.2 Neuralgia and neuritis, unspecified
S04 Injury of cranial nerve
S14 Injury of nerves and spinal cord at neck level
S24 Injury of nerves and spinal cord at thorax level
S34 Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level

S44 Injury of nerves at shoulder and upper arm level
S54 Injury of nerves at forearm level
S64 Injury of nerves at wrist and hand level
S74 Injury of nerves at hip and thigh level
S84 Injury of nerves at lower leg level
S94 Injury of nerves at ankle and foot level
Migraine headache prophylaxis
G43 Migraine
Chronic musculoskeletal pain
M50 Cervical disc disorders
M51 Thoracic, thoracolumbar, and lumbosacral...
M53 Other and unspecified dorsopathies, not ...
M54 Dorsalgia
Fibromyalgia
M79.7 Fibromyalgia
Diabetes
E08XXX-E13.XXX

Appendix 3: List of Opioids

GENERIC NAME	BRAND NAME	FORM
ACETAMINOPHEN WITH CODEINE	ACETAMINOPHEN W/CODEINE	ELIXIR
ACETAMINOPHEN WITH CODEINE	ACETAMINOPHEN-CODEINE	SOLUTION
ACETAMINOPHEN WITH CODEINE	ACETAMINOPHEN-CODEINE	TABLET
ACETAMINOPHEN WITH CODEINE	CAPITAL W-CODEINE	ORAL SUSP
ACETAMINOPHEN WITH CODEINE	TYLENOL-CODEINE NO.3	TABLET
ACETAMINOPHEN WITH CODEINE	TYLENOL-CODEINE NO.4	TABLET
BUPRENORPHINE	BUPRENORPHINE	PATCH TDWK
BUPRENORPHINE	BUTRANS	PATCH TDWK
BUPRENORPHINE HCL	BELBUCA	FILM
BUTALBIT/ACETAMIN/CAFF/CODEINE	BUTALB-ACETAMINOPH-CAFF-CODEIN	CAPSULE
BUTALBIT/ACETAMIN/CAFF/CODEINE	FIORICET WITH CODEINE	CAPSULE
BUTORPHANOL TARTRATE	BUTORPHANOL TARTRATE	SPRAY
CODEINE SULFATE	CODEINE SULFATE	TABLET
CODEINE/BUTALBITAL/ASA/CAFFEIN	ASA-BUTALB-CAFFEINE-CODEINE	CAPSULE
CODEINE/BUTALBITAL/ASA/CAFFEIN	ASCOMP WITH CODEINE	CAPSULE
CODEINE/BUTALBITAL/ASA/CAFFEIN	BUTALBITAL COMPOUND-CODEINE	CAPSULE
CODEINE/BUTALBITAL/ASA/CAFFEIN	FIORINAL WITH CODEINE #3	CAPSULE
FENTANYL	DURAGESIC	PATCH TD72
FENTANYL	FENTANYL	PATCH TD72
FENTANYL	SUBSYS	SPRAY
FENTANYL CITRATE	ABSTRAL	TAB SUBL
FENTANYL CITRATE	ACTIQ	LOZENGE HD
FENTANYL CITRATE	FENTANYL CITRATE	LOZENGE HD
FENTANYL CITRATE	FENTORA	TABLET EFF

FENTANYL CITRATE	LAZANDA	SPRAY/PUMP
HYDROCODONE BITARTRATE	HYSINGLA ER	TAB ER 24H
HYDROCODONE BITARTRATE	ZOHYDRO ER	CAP ER 12H
HYDROCODONE/ACETAMINOPHEN	CO-GESIC	TABLET
HYDROCODONE/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	SOLUTION
HYDROCODONE/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET
HYDROCODONE/ACETAMINOPHEN	LORCET	TABLET
HYDROCODONE/ACETAMINOPHEN	LORCET HD	TABLET
HYDROCODONE/ACETAMINOPHEN	LORCET PLUS	TABLET
HYDROCODONE/ACETAMINOPHEN	LORTAB	SOLUTION
HYDROCODONE/ACETAMINOPHEN	LORTAB	TABLET
HYDROCODONE/ACETAMINOPHEN	NORCO	TABLET
HYDROCODONE/ACETAMINOPHEN	VICODIN	TABLET
HYDROCODONE/ACETAMINOPHEN	VICODIN ES	TABLET
HYDROCODONE/ACETAMINOPHEN	VICODIN HP	TABLET
HYDROCODONE/ACETAMINOPHEN	ZAMICET	SOLUTION
HYDROCODONE/IBUPROFEN	HYDROCODONE-IBUPROFEN	TABLET
HYDROCODONE/IBUPROFEN	IBUDONE	TABLET
HYDROCODONE/IBUPROFEN	REPREXAIN	TABLET
HYDROCODONE/IBUPROFEN	XYLON 10	TABLET
HYDROMORPHONE HCL	DILAUDID	LIQUID
HYDROMORPHONE HCL	DILAUDID	TABLET
HYDROMORPHONE HCL	EXALGO	TAB ER 24H
HYDROMORPHONE HCL	HYDROMORPHONE ER	TAB ER 24H
HYDROMORPHONE HCL	HYDROMORPHONE HCL	LIQUID
HYDROMORPHONE HCL	HYDROMORPHONE HCL	SUPP.RECT
HYDROMORPHONE HCL	HYDROMORPHONE HCL	TABLET
IBUPROFEN/OXYCODONE HCL	OXYCODONE HCL-IBUPROFEN	TABLET
LEVORPHANOL TARTRATE	LEVORPHANOL TARTRATE	TABLET
MEPERIDINE HCL	DEMEROL	TABLET
MEPERIDINE HCL	MEPERIDINE HCL	SOLUTION
MEPERIDINE HCL	MEPERIDINE HCL	TABLET
METHADONE HCL	DISKETS	TABLET SOL
METHADONE HCL	DOLOPHINE HCL	TABLET
METHADONE HCL	METHADONE HCL	ORAL CONC
METHADONE HCL	METHADONE HCL	SOLUTION
METHADONE HCL	METHADONE HCL	TABLET
METHADONE HCL	METHADONE HCL	TABLET SOL
METHADONE HCL	METHADONE INTENSOL	ORAL CONC
METHADONE HCL	METHADOSE	ORAL CONC
METHADONE HCL	METHADOSE	TABLET SOL
MORPHINE SULFATE	ARYMO ER	TAB PO ER
MORPHINE SULFATE	KADIAN	CAP ER PEL
MORPHINE SULFATE	MORPHINE SULFATE	SOLUTION
MORPHINE SULFATE	MORPHINE SULFATE	SUPP.RECT
MORPHINE SULFATE	MORPHINE SULFATE	SYRINGE
MORPHINE SULFATE	MORPHINE SULFATE	TABLET
MORPHINE SULFATE	MORPHINE SULFATE ER	CAP ER PEL
MORPHINE SULFATE	MORPHINE SULFATE ER	CPMP 24HR
MORPHINE SULFATE	MORPHINE SULFATE ER	TABLET ER
MORPHINE SULFATE	MS CONTIN	TABLET ER
MORPHINE SULFATE/NALTREXONE	EMBEDA	CAP ER PO
OPIUM/BELLADONNA ALKALOIDS	BELLADONNA-OPIUM	SUPP.RECT
OXYCODONE HCL	OXAYDO	TABLET ORL
OXYCODONE HCL	OXYCODONE HCL	CAPSULE
OXYCODONE HCL	OXYCODONE HCL	ORAL CONC
OXYCODONE HCL	OXYCODONE HCL	SOLUTION
OXYCODONE HCL	OXYCODONE HCL	SYRINGE
OXYCODONE HCL	OXYCODONE HCL	TABLET
OXYCODONE HCL	OXYCODONE HCL ER	TAB ER 12H
OXYCODONE HCL	OXYCONTIN	TAB ER 12H
OXYCODONE HCL	ROXICODONE	TABLET
OXYCODONE HCL/ACETAMINOPHEN	ENDOCET	TABLET
OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE-ACETAMINOPHEN	SOLUTION
OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE-ACETAMINOPHEN	TABLET
OXYCODONE HCL/ACETAMINOPHEN	PERCOCET	TABLET
OXYCODONE HCL/ACETAMINOPHEN	PRIMLEV	TABLET
OXYCODONE HCL/ASPIRIN	OXYCODONE HCL-ASPIRIN	TABLET

OXYCODONE MYRISTATE	XTAMPZA ER	CAP SPR 12
OXYMORPHONE HCL	OPANA	TABLET
OXYMORPHONE HCL	OPANA ER	TAB ER 12H
OXYMORPHONE HCL	OXYMORPHONE HCL	TABLET
OXYMORPHONE HCL	OXYMORPHONE HCL ER	TAB ER 12H
PENTAZOCINE HCL/NALOXONE HCL	PENTAZOCINE-NALOXONE HCL	TABLET
PROPOXYPHENE HCL	PROPOXYPHENE HCL	CAPSULE
PROPOXYPHENE HCL/ACETAMINOPHEN	PROPOXYPHENE HCL-ACETAMINOPHEN	TABLET
TAPENTADOL HCL	NUCYNTA	TABLET
TAPENTADOL HCL	NUCYNTA ER	TAB ER 12H

TRAMADOL HCL	CONZIP	CPBP 17-83
TRAMADOL HCL	CONZIP	CPBP 25-75
TRAMADOL HCL	TRAMADOL HCL	TABLET
TRAMADOL HCL	TRAMADOL HCL ER	CPBP 17-83
TRAMADOL HCL	TRAMADOL HCL ER	CPBP 25-75
TRAMADOL HCL	TRAMADOL HCL ER	TAB ER 24H
TRAMADOL HCL	TRAMADOL HCL ER	TBMP 24HR
TRAMADOL HCL	ULTRAM	TABLET
TRAMADOL HCL/ACETAMINOPHEN	TRAMADOL HCL-ACETAMINOPHEN	TABLET
TRAMADOL HCL/ACETAMINOPHEN	ULTRACET	TABLET

Appendix 4. Health Outcome Codes

ED Visits	Procedure Codes OR	99281-99285, 99288
	Revenue Center Codes	0450-0459 or 0981
Hospitalizations	Claim Type = I	Claim Type = I

Short-acting Opioid Analgesics

Goals:

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

Length of Authorization:

7 to 30 days (except 12 months for end-of-life or cancer-related pain)

Covered Alternatives:

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

Requires a PA:

- Non-preferred short-acting opioids and opioid combination products.
- All short-acting products prescribed for more than 7 days.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- This PA does not apply to pediatric use of codeine products, which is subject to separate clinical PA criteria.

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

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

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

2. Is the diagnosis funded by the OHP? Note: conditions such as fibromyalgia, TMJ, pelvic pain syndrome and tension headache are not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP. For patients with a history of chronic opioid use, short-term approval may be considered if a patient-specific taper plan is documented or for up to 30 days to allow providers time to develop a taper plan. Subsequent approvals must document progress toward the taper. Note: Management of opioid dependence is funded by the OHP.
3. Is the requested medication a preferred agent?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being treated for cancer-related pain (ICD10 G89.3) or under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months.	**No:** Go to #6
6. Is the prescription for a short-acting fentanyl product? Note: Short-acting transmucosal fentanyl products are designed for breakthrough cancer pain only. This PA does not apply to transdermal fentanyl patches.	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #7

7. Is the opioid prescribed for pain related to migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber reviewed at least once in the past 3 months the scheduled substances the patient has recently been prescribed from other providers?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Did the patient's pain originate from acute injury, flare, or surgery that occurred in the last 6 weeks?	**Yes:** Go to #10	**No:** Go to #15
10. Has at least one non-opioid analgesic (e.g., NSAID, acetaminophen, and/or muscle relaxant) been tried and found to be ineffective or are contraindicated?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #12	**No:** Approve for up to 30 days
12. Has the prescriber also developed a plan with the patient to stay active (home or prescribed exercise regimen) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is this the first opioid prescription the patient has received for this pain condition?	**Yes:** Approve for up to 7 days	**No:** Go to #14

14. Can the prescriber provide documentation of sustained improvement in function of at least 30% compared to baseline with prior use of opioid analgesics (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, and MSPQ)?	**Yes:** Approve for up to 7 days	**No:** Pass to RPh. Deny; medical appropriateness.
15. Has the patient been prescribed opioid analgesics for more than 6 weeks?	**Yes:** Go to #16	**No:** Go to #10
16. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale.*	**Yes:** Document tool used to measure pain and/or function. Go to #17	**No:** Pass to RPh. May approve for up to 30 days one time. For future claims without documentation: deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
17. Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
18. Is the opioid prescription for pain associated with a back or spine condition?	**Yes:** Go to #19	**No:** Go to #20

19. Have any of the following therapies also been prescribed and utilized by the patient: spinal manipulation, physical therapy, yoga or acupuncture?	**Yes:** Document additional therapy. Approve for up to 7 days. Note: Risks outweigh benefits for back and spine conditions. OHP will not fund chronic use of opioids for back or spine conditions beginning 1/1/2018. Prescriber must develop a taper plan with the patient with a quit date before 1/1/2018. OHP funds treatment for patients who have become dependent or addicted to opioid analgesics.	**No:** Pass to RPh. Deny; medical appropriateness.
20. Does the total daily opioid dose exceed 90 MME (Table 1)?	**Yes:** Pass to RPh. May approve one time. For future claims: deny; medical appropriateness. For patients with a history of chronic opioid use, short-term approval may be considered if a patient-specific taper plan is documented or for up to 30 days to allow providers time to develop a taper plan. Subsequent approvals must document progress toward the taper. Note: Management of opioid dependence is funded by the OHP.	**No:** Approve for up to 30 days.

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

Clinical Notes:

How to Discontinue Opioids. Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)
Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

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

Symptoms and Treatment of Opioid Withdrawal.

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

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

Questions and answers about opioid coverage criteria effective August 21, 2017

Where can I find the new PA criteria for both short- and long-acting opioids?

On or after August 21, 2017, you can find the new PA criteria at www.orpdl.org/drugs under the "Analgesics" category.

Which opioids are restricted to 7 days or less for acute conditions?

Short-acting opioids such as hydrocodone/acetaminophen, oxycodone, and tramadol are restricted to 7 days or less for acute conditions. Long-acting opioids such as fentanyl and extended release morphine sulfate do not have this restriction.

You can find a comprehensive list of preferred and non-preferred short- and long-acting opioids on the Preferred Drug List (PDL) website.

- Short-acting: http://www.orpdl.org/drugs/drugclass.php?cid=1076.
- Long-acting: http://www.orpdl.org/drugs/drugclass.php?cid=1050.

Why are short-acting opioids restricted to 7 days or less for acute conditions?

This decision was based on the 2016 CDC guideline recommendations and will coincide with the Health Evidence Review Commission's 2014 coverage guidance.

What criteria apply to both short- and long-acting opioids?

Criteria for both short- and long-acting opioids require:

- A prescription that:
  - Is for a diagnosis which is funded by the OHP
  - Is not for pain associated with migraine or other type of headache, and
  - Does not exceed a total daily opioid dose of 90 morphine milligram equivalents (MME) per day.
- Documented verification that the patient:
  - Is not high-risk for opioid misuse or abuse,
  - Is not concurrently on other short- or long-acting opioids, and
  - Has sustained improvement of at least 30 percent in pain, function, or quality of life in the past 3 months (compared to baseline).

Do the new criteria apply to cancer-related pain or palliative care services?

No. Besides requiring an OHP-funded diagnosis, the additional new prior authorization criteria requirements do not apply if a patient is:

- Being treated for cancer-related pain (ICD-10 G89.3), or
- Under palliative care services (ICD-10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying.

Providing the ICD-10 diagnosis code on the prescription order and submitting it on the pharmacy claim may expedite the approval process.

Questions?

- **About pharmacy point of sale and prior authorizations for fee-for-service prescriptions:** Call the Oregon Pharmacy Call Center at 1-888-202-2126.
- **About physical health prescriptions for patients in a coordinated care organization (CCO):** Contact the CCO.