Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 25, 2017 1:00 - 5:00 PM
Barbara Roberts Human Services Building, HSB 137 A-D
500 Summer St. NE
Salem, OR 97301

MEETING AGENDA

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

	I. CALL TO ORDER	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	B. Origer (Chair)
	D. Department Update	D. Weston (OHA)
	II. DUR OLD BUSINESS	
1:10 PM	A. Hepatitis C Policy Update	R. Citron (OSU)
	B. Updated DAA Criteria	
	C. Public Comment	
	D. Discussion of Clinical Recommendations to OHA	
	III. DUR ACTIVITIES	
1:30 PM	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (DXC)
	C. RetroDUR Report	R. Citron (OSU)
	D. Oregon State Drug Review Newsletter Articles	K. Sentena (OSU)
	1. Non-Analgesics for Pain Management	
	2. Management of Opioid Use Disorder	
	IV. DUR NEW BUSINESS	
1:50 PM	A. HERC Novel Treatments: Low Cost Effectiveness or Marginal Clinical Benefit Policy	R. Citron (OSU)
	1. Proposed P and T Policy	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

2:10 PM	B. Pediatric Antipsychotic Metabolic Monitoring 1. Policy Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:25 PM	C. Non-Vitamin K Antagonists Oral Anticoagulants (NOACs) 1. Anticoagulant Literature Scan 2. Policy Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	K. Vo (OSU) K. Sentena (OSU)
2:40 PM	D. Proton Pump Inhibitors 1. PPI/H2RA Literature Scan 2. Policy Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	M. Smith (OSU) K. Sentena (OSU)
2:55 PM	BREAK	
	V. PREFERRED DRUG LIST NEW BUSINESS	
3:10 PM	A. Ophthalmic VEGF Inhibitor Class Update 1. Class Update/Prior Authorization 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:20 PM	B. Tetracycline Antibiotics Class Update 1. Class Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
3:30 PM	C. Literature Scans 1. ACEIs, ARBs, DRIs and Entresto (sacubitril/valsartan) 2. Anaphylaxis Scans 3. Antianginal Agents 4. Otic Antibiotics 5. Public Comment 6. Discussion of Clinical Recommendations to OHA	 D. Moretz (OSU) K. Sentena (OSU) M. Herink (OSU) S. Servid (OSU)
3:50 PM	D. Abbreviated Drug Reviews 1. Intrarosa® (prasterone) 2. Eucrisa® (crisaborole 2%) 3. Amulez® (aminolevulinic acid 10%) 4. Levulan® (aminolevulinic acid 20%) 5. Rhofade® (oxymetazoline 1%) 6. Belviq® (lorcaserin) 7. Public Comment 8. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)

4:00 PM VI. EXECUTIVE SESSION

4:50 PM VII. RECONVENE for PUBLIC RECOMMENDATIONS

5:00 PM VIII. ADJOURN

Drug Use Research & Management Program
OHA Health Systems Division
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
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
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019

Drug Use Research & Management Program
OHA Health Systems Division
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 23, 2017, 1:00-5:00 PM
Human Services Building
Salem, OR 97301

MEETING MINUTES

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

Members Present: Kelley Burnett, DO; Rich Clark, MD, MPH; Walter Hardin, D.O., MBA; Tracy Klein, PhD, FNP; Phil Levine, PhD; Caryn Mickelson, PharmD; James Slater, PharmD; Cathy Zehrung, RPh

Members Present by Phone: Stacy Ramirez, PharmD;

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Dee Weston; Sarah Servid, PharmD; Deanna Moretz, PharmD, BCPS; Lindsay Newton; Megan Herink, PharmD, BCPS; Melissa Smith, PharmD; Kim Vo, PharmD;

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

Audience: Rick Frees, Vertex; Melissa Snider, BioMarin; Jeana Colabianchi, Sunovion; David Baheim, Genertech; Kim Laubmeier, Sunovion; Ron Abrahem, Sunovion; Lyle Laird, Sunovion; Bobbi Jo Duim, Bily; Mary Kembus, Novartis; Matt Ueda, Purdue; *Stuart O'Brochta, Gilead; Lisa Boyle, WVP Health Authority; Robin Traver, Umpqua Health; *Lynda Finch, Biogen; *Lisa Borland, Sarepta; Mike Donabedian, Sarepta; *Erika Finanger, OHSU; Dana Koehn, Biomeratin; Matt Seibt, Biogen

(*) Provided verbal testimony

Written testimony provided: *Erika Finager, MD, OHSU; Barry Russman, MD, OHSU; Michael Sussman, MD, Shriners Hospital

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare.
C. Approval of agenda and January minutes presented by Mr. Citron. (pages 5 - 9)

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

D. OHA update presented by Dr. Jim Rickards regarding Hep C PA criteria and the MOU. Committee will be sent a copy of the MOU once all of the documents are finalized.

II. HEALTH EVIDENCE REVIEW COMMISSION (HERC) UPDATE

HERC update presented by Darren Coffman. In the future, when a drug is reviewed that the Committee should be considered by HERC for one of the new lines on the Prioritized List, they should make that recommendation to the OHA so it can be called out in the minutes (Statement of intent).

III. DUR ACTIVITIES

A. Quarterly Utilization Reports
B. ProDUR Report
C. RetroDUR Report
D. Oregon State Drug Reviews
    1. Guideline and Policy Updates for Use of Opioids for Non-Cancer Pain and Opioid Use Disorder.
    2. Treatment of Gout.

IV. PREFERRED DRUG LIST NEW BUSINESS

A. Hepatitis B Class Update (pages 26 - 38)
Dr. Smith presented the class update and following recommendation:

1. Maintain tenofovir or entecavir, as preferred agents on the PMPDP and tenofovir alafenamide as non-preferred.
2. Approve updated PA criteria as presented

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

B. Non-analgesics for Pain Review (pages 39 - 84)
Dr. Moretz presented the class update and the following recommendation:

1. Approve proposed PA criteria to restrict use to funded pain conditions and include separate PA criteria with the following restrictions: approve for 90 days, renew for document response and if there is a response, approve for a year for the following medications. Bring back in November to review and address quantity limits:
    a. Pregabalin
    b. Milnacipran

c. Lidocaine Patch
d. Topiramate Extended Release (non-preferred products)

2. Add quantity limit of 3 patches/24 hours for topical lidocaine patches which is the maximum approved daily does to insure safe use.
3. Retire “Drug used for non-funded Pain” criteria

ACTION: Amended proposed PA criteria to remove lifetime approval and added if documented response to approve 1 year. Asked staff to bring back in November to evaluate need for quantity limits. Motion to approve, 2nd. All in favor. Approved.

C. Skeletal Muscle Relaxants Class Update (pages 85 - 99)

Dr. Vo presented the scan and following recommendation:

1. Approve revised PA criteria to limit approval to 3 months.
2. Evaluate comparative costs in executive session.

ACTION: Amended proposed PA criteria to change length of authorization from 3 to 6 months, added question after carisoprodol to deny if member on opioids and to change length of approval for carisoprodol to 3 months. Motion to approve, 2nd. All in favor. Approved.

D. Tramadol Classification and Review (pages 100 – 115)

Dr. Herink presented to drug review and recommendation:

1. Maintain tramadol in current opioid prior authorization policy.

E. Sedatives Class Review (pages 116-138)

Dr. Servid presented the following class update and recommendations:

1. Make benzodiazepine sedatives non-preferred due to limited efficacy data.
2. Approve amended proposed changes to PA criteria to restrict use of sedatives to OHP-funded conditions, to prevent therapeutic duplication, and to apply quantity limits of 30 tablets/60 days for all agents in the class.
3. Apply quantity limits to zolpidem to reduce use above the maximum daily FDA recommended dose.
    a. Zolpidem IR: 10 mg for males and 5 mg for females
    b. Zolpidem ER: 12.5 mg for males and 6.25 mg for females

ACTION: Amended to include requiring a PA for zolpidem and include opioid and all benzodiazepine use to question #6. Motion to approve, 2nd. All in favor. Approved.

F. Abbreviated Drug Reviews (pages 172-176)

Dr. Servid and Dr. Moretz presented the class update along with the following recommendations:

1. Cholbam® (cholic acid).
    a. Refer PA requests to the Medical Director.

2. Exondys 51™ (etiplirsen).
    a. Refer PA requests to the Medical Director.

3. Spinraza™ (nusinersen).
    a. Approve proposed PA criteria and apply to both pharmacy and physician administered claims.

ACTION: Amended wording in PA for Spinraza™ to re-phrase wording for neurologist to specialist and to refer requests for PA renewal at 12 months to Medical Director. Motion to approve as amended, 2nd. All in favor. Approved.

V. EXECUTIVE SESSION

VI. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Hepatits B Class Update (pages 26 - 38)
*__ACTION:__ No changes to the PDL.
Motion, 2nd, All in Favor. Approved.

B. Non-analgesics for Pain Review (pages 39 - 84)
*__ACTION:__ Make gabapentin tablets preferred. Recommend step therapy to require trial of gabapentin before Pregabalin approval.
Motion, 2nd, Majority in Favor. One opposed. Approved.

C. Skeletal Muscle Relaxants Class Review (pages 85 - 99)
*__ACTION:__ No changes to the PDL.
Motion, 2nd, All in Favor. Approved

D. Sedatives Class Update (pages 116 - 138)
*__ACTION:__ No changes to the PDL.
Motion, 2nd, All in Favor. Approved

VII. ADJOURN

ELLEN F. ROSENBLUM
Attorney General

FREDERICK M. BOSS
Deputy Attorney General

DEPARTMENT OF JUSTICE
TRIAL DIVISION

MEMORANDUM

DATE: January 6, 2017

TO: Beth Englander
Marisa Samuelson
Stephen S. Walters
Oregon Law Center

Kevin Costello
Center for Health Law & Policy Innovation
Harvard Law School

FROM: Renee Stineman, Attorney-in-Charge
Special Litigation Section

SUBJECT: Updated Memorandum of Understanding between Oregon Health Authority (OHA) and Oregon Law Center and Center for Health Law & Policy Innovation (collectively, OLC)

OHA is committed to prioritizing essential services and considers expansion of coverage for Hepatitis C (HCV) treatment to be an important priority for Oregonians. Currently, OHA's coverage criteria for Oregon Health Plan (OHP) authorizes treatment of stage F3 and F4 HCV disease, with limited coverage of some stage F2 disease (such as patients who are also HIV-positive or have had a liver transplant). Newly developed, direct acting anti-viral medications (DAAs) have significantly increased the cost of HCV treatment. OHA has spent over $95.5 million on treating HCV at this coverage level since release of the DAAs. The agency's and the Governor's proposed budgets reflect the desire to expand HCV treatment to all Oregon Health Plan (OHP) members with stage F2 stage of the disease by January 1, 2018, if the budgets are funded to the requested levels.

The OLC and CHLPI have threatened to file a lawsuit against OHA alleging that the agency's current coverage criteria for OHP for HCV treatment violates federal Medicaid law. OHA admits no liability relating to the proposed lawsuit.

The agency has a process for establishing prioritization of essential services, and in accordance with that process, the agency plans to expand coverage of HCV, as outlined in this Memorandum of Understanding.

100 SW Market Street, Portland, OR 97201
Telephone: (971) 673-1880 Fax: (971) 673-5000 TTY: (800) 735-2900 www.doj.state.or.us

In furtherance of OHA's plan for expanding OHP coverage for HCV treatment, OHA will:

1. Expand coverage to all OHP members for HCV treatment with HCV stage F-2 by January 1, 2018, conditioned on funding by the Oregon legislature in the 2017 legislative session;

2. Not seek re-prioritization of HCV treatment by F-scores on the Prioritized List;

3. Advocate for legislative approval of funding in the 2017 legislative session in line with OHA's Policy Option Package;

4. Continue to ensure its Coordinated Care Organization (CCO) coverage criteria are properly aligned with Oregon's Fee for Service (FFS) criteria for HCV/DAA coverage. For example, OHA has developed and included within the current CCO contracts a risk corridor that requires CCOs to use the exact FFS criteria. The risk corridor incentivizes CCOs to comply with this requirement through funding agreements.

5. Increase communication with HCV advocates and OLC by providing quarterly summaries of reported data on the number of DAA treatments provided to any OHP member reporting during the immediately prior quarter, broken down between CCO and FFS, in a form to be developed by OHA. The reporting will begin 30 days after the close of the second quarter of 2017 and the first report will cover the first quarter of 2017. In addition, OHA will agree to explore ways to develop a system to efficiently and accurately collect data on denial of DAA treatment coverage and to implement such a system within one year;

6. OHA agrees to receive bi-monthly quarterly updates from OLC on OHP members who are denied HCV treatment and take action when appropriate, as determined by OHA. Reports should be provided by email to Heather Johnson, at heather.n.johnson@dhsoha.state.or.us and Rhonda Busek, at rhonda.j.busek@state.or.us ;

7. Continue to take reasonable steps to ensure CCOs comply with contractual and legal obligations to avoid inappropriate barriers to treatment, including but not limited to, monitoring CCO denials for DAA treatment upon completion of the denial data collection system described in paragraph 5 above;

8. Perform a mid-2017 review of expenditures for HCV treatment to inform OHA in considering possible reinvesting funding previously allocated for HCV treatment but not spent for further expansion of HCV coverage in 2018 and, upon completion, report to OLC any decisions by OHA resulting from that review;

9. Modify its prior authorization criteria to conform to the MOU in not more than 90 days per paragraph 9 and again in not more than 9 months per paragraph 10 (draft attached hereto as Appendix A) as soon as reasonably practicable (providing a copy of these modifications to OLC) as follows, which is anticipated to take 60 to 90 days, but no more than 90 days, from execution of this MOU to implement through rule changes:

a. Reduce required proof of life expectancy from 5 years or more to 1 year or more;

b. Remove specialists restriction for F0, F1, F2 and F3 DAA prescribing. For F3 only, specialist restriction will be removed only for that period from when the member has sought treatment by a specialist and when the member begins receiving treatment by a specialist, so as not to delay DAA treatment while a member is waiting for a specialist to become available;

c. Implement a standard for members with test results that show an F score range (ie: between F2 and F-3) that either (1) requires application of the highest F score in the range for determining coverage (for example, if a member's test result shows an F score of between F-2 and F-3, the member will be considered to have stage F-3 for purposes of coverage) or (2) require one additional, more specific, testing of an individual, if the higher stage is not applied for lack of specificity, however, additional testing may not be limited to biopsy (e.g. coverage cannot be contingent on member consenting to biopsy) and must include the option of noninvasive testing, such as elastography. Any resulting additional testing will not count against limits on number of covered testing per year. After one additional test, if a range still exists, the highest F score in the range will apply for determining coverage; and

d. OHA will distribute educational materials or other training to providers on HVC treatment and prior authorization criteria upon implementation of these modifications.

10. Expand the prior authorization criteria for HCV treatment as follows, which is anticipated to take approximately 6 to 9 months, but no more than 9 months, from execution of this MOU to implement:

a. To apply criteria currently in place for stage F-2 disease to stage F-1 and F-0 disease for OHP members who are co-infected with HIV,

b. To include coverage for members able to provide sufficient documentation of labs or biopsy showing fast progressing fibrosis that would require treatment earlier than the approved fibrosis stage. Determination of the definition of fast progressing fibrosis will be made consistent with guidance by the Health Evidence Review Commission or Pharmacy and Therapeutics Committee, whichever OHA determines is the appropriate forum to consider the matter. In this process, OHA agrees to obtain and consider input from experts in the area of HCV treatment, including

Dr. Benner. OHA will have this matter considered by the appropriate forum during the calendar year 2017 and will implement the changes during the 2018 calendar year, contingent on adequate funding; and

c. To provide coverage for additional extrahepatic manifestations and/or comorbidities consistent with guidance by the Health Evidence Review Commission or Pharmacy and Therapeutics Committee, whichever OHA determines is the appropriate forum to consider the matter. In this process, OHA agrees to obtain and consider input from experts in the area of HCV treatment, including Dr. Benner. OHA intends to have this matter considered by the appropriate forum during the calendar year 2017 with the goal of implementation during the 2018 calendar year, contingent on adequate funding.

11. Perform a mid-2018 review of expenditures for HCV treatment to inform OHA in considering the possibility of expanding to F-0 in the next biennium budget request and, upon completion, report to OLC any decisions by OHA resulting from that review.

OHA commits to make good faith efforts to accomplish the above-described changes and results. However, this memorandum shall not be enforceable in court and does not constitute a contract or other enforceable promise.

OHA's commitment to these aims includes a commitment to take reasonable steps to obtain funding, where needed, from the Oregon Legislative Assembly to accomplish this plan. If adequate funding is not authorized, OHA will assess which of these goals, if any, it will pursue. While OHA welcomes comment and cooperation from OLC, OHA maintains that it has ultimate discretion to determine the time and the manner in which the above-described changes and results are pursued.

OLC understands this memorandum to reflect OHA's intent. In support of that intent, OLC and CHLPI's current clients intend to refrain from filing a lawsuit pending the outcome of the 2017 legislative process and OHA's compliance with this MOU. OLC's clients may pursue litigation if the agency does not receive the funding it has requested on which the above commitments are predicated, or at any time before or after the conclusion of the 2017 session if the commitments expressed in this MOU are not followed.

The provisions of this memorandum are understood to apply from January 10, 2017, to the end of the next biennium (June 30, 2019).

Oregon Law Center and CHLPI Clients

[redacted]

Named Plaintiff 1

Date: March 3, 17

[redacted]

Named Plaintiff 2

Date: 3-13-17

Oregon Health Authority

Lynne Saxton

Lynne Saxton, Director

Date: 3-14-17

7970386-v12/RS7/rh2

Hepatitis C Direct-Acting Antivirals

Goals:

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

Length of Authorization:

- 8-12 weeks

Requires PA:

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has all of the following pre-treatment testing been documented: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient d. Current HBV status of patient e. Pregnancy test in past 30 days for a woman of child-bearing age; and f. History of previous HCV treatment and outcome? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis.	**Yes:** Record results of each test and go to #5	**No**: Pass to RPh. Request updated testing.

Approval Criteria		
5. Has the patient failed treatment with <u>any</u> of the following HCV NS5A inhibitors: a) Daclatasvir plus sofosbuvir; b) Ledipasvir/sofosbuvir; c) Paritaprevir/ritonavir/ombitasvir plus dasabuvir; d) Elbasvir/grazoprevir; <u>or</u> e) Sofosbuvir/velpatasvir)? <u>Note</u>: Patients who failed treatment with sofosbuvir +/- ribavirin or PEGylated interferon can be retreated (see table below).	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: If urgent retreatment is needed, resistance testing must be done to indicate susceptibility to prescribed regimen. Refer to medical director for review.	**No:** Go to #6
6. Which regimen is requested?	Document and go to #7	
7. Does the patient have HIV coinfection AND: A biopsy, imaging test (transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE], or serum test if the above are not available (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF]) to indicate fibrosis (METAVIR F2) AND the patient is under treatment by a specialist with experience in HIV?	**Yes:** Go to #12 Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy For results falling in a range (e.g. F2 to F3), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.	**No:** Go to #8

Approval Criteria		
8. Does the patient have: a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); or Clinical, radiologic or laboratory evidence of complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)**?**	**Yes:** Go to #11 Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy. However, if imaging testing is not regionally available, a serum test (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF]) can be used to confirm METAVIR F3 or F4. For results falling in a range (e.g. F2 to F3), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.	**No:** Go to #9
9. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV)? a) Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c) Porphyria cutanea tarda	**Yes:** Go to #11	**No:** Go to #10

Approval Criteria		
10. Is the patient in one of the following transplant settings: a) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or b) Post solid organ transplant?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. If METAVIR F4: Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR F3: Is the regimen prescribed by, OR is the patient in the process of establishing care with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR ≤F2: The regimen does not need to be prescribed by or in consultation with a specialist?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.
12. In the previous 6 months: • Has the patient actively abused alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); OR • Has the patient been diagnosed with a substance use disorder; OR • Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #13	**No:** Go to #14
13. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes**: Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
15. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #16	**No:** Go to #17
16. Has the patient had a baseline NS5a resistance test show a resistant variant to one of the agents in #16?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #17
17. Is the prescribed drug regimen a recommended regimen based on the patient's genotype and cirrhosis status?	**Yes:** Approve for 8-12 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: October 2015 - September 2016

Eligibility	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
Total Members (FFS & Encounter)	1,055,600	1,018,999	1,033,098	1,045,449	1,066,593	1,076,454	1,058,671	1,045,530	1,034,285	1,018,479	1,005,560	991,736	1,037,538
FFS Members	143,529	146,793	125,393	132,175	136,513	132,588	150,635	144,444	140,048	145,488	143,283	149,942	140,903
OHP Basic with Medicare	30,825	30,889	30,968	31,349	31,408	31,594	31,864	32,133	32,393	32,597	32,574	32,707	31,775
OHP Basic without Medicare	14,234	14,190	13,045	13,175	12,913	13,091	13,272	13,285	13,242	13,155	13,263	13,490	13,363
ACA	98,470	101,714	81,380	87,651	92,192	87,903	105,499	99,026	94,413	99,736	97,446	103,745	95,765
Encounter Members	912,071	872,206	907,705	913,274	930,080	943,866	908,036	901,086	894,237	872,991	862,277	841,794	896,635
OHP Basic with Medicare	40,037	39,946	39,951	39,907	40,356	40,276	39,984	39,968	40,100	40,186	40,383	40,452	40,129
OHP Basic without Medicare	84,019	73,277	73,440	72,813	72,503	71,622	70,953	70,303	69,870	69,438	68,793	67,857	72,074
ACA	788,015	758,983	794,314	800,554	817,221	831,968	797,099	790,815	784,267	763,367	753,101	733,485	784,432

Gross Cost Figures for Drugs	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	YTD Sum
Total Amount Paid (FFS & Encounter)	$67,278,306	$65,077,107	$70,985,391	$69,012,644	$71,231,314	$76,293,327	$69,572,306	$69,657,860	$71,527,618	$59,483,562	$63,604,907	$61,284,216	$815,008,558
Mental Health Carve-Out Drugs	$10,910,909	$10,465,263	$11,525,664	$11,123,937	$11,458,583	$10,391,034	$8,266,983	$8,415,904	$8,373,767	$7,828,845	$8,463,392	$7,898,423	$115,122,703
OHP Basic with Medicare	$1,048	$778	$1,762	$1,137	$427	$367	$639	$737	$407	$820	$373	$753	$9,248
OHP Basic without Medicare	$4,857,094	$4,677,458	$5,196,523	$4,792,656	$4,967,150	$4,383,795	$3,409,735	$3,476,675	$3,509,385	$3,259,463	$3,506,608	$3,345,835	$49,382,377
ACA	$6,013,855	$5,730,014	$6,262,246	$6,256,433	$6,417,265	$5,943,420	$4,804,360	$4,879,454	$4,808,537	$4,508,831	$4,883,518	$4,491,462	$64,999,393
FFS Physical Health Drugs	$3,328,523	$3,265,670	$3,012,897	$3,188,798	$3,396,213	$3,605,985	$3,528,812	$3,304,226	$3,601,188	$3,245,720	$3,720,179	$3,635,433	$40,833,644
OHP Basic with Medicare	$213,642	$208,276	$213,494	$217,533	$219,701	$231,250	$195,403	$210,645	$254,087	$205,912	$250,773	$196,675	$2,617,389
OHP Basic without Medicare	$1,044,806	$997,070	$900,678	$960,209	$991,112	$1,032,076	$961,971	$960,083	$998,538	$942,659	$1,121,065	$1,071,303	$11,981,570
ACA	$1,976,843	$1,979,008	$1,800,053	$1,911,995	$2,070,014	$2,238,390	$2,292,537	$2,049,132	$2,251,292	$2,013,922	$2,247,058	$2,263,245	$25,093,488
FFS Physician Administered Drugs	$1,431,003	$1,254,345	$1,256,139	$1,373,875	$1,350,412	$1,460,590	$1,449,041	$1,583,420	$1,871,199	$1,511,344	$1,564,161	$1,783,999	$17,889,528
OHP Basic with Medicare	$196,476	$165,016	$240,743	$306,413	$331,755	$388,002	$392,610	$285,007	$373,112	$297,469	$325,598	$399,105	$3,701,306
OHP Basic without Medicare	$256,385	$233,226	$284,713	$261,443	$300,437	$312,508	$213,648	$314,909	$253,678	$219,152	$210,779	$388,473	$3,249,353
ACA	$787,330	$593,487	$524,405	$561,477	$489,470	$536,620	$631,292	$762,996	$944,400	$704,669	$769,391	$759,357	$8,064,894
Encounter Physical Health Drugs	$43,554,115	$42,239,208	$46,184,417	$44,668,326	$46,141,589	$50,966,039	$47,614,193	$47,243,852	$48,390,563	$38,156,261	$39,966,970	$38,762,711	$533,888,243
OHP Basic with Medicare	$155,587	$144,187	$141,081	$127,242	$135,041	$138,439	$135,436	$133,354	$128,970	$120,287	$137,878	$129,295	$1,626,798
OHP Basic without Medicare	$12,111,782	$11,404,734	$12,594,774	$12,087,160	$12,283,602	$13,578,473	$12,652,084	$12,436,345	$12,763,197	$10,943,983	$12,015,071	$11,394,877	$146,266,080
ACA	$31,081,608	$30,409,462	$33,123,125	$32,065,472	$33,344,093	$36,797,740	$34,375,166	$34,215,144	$35,034,388	$26,756,313	$27,398,915	$26,826,630	$381,428,057
Encounter Physician Administered Drugs	$8,053,756	$7,852,622	$9,006,274	$8,657,708	$8,884,517	$9,869,678	$8,713,276	$9,110,457	$9,290,902	$8,741,393	$9,890,205	$9,203,651	$107,274,440
OHP Basic with Medicare	$157,361	$146,258	$218,291	$262,954	$253,268	$262,780	$207,879	$246,112	$213,931	$171,629	$222,994	$179,285	$2,542,741
OHP Basic without Medicare	$2,205,818	$2,273,613	$2,198,540	$2,063,675	$2,442,206	$2,388,214	$2,099,944	$2,205,790	$2,404,518	$2,200,277	$2,279,233	$2,031,583	$26,793,409
ACA	$5,558,386	$5,285,575	$6,424,173	$6,136,654	$6,004,269	$7,041,522	$6,204,975	$6,521,778	$6,528,350	$5,716,872	$6,747,658	$6,638,462	$74,808,675

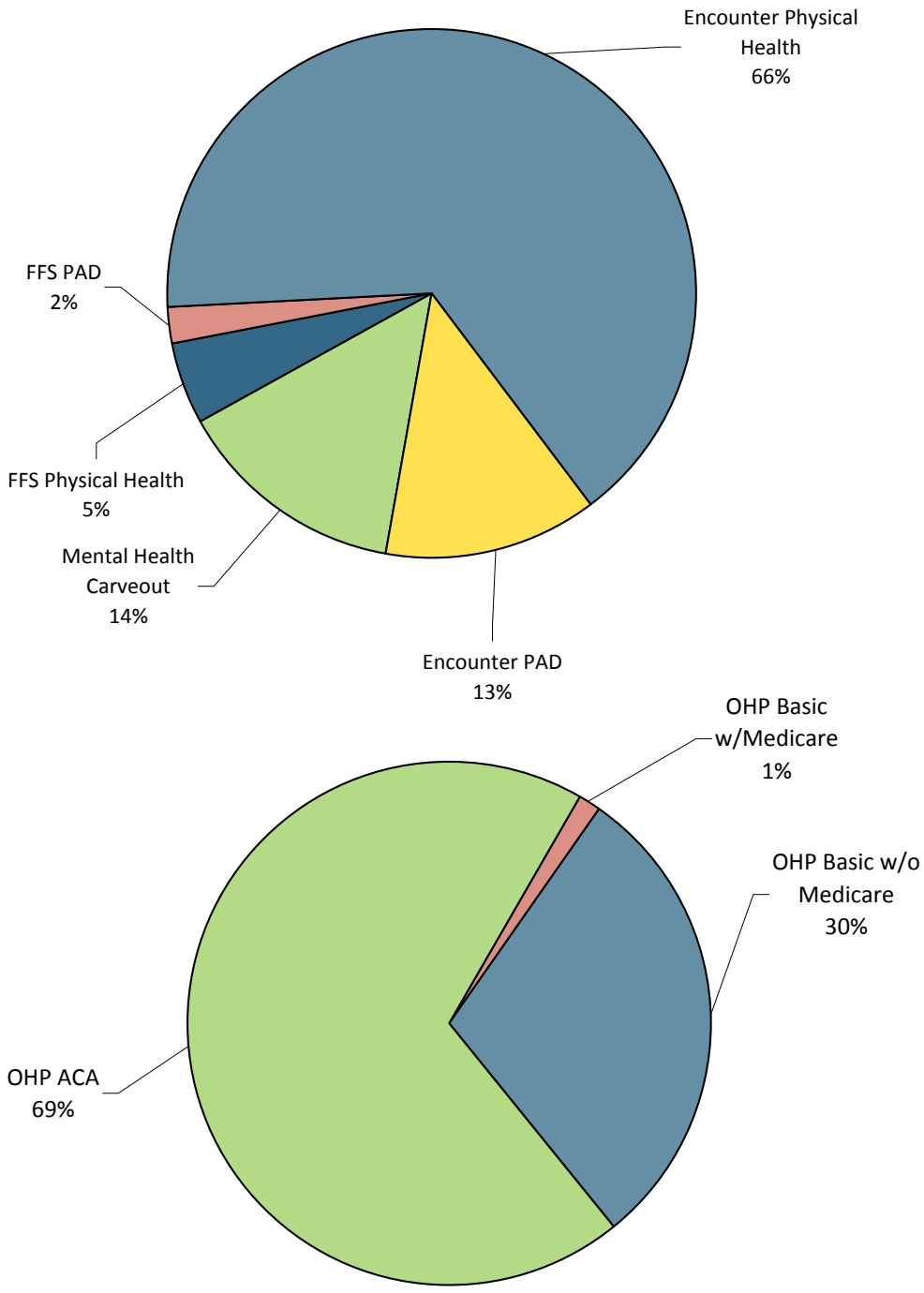
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last Updated: April 19, 2017

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: October 2015 - September 2016

YTD Percent Paid Amounts



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

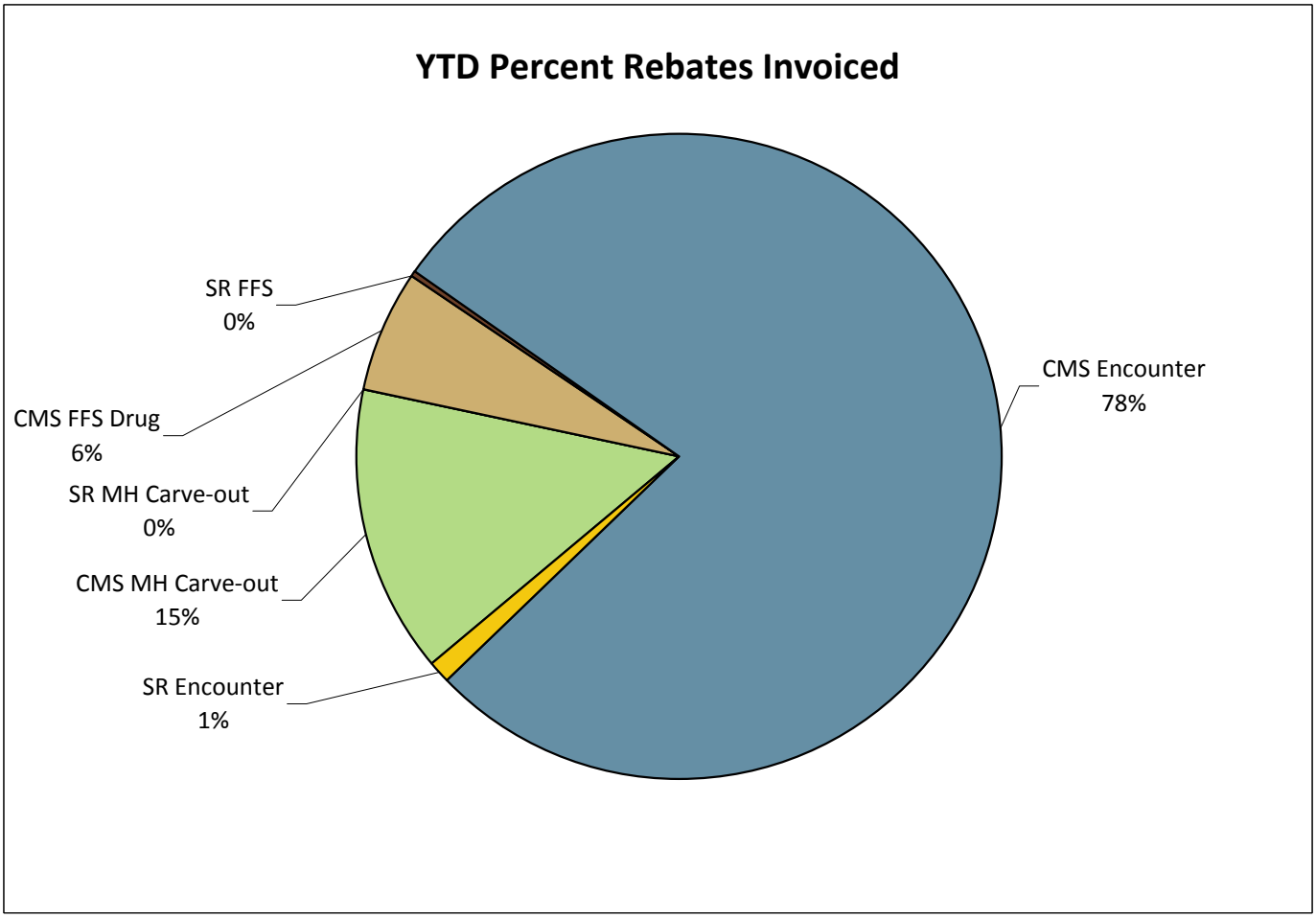
Last Updated: April 19, 2017

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: October 2015 - September 2016

Quarterly Rebates Invoiced	2015-Q4	2016-Q1	2016-Q2	2016-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$95,363,179	$106,862,135	$101,827,674	$100,903,652	$404,956,640
CMS MH Carve-out	$18,186,329	$19,024,404	$11,113,522	$10,711,491	$59,035,745
SR MH Carve-out					$0
CMS FFS Drug	$5,134,065	$6,215,308	$6,774,528	$5,899,027	$24,022,928
SR FFS	$283,467	$262,200	$292,764	$312,105	$1,150,536
CMS Encounter	$70,395,638	$80,776,992	$82,079,271	$82,568,204	$315,820,105
SR Encounter	$1,363,680	$583,230	$1,567,590	$1,412,825	$4,927,325

Quaterly Net Drug Costs	2015-Q4	2016-Q1	2016-Q2	2016-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$107,977,625	$109,675,150	$108,930,110	$83,469,033	$410,051,918
Mental Health Carve-Out Drugs	$14,715,507	$13,949,149	$13,943,133	$13,479,168	$56,086,957
FFS Phys Health + PAD	$8,131,045	$7,898,365	$8,270,595	$9,249,703	$33,549,708
Encounter Phys Health + PAD	$85,131,073	$87,827,635	$86,716,382	$60,740,162	$320,415,253



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

Last Updated: April 19, 2017

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: October 2015 - September 2016

PMPM Drug Costs (Rebates not Included)	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$63.73	$63.86	$68.71	$66.01	$66.78	$70.87	$65.72	$66.62	$69.16	$58.40	$63.25	$61.79	$65.41
Mental Health Carve-Out Drugs	$10.34	$10.27	$11.16	$10.64	$10.74	$9.65	$7.81	$8.05	$8.10	$7.69	$8.42	$7.96	$9.24
FFS Physical Health Drugs	$23.19	$22.25	$24.03	$24.13	$24.88	$27.20	$23.43	$22.88	$25.71	$22.31	$25.96	$24.25	$24.18
FFS Physician Administered Drugs	$9.97	$8.54	$10.02	$10.39	$9.89	$11.02	$9.62	$10.96	$13.36	$10.39	$10.92	$11.90	$10.58
Encounter Physical Health Drugs	$47.75	$48.43	$50.88	$48.91	$49.61	$54.00	$52.44	$52.43	$54.11	$43.71	$46.35	$46.05	$49.56
Encounter Physician Administered Drugs	$8.83	$9.00	$9.92	$9.48	$9.55	$10.46	$9.60	$10.11	$10.39	$10.01	$11.47	$10.93	$9.98

Claim Counts	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
Total Claim Count (FFS & Encounter)	1,035,280	978,543	1,040,307	1,031,249	1,050,130	1,134,106	1,046,405	1,049,544	1,043,318	887,386	948,861	919,100	1,013,686
Mental Health Carve-Out Drugs	153,832	146,414	157,709	152,945	153,459	164,673	153,125	154,674	154,941	145,125	156,156	146,170	153,269
FFS Physical Health Drugs	72,499	71,051	68,040	68,179	70,669	74,629	71,753	70,932	68,788	64,242	70,166	67,875	69,902
FFS Physician Administered Drugs	11,849	10,878	11,575	12,186	12,116	13,089	13,618	14,001	14,679	14,918	15,201	14,660	13,231
Encounter Physical Health Drugs	714,549	672,651	718,646	709,988	726,903	787,398	718,165	720,434	708,751	571,638	612,013	600,147	688,440
Encounter Physician Administered Drugs	82,551	77,549	84,337	87,951	86,983	94,317	89,744	89,503	96,159	91,463	95,325	90,248	88,844

Amount Paid per Claim (Rebates not Included)	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$64.99	$66.50	$68.24	$66.92	$67.83	$67.27	$66.49	$66.37	$68.56	$67.03	$67.03	$66.68	$66.99
Mental Health Carve-Out Drugs	$70.93	$71.48	$73.08	$72.73	$74.67	$63.10	$53.99	$54.41	$54.04	$53.95	$54.20	$54.04	$62.55
FFS Physical Health Drugs	$45.91	$45.96	$44.28	$46.77	$48.06	$48.32	$49.18	$46.58	$52.35	$50.52	$53.02	$53.56	$48.71
FFS Physician Administered Drugs	$120.77	$115.31	$108.52	$112.74	$111.46	$111.59	$106.41	$113.09	$127.47	$101.31	$102.90	$121.69	$112.77
Encounter Physical Health Drugs	$60.95	$62.80	$64.27	$62.91	$63.48	$64.73	$66.30	$65.58	$68.28	$66.75	$65.30	$64.59	$64.66
Encounter Physician Administered Drugs	$97.56	$101.26	$106.79	$98.44	$102.14	$104.64	$97.09	$101.79	$96.62	$95.57	$103.75	$101.98	$100.64

Amount Paid per Claim - Multi Source Drugs (Rebates not Included)	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$29.81	$29.74	$29.73	$29.07	$29.38	$27.56	$25.91	$25.71	$25.60	$25.20	$24.63	$23.71	$27.17
Mental Health Carve-Out Drugs	$55.79	$56.14	$56.59	$56.40	$56.79	$44.79	$35.31	$34.68	$33.95	$33.61	$33.26	$32.45	$44.15
FFS Physical Health Drugs	$23.40	$22.32	$22.22	$22.66	$22.49	$23.40	$22.98	$22.50	$22.14	$23.15	$22.82	$22.03	$22.68
Encounter Physical Health Drugs	$24.60	$24.52	$24.30	$23.56	$24.04	$24.20	$24.12	$24.03	$24.04	$23.21	$22.55	$21.68	$23.74

Amount Paid per Claim - Single Source Drugs (Rebates not Included)	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$487.22	$535.10	$576.10	$577.95	$583.17	$596.62	$611.83	$605.36	$639.21	$622.47	$607.05	$572.56	$584.55
Mental Health Carve-Out Drugs	$546.53	$547.81	$578.60	$581.59	$610.83	$618.16	$609.37	$623.23	$635.18	$642.20	$649.03	$655.11	$608.14
FFS Physical Health Drugs	$338.39	$369.83	$364.68	$380.48	$399.41	$393.61	$415.42	$379.29	$465.10	$422.03	$453.54	$448.40	$402.52
Encounter Physical Health Drugs	$496.11	$550.22	$594.24	$596.19	$598.07	$613.35	$630.91	$625.24	$656.10	$642.07	$619.18	$576.98	$599.89

Multi-Source Drug Use Percentage	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
Multi-Source Drug Use Percentage	93.1%	93.4%	93.7%	93.8%	93.7%	93.7%	93.7%	93.7%	93.6%	93.7%	93.5%	93.1%	93.6%
Mental Health Carve-Out Drugs	96.9%	96.9%	96.8%	96.9%	96.8%	96.8%	96.7%	96.6%	96.7%	96.7%	96.6%	96.5%	96.7%
FFS Physical Health Drugs	92.9%	93.2%	93.6%	93.3%	93.2%	93.3%	93.3%	93.2%	93.2%	93.1%	93.0%	92.6%	93.2%
Encounter Physical Health Drugs	92.3%	92.7%	93.0%	93.1%	93.1%	93.1%	93.0%	93.1%	93.0%	93.0%	92.8%	92.3%	92.9%

Preferred Drug Use Percentage	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Avg Monthly
Preferred Drug Use Percentage	86.82%	86.86%	86.76%	86.65%	86.87%	87.02%	86.56%	86.30%	86.02%	85.84%	85.66%	85.45%	86.4%
Mental Health Carve-Out Drugs	76.12%	76.10%	76.21%	76.25%	75.91%	77.60%	76.14%	75.51%	75.28%	75.17%	75.02%	75.00%	75.9%
FFS Physical Health Drugs	95.17%	95.84%	95.57%	95.45%	95.37%	95.37%	95.22%	95.24%	95.14%	95.34%	95.37%	95.20%	95.4%
Encounter Physical Health Drugs	88.21%	88.17%	88.15%	87.97%	88.30%	88.14%	87.86%	87.72%	87.43%	87.44%	87.22%	86.88%	87.8%

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 19, 2017

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2017

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$4,232,127	11.0%	4,101	$1,032	Y
2	STRATTERA	ADHD Drugs	$2,050,382	5.3%	4,718	$435	Y
3	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,480,328	3.8%	919	$1,611	V
4	QUETIAPINE FUMARATE ER	Antipsychotics, 2nd Gen	$1,343,686	3.5%	2,423	$555	V
5	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$806,584	2.1%	12,572	$64	V
6	ABILIFY MAINTENA	Antipsychotics, Parenteral	$711,378	1.8%	432	$1,647	Y
7	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$620,045	1.6%	1,231	$504	V
8	FLUOXETINE HCL	Antidepressants	$601,623	1.6%	30,112	$20	Y
9	SAPHRIS	Antipsychotics, 2nd Gen	$574,916	1.5%	881	$653	Y
10	DULOXETINE HCL	Antidepressants	$559,591	1.5%	26,347	$21	V
11	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$462,380	1.2%	1,490	$310	V
12	SERTRALINE HCL	Antidepressants	$445,882	1.2%	38,059	$12	Y
13	PRISTIQ	Antidepressants	$431,145	1.1%	1,334	$323	V
14	TRAZODONE HCL	Antidepressants	$427,936	1.1%	37,128	$12	
15	VENLAFAXINE HCL ER	Antidepressants	$413,445	1.1%	1,841	$225	V
16	RISPERDAL CONSTA	Antipsychotics, Parenteral	$410,002	1.1%	549	$747	Y
17	VRAYLAR	Antipsychotics, 2nd Gen	$393,150	1.0%	380	$1,035	V
18	INVEGA TRINZA	Antipsychotics, Parenteral	$374,376	1.0%	72	$5,200	V
19	REXULTI	Antipsychotics, 2nd Gen	$352,311	0.9%	373	$945	V
20	BUPROPION XL	Antidepressants	$346,859	0.9%	17,881	$19	V
21	Factor Viii Recombinant Nos	Physican Administered Drug	$331,825	0.9%	5	$66,365	
22	VIIBRYD	Antidepressants	$316,339	0.8%	1,342	$236	V
23	SEROQUEL XR	Antipsychotics, 2nd Gen	$300,051	0.8%	572	$525	V
24	LANTUS	Diabetes, Insulins	$289,079	0.8%	875	$330	Y
25	TRINTELLIX	Antidepressants	$281,924	0.7%	804	$351	V
26	AMITRIPTYLINE HCL	Antidepressants	$277,110	0.7%	15,959	$17	Y
27	LAMOTRIGINE	Antiepileptics (oral & rectal)	$276,648	0.7%	21,210	$13	Y
28	HARVONI	Hepatitis C, Direct-Acting Antivirals	$275,297	0.7%	9	$30,589	Y
29	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$264,899	0.7%	4,165	$64	Y
30	Infliximab Not Biosimil 10mg	Physican Administered Drug	$260,628	0.7%	126	$2,068	
31	SPINRAZA	STC 99 - Miscellaneous	$250,000	0.6%	1	$250,000	
32	CITALOPRAM HBR	Antidepressants	$249,199	0.6%	25,717	$10	Y
33	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$248,510	0.6%	14,536	$17	
34	Rituximab Injection	Physican Administered Drug	$239,714	0.6%	62	$3,866	
35	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$236,373	0.6%	71	$3,329	
36	ESCITALOPRAM OXALATE	Antidepressants	$235,641	0.6%	19,737	$12	Y
37	ENBREL	Biologics for Autoimmune Conditions	$235,576	0.6%	58	$4,062	Y
38	VENLAFAXINE HCL ER	Antidepressants	$215,772	0.6%	13,933	$15	Y
39	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$215,696	0.6%	1,472	$147	
40	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$212,365	0.6%	629	$338	V
		Top 40 Aggregate:	**$22,250,794**		**304,126**	**$9,443**	
		All FFS Drugs Totals:	**$38,511,808**		**683,025**	**$571**	

Notes
- FFS Drug Costs only, rebates excluded
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last updated: April 19, 2017

ProDUR Report for January through March 2017

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
DA (Drug/Allergy Interaction)	Set alert/Pay claim	30	4	0	26	0.02%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,766	400	1	1,365	1.40%
DD (Drug/Drug Interaction)	Set alert/Pay claim	190	49	0	141	0.10%
ER (Early Refill)	Set alert/Deny claim	84,871	16,827	128	67,896	69.27%
ID (Ingredient Duplication)	Set alert/Pay claim	23,756	6,473	16	17,253	19.33%
LD (Low Dose)	Set alert/Pay claim	898	195	0	697	0.70%
LR (Late Refill/Underutilization)	Set alert/Pay claim	8	5	0	3	0.01%
MC (Drug/Disease Interaction)	Set alert/Pay claim	1,018	284	2	732	0.80%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,403	467	9	924	1.10%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	127	69	0	58	0.08%
TD (Therapeutic Duplication)	Set alert/Pay claim	8,370	2,530	1	5,830	6.83%
	Totals	**122,437**	**27,303**	**157**	**94,925**	**99.65%**

ProDUR Report for January through March 2017

Top Drugs in Early Refill

DUR Alert	Drug Name	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	5	10	37	0	108	0
	Hydrocodone/APAP	2	1	19	0	32	0
	Oxycodone	5	2	31	0	37	0
	Lorazepam	0	8	51	1	114	0
	Alprazolam	6	7	43	1	57	0
	Lamictal (Lamotrigine)	12	50	229	0	348	0
	Abilify (Aripiprazole)	14	22	81	1	202	0
	Seroquel (Quetiapine)	16	37	152	0	317	0
	Risperdal (Risperidone)	11	17	72	0	181	2
	Wellbutrin (Bupropion)	35	51	118	0	317	0
	Zoloft (Sertraline)	22	55	354	1	398	1
	Prozac (Fluoxetine)	12	39	181	2	283	0
	Celexa (Citalopram)	18	28	101	0	198	0
	Trazodone	34	52	238	1	452	1
	Cymbalta (Duloxetine)	25	44	128	1	282	0
	TOTALS =	**217**	**423**	**1835**	**8**	**3326**	**4**

		Nov and Dec 2016	Nov and Dec 2016	Nov and Dec 2016		Jan and Feb 2017	Jan and Feb 2017	Jan and Feb 2017		March and April 2017	March and April 2017	March and April 2017
HICL Sequence Number	**Generic Drug Name**	**# ER Alerts**	**# Overridden**	**Percent Overridden**		**# ER Alerts**	**# Overridden**	**Percent Overridden**		**# ER Alerts**	**# Overridden**	**Percent Overridden**
6438	FENTANYL	4	1	25.00%		8	4	50.00%		3	0	50.00%
1730	HYDROCODONE/ACETAMINOPHEN	106	38	35.85%		105	51	48.57%		79	32	48.57%
1695	HYDROMORPHONE HCL	15	3	20.00%		10	6	60.00%		9	5	60.00%
1745	METHADONE HCL	0	0	0.00%		2	1	50.00%		1	0	50.00%
1694	MORPHINE SULFATE	16	7	43.75%		25	6	24.00%		23	5	24.00%
1742	OXYCODONE HCL	125	43	34.40%		135	52	38.52%		115	42	38.52%
1741	OXYCODONE HCL/ACETAMINOPHEN	41	16	39.02%		47	19	40.43%		27	15	40.43%
8317	TRAMADOL HCL	50	5	10.00%		40	10	25.00%		31	5	25.00%
	ALL OPIOIDS =	**357**	**113**	**31.65%**		**372**	**149**	**40.05%**		**288**	**104**	**36.11%**

Opioid daily morphine equivalent quantity limits were reduced from 120 MEQ to 90 MEQ on 1/1/2017

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 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	50	17	9	
		Total Faxes Successfully Sent	37	7	3	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	15	5		
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	7	2		
		Prescriptions Unchanged after 3 Months of Fax Sent	21			
		Safety Monitoring Profiles Identified	1	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$35,464	$10,435		

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 2016 - 2017

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

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 2016 - 2017

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

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
March 2017 Volume 7, Issue 2

Non-Analgesics for Pain Management

By Deanna Moretz, PharmD, BCPS, OSU College of Pharmacy Drug Utilization Research and Management

Due to the adverse impact of prolonged long term opiate therapy including overdose, abuse, and dependence, there is increased interest in alternative therapies to manage chronic non-cancer pain.[1] Antidepressants and antiepileptics are two classes of medications that have been studied in neuropathic and other chronic pain conditions. The interpretation of pain trials is difficult to a number of potential biases in study design. Most of the trials are of short duration with a small number of subjects. In addition to evaluating the risk of potential biases, it is difficult to compare studies because randomized controlled trials (RCTs) differ substantially in research design.[2] The outcomes have also varied; newer RCTs have used measures such as daily numeric ratings of pain intensity and measures of health-related quality of life that were not collected in many older RCTs.[3] In general, most trials of effective treatments have found that less than 50% of patients achieve satisfactory pain relief.[3] The focus of this review will be on the comparative safety and effectiveness of non-analgesics such as antidepressants, antiepileptics and topical lidocaine used to manage various pain conditions outlined in **Table 1**.

Table 1. FDA approved pain indications for selected medications[4–8]

Condition	Duloxetine	Milnacipran	Gabapentin	Pregabalin	Carbamazepine	Topical Lidocaine
Diabetic Neuropathy	X			X		
Postherpetic Neuropathy			X	X		X
Fibromyalgia		X		X		
Chronic Musculoskeletal Pain						
Trigeminal Neuralgia					X	
Neuropathic pain associated with spinal cord injury				X		

Tricyclic Antidepressants in Neuropathic Pain

Tricyclic antidepressants, which include amitriptyline, imipramine, nortriptyline and desipramine, have been shown to be effective in the off-label treatment of a variety of painful neuropathic conditions including diabetic peripheral neuropathy (DPN), post-herpetic neuropathy (PHN), polyneuropathy, and post-stroke pain.[9] Guidelines for neuropathic pain prefer nortriptyline and desipramine, over amitriptyline because they provide comparable pain relief while causing fewer anticholinergic side effects.[3]

The most recent Cochrane review evaluating the safety and efficacy of amitriptyline in neuropathic pain was published in 2015.[10] In a pooled analysis from the DPN, PHN and mixed neuropathic pain trials (n=382, 4 trials), amitriptyline was shown to be more beneficial than placebo in managing neuropathic pain (Relative Risk (RR) 2.0; 95% CI 1.5 to 2.8). [10] Due to the small sample size in many of these studies, they are at high risk for bias which compromises the quality of the evidence. More participants who received amitriptyline experienced at least one adverse event compared to placebo (55% vs. 36%, respectively; RR 1.5; 95% CI 1.3 to 1.8).[10] The number needed to harm (NNH) for one additional harmful outcome was 5 (95% CI 3.6 to 9.1).[10] Serious adverse events were rare.

A 2014 Cochrane review examined the efficacy of desipramine in 5 studies that treated 177 participants with DPN or PHN.[11] Desipramine doses ranged from 100 mg to 150 mg once daily following titration. Low quality evidence in individual studies indicated some improvement in pain relief with desipramine compared with placebo. There was insufficient data for active treatment comparisons.[11] Participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo.[11]

In summary, very low quality evidence demonstrates the marginal benefit of TCAs in managing neuropathic pain. Most of these studies are older and contain methodological deficiencies which makes it difficult to apply their results to patient care. In addition, the adverse effects of TCAs, particularly in elderly patients, are well documented and limit their use. The possibility of over sedation leading to increased risk of falling and possible bone fracture is particularly problematic in older patients.

Serotonin and Norepinephrine Reuptake Inhibitors in Neuropathic Pain

Another class of antidepressants, the serotonin and norepinephrine reuptake inhibitors (SNRIs), has also shown efficacy in treating peripheral neuropathic pain and other chronic pain conditions.[3] Specific SNRI's studied in pain management include duloxetine, milnacipran, and venlafaxine. Only duloxetine and milnacipran have FDA approved indications for treating specific pain conditions as summarized in **Table 1**. Milnacipran does not have FDA approval for management of depression and is only indicated for treatment of fibromyalgia. Although venlafaxine has been studied in pain management, it is primarily used to treat depression. Duloxetine has emerged as the SNRI with the most evidence to support its use in managing a variety of pain conditions including neuropathy, fibromyalgia, and chronic musculoskeletal pain.

A 2014 Cochrane review assessed the benefits and harms of duloxetine in treating painful neuropathy and chronic pain.[9] Duloxetine 60 mg once daily was shown to be effective compared to placebo in treatment of painful DPN, with a RR for ≥ 50% pain reduction at 12 weeks of 1.73 (95% CI 1.44 to 2.08).[12] The estimated NNT was 5 (95% CI 4 to 7).[9] When compared to placebo in 48 patients with central neuropathic pain, duloxetine showed no effect in improving pain over 12 weeks as measured on a 1-10 Visual Analog Scale (VAS) (Mean Difference (MD) -1.0; 95% CI -2.05 to 0.05).[9] Adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect.[9] Serious adverse events were rare. However, 12.6% of trial participants stopped duloxetine due to adverse effects.[12] Moderate quality evidence supports the efficacy of duloxetine in treating DPN when compared to placebo. Adverse effects such as nausea, drowsiness, dry mouth and constipation increase when patients are titrated up to 120 mg per day of duloxetine.

Antiepileptics in Neuropathic Pain

The first antiepileptic used in clinical trials to treat a neuropathic pain disorder was carbamazepine. Carbamazepine and its derivative oxcarbazepine are used for the treatment of trigeminal neuralgia, but have not been shown to be as effective in treating other neuropathic pain disorders.[3] Gabapentin and pregabalin have both been shown to be effective when compared with placebo in treating painful DPN, PHN, polyneuropathy, neuropathic cancer pain, central post-stroke pain, and spinal cord injury pain.[3] Other antiepileptic drugs such as topiramate, valproic acid, levetiracetam, zonisamide, tiagabine and lamotrigine have been studied for various neuropathic pain disorders; however, evidence of their effectiveness is lacking.[3] A 2007 systematic review of lamotrigine for acute and chronic pain concluded it does not have a place in the treatment of pain, given other more effective therapies.[13]

A 2013 Cochrane review assessed the evidence for antiepileptics in treatment of neuropathic pain.[11] Ninety-one studies including 17,955 subjects were included in the review. Antiepileptics studied for management of neuropathic pain included carbamazepine, gabapentin, lacosamide, lamotrigine, oxcarbazepine, pregabalin, topiramate, and valproic acid. Most of the studies were conducted over short durations (i.e., 6 weeks) in small sample sizes.

Trials for gabapentin versus placebo in DPN utilized a wide range of doses from 600 to 3600 mg per day to reduce pain intensity by 50% from baseline (RR 1.8; 95% CI 1.4-2.2) with a NNT of 5 (95% CI 4.3-9.0).[14] In contrast, relief of PHN with gabapentin required higher daily doses (1800-3600 mg) for at least a 50% reduction in pain intensity compared to placebo (RR 1.7; 95% CI 1.3-2.2) with a NNT of 8 (95% CI 6-14) in 3 studies comprised of 892 subjects.[11] Pregabalin 300

mg and 600 mg once daily gave similar results relative to placebo in reducing PHN pain intensity by 50% from baseline (RR 2.7; 95% CI 1.9-4.0 and RR 2.8; 95% CI 2.0-3.9, respectively).[11] For relief of central neuropathic pain, the only data available was with pregabalin 600 mg once daily. In 2 studies with a total of 176 patients, pregabalin compared to placebo showed a 50% pain reduction with a RR of 3.6 (95% CI 1.5-8.4) and NNT of 6 (95% CI 4-14).[11] Moderate quality evidence indicated little or no effect for lamotrigine, oxcarbazepine and topiramate in treatment of neuropathic pain.[11] There was insufficient evidence of efficacy for valproic acid, lacosamide, levetiracetam, and phenytoin in treatment of neuropathic pain.[11] Withdrawals due to adverse events were much higher with antiepileptics than placebo except for carbamazepine, where studies were of short duration, and for the low dose of pregabalin 150 mg once daily.[11] Numbers needed to harm (NNH) decreased as doses increased for pregabalin and lacosamide. About 80% of participants experienced an adverse event with an antiepileptic, compared to about 70% of participants receiving placebo.[11]

Moderate quality evidence supports the utilization of gabapentin and pregabalin in managing peripheral neuropathic pain. Pregabalin has the additional FDA indication to manage central neuropathic pain due to spinal cord injury. Carbamazepine is FDA approved for treating trigeminal neuralgia. Of note, patient withdrawals due to adverse effects with the antiepileptics were higher compared to placebo. Significant adverse effects include central nervous system depression, dry mouth, blurred vision, and peripheral edema.

Lidocaine Patch in Neuropathic Pain

The lidocaine patch is approved for relief of pain associated with PHN.[7] The FDA approval was based on one unpublished trial in a single dose study in 35 PHN patients whose pain intensity was monitored over 12 hours.[6] After reviewing the initial study, the FDA requested more data. Therefore, an additional open label, multiple dose, 2-week treatment trial was conducted in 32 subjects who had responded in the previous study. Statistically significant differences favoring the lidocaine patch over observation (no treatment) were noted in terms of time to exit from the trial (14 versus 3.8 days; p <0.001).[7] A 2014 Cochrane review found insufficient evidence to support the use of topical lidocaine formulations for peripheral neuropathic pain.[15]

Pharmacologic Treatments for Lower Back Pain

A 2016 Agency for Healthcare Research and Quality (AHRQ) report of noninvasive treatments for lower back pain (LBP) evaluated systematic reviews of pharmacologic treatments for nonradicular or radicular LBP.[16] Most of the trials enrolled patients with pain symptoms of at least moderate intensity (> 5 on a 0-10 numeric rating scale for pain).[15] Pain intensity was the most commonly reported outcome. Pharmacological treatments included nonsteroidal anti-inflammatory drugs, acetaminophen, opiates, muscle relaxants, antiepileptics, and antidepressants.[15] For LBP, one systematic review found no differences in pain between TCAs and placebo (4 trials; Standardized Mean Difference (SMD) = -0.10; 95% CI -0.51 to 0.31; I2 = 32%).[15] Three placebo-controlled trials of moderate quality evaluated duloxetine in management of chronic LBP and found duloxetine was associated with lower pain intensity (differences: 0.58 to 0.74 on a 0-10 scale) and better function (differences 0.58 to 0.74 on the Brief Pain Inventory-Interference on a 0 -10 scale) than placebo.[15] No studies compared TCAs with duloxetine. Moderate quality evidence showed TCAs were associated with high risk of adverse events compared with placebo, although there was no difference in the risk of serious adverse effects.[15] There was insufficient evidence to evaluate the effect of antiepileptics on controlling acute nonradicular LBP.[15]

Guidelines

The International Association for the Study of Pain (IASP) 2015 guidelines support the use of pregabalin, gabapentin, and duloxetine as first line agents for treatment of neuropathic pain based on their panel's assessment of high quality evidence.[16] Moderate to low quality evidence supports the use of TCAs as first line agents in managing neuropathic pain. Lidocaine patches are no longer recommended as first line agents due to the weak quality of evidence supporting their efficacy.[16] The National Institute for Health and Care Excellence (NICE) 2014 guidelines support IASP recommendations.[17]

Conclusions

Most of the studies evaluating treatment of pain are small, of short duration, and may overestimate treatment effect, so they are graded as low to moderate quality. Moderate quality evidence supports the safety and efficacy of duloxetine and pregabalin as alternatives to morphine in managing several non-cancer pain conditions including DPN, PHN and central neuropathic pain. Duloxetine has also shown to be marginally effective in managing lower back pain. Although the TCAs may be considered as morphine alternatives to managing pain, their adverse effects often limit patient satisfaction.

Peer Reviewed By: Dr. Bill Origer, MD, Faculty, Samaritan Family Medicine Residency and Jonathan White, PharmD, BCPS, Clinical Specialist, Primary Care, Providence Medical Group

References:

1. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep*. 2016;65. doi:10.15585/mmwr.rr6501e1er.
2. Moore RA, Derry S, Wiffen PJ. Challenges in design and interpretation of chronic pain trials. [Review]. *Journal of Anaesthesia*. 2013;111(1):38-45. doi:10.1093/bja/aet126.
3. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*. 2009;122(10 Suppl):S22-32. doi:10.1016/j.amjmed.2009.04.007.
4. Carbamazepine Prescribing Information. East Hanover, NJ. Novartis. September 2015. https://www.drugs.com/carbamazepine.html. Accessed December 27, 2016.
5. Cymbalta (duloxetine) Prescribing Information. Indianapolis, IN. Lilly, USA. October, 2016. http://pi.lilly.com/us/cymbalta-pi.pdf. Accessed December 27, 2016.
6. Effexor XR (venlafaxine) Prescribing Information. Philadelphia, PA. Wyeth Pharmaceuticals, Inc. October, 2016. http://labeling.pfizer.com/showlabeling.aspx?id=100. Accessed December 27, 2016.
7. Lidoderm (Lidocaine Patch 5%) Prescribing Information. Mlavern, PA. Endo Pharmaceuticals. January, 2015. http://www.endo.com/File%20Library/Products/Prescribing%20Information/LIDODERM_prescribing_information.html. Accessed December 27, 2016.
8. Savella (milnacipran) Prescribing Information. Irvine, CA. Allergen USA, Inc. August 2016. https://www.savella.com/. Accessed December 27, 2016.
9. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132(3):237-251. doi:10.1016/j.pain.2007.08.033.
10. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015;(7):CD008242. doi:10.1002/14651858.CD008242.pub3.
11. Hearn L, Moore RA, Derry S, Wiffen PJ, Phillips T. Desipramine for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2014;(9):CD011003. doi:10.1002/14651858.CD011003.pub2.
12. Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev*. 2014;(1):CD007115. doi:10.1002/14651858.CD007115.pub3.
13. Wiffen PJ, Derry S, Moore RA. Lamotrigine for chronic neuropathic pain and fibromyalgia in adults. [Review][Update of Cochrane Database Syst Rev. 2011;(2):CD006044; PMID: 21328280]. *Cochrane Database of Systematic Reviews*. 2013. doi:10.1002/14651858.CD006044.pub4.
14. Wiffen PJ, Derry S, Moore RA, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. [Review]. *Cochrane Database of Systematic Reviews*. 2013. doi:10.1002/14651858.CD010567.pub2.
15. Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2014;(7):CD010958. doi:10.1002/14651858.CD010958.pub2.
16. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatments for Low Back Pain - AHRQ Comparative Effectiveness Reviews. 2016. http://www.ncbi.nlm.nih.gov/books/NBK350276/. Accessed January 4, 2017.
17. Centre for Clinical Practice at NICE (UK). *Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-Specialist Settings*. London: National Institute for Health and Care Excellence, (UK); 2013. http://www.ncbi.nlm.nih.gov/books/NBK266257/. Accessed December 28, 2016.

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
April 2017 Volume 7, Issue 3

Management of Opioid Use Disorder

Andrew Gibler, PharmD, Drug Use Research and Management, Oregon State University College of Pharmacy

Increased abuse of prescription opioids and subsequent increases in accidental opioid-related deaths have caught the attention of policy makers in the United States (U.S.) and in Oregon. On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs and improve community access to naloxone.[1] In January 2017, the Oregon Health Plan (OHP) removed restrictions for Suboxone®, and its generic sublingual tablet and film formulations, and for Vivitrol®, a naltrexone extended-release injectable formulation, in fee-for-service patients.[2] This article will summarize medication treatment options for patients with opioid use disorder.

Substance Use Disorders

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.* (DSM-V), substance use disorders (SUDs) are associated with a pattern of inappropriate substance use that adversely affects one's personal or professional life.[3] In persons with an SUD, there is an underlying change in the way the brain functions that can persist beyond detoxification and result in repeated relapses and intense cravings when exposed to certain stimuli.[3] These addictive substances alter brain circuitry involved in complex functions like motivation and decision-making and diminish natural reward mechanisms for essential substances like food and water.[4] Pleasure normally experienced with stimuli like food or social interactions is diminished with repeated use of addicting substances.[4] A specific example of an SUD is opioid use disorder which is a result of opioid abuse. It is a chronic, relapsing disease that often occurs with other SUDs and has had significant economic, personal and public health consequences for many victims.[5]

Opioid Use Disorder

Opioid analgesics have been used for decades to manage pain, but they can also produce feelings of dysphoria and sedation which places them at high risk for misuse and abuse. In addition, tolerance to regular use of an opioid analgesic can result in the need over time for higher doses to achieve analgesia. From 2007 to 2014, the number of private insurance claim lines with an opioid dependence diagnosis increased 3,203%, with most of the claims associated with persons between 19-35 years of age.[6] With ease of accessibility to opioids, it is imperative that physicians understand how to recognize opioid use disorder and navigate treatment strategies with their patients. Opioid use disorder is defined by DSM–V when at least 2 criteria outlined in Table 1 are met in the last 12 months.[3]

Table 1. DSM-V Criteria for Opioid Use Disorder (≥2 met in last 12 months).[3]

1. Opioid(s) often taken in larger amounts or over a longer time than intended.
2. Persistent desire or unsuccessful efforts to cut down or control opioid use.
3. Excessive time spent to obtain or use an opioid, or recover from its effects.
4. Urge to use opioids; opioid craving.
5. Failure to fulfill important obligations at work, school, or home because of recurrent opioid use.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous (e.g., while driving).
9. Continued opioid use despite knowledge of such use being a persistent physical or psychological problem.
10. Opioid tolerance (need for increased amounts of opioid for effect or diminished effect with same dose).*
11. Opioid withdrawal or need opioid to relieve withdrawal.*

*Note: These criteria not considered to be met when taking opioids as prescribed.

Treatment Strategies

For patients who seek help for opioid use disorder, a thorough patient medical and mental health evaluation should be performed before treatment is started. This should include screening for other SUDs, infectious diseases (e.g., hepatitis C, HIV, tuberculosis) and pregnancy.[5] Patients with concomitant SUDs or concurrent use of alcohol, sedatives, hypnotics or anxiolytics may require a higher level of care and closer monitoring.[5]

The setting in which treatment is provided is just as important as the specific medication selected.[5] For treatment of opioid withdrawal (detoxification), symptoms may be monitored closely at the appropriate level of care (inpatient or outpatient setting). For maintenance therapy, opioid treatment programs (i.e., 'methadone clinics') offer daily supervised dosing of methadone, and increasingly of buprenorphine. Office-based maintenance treatment, which is limited to buprenorphine by Federal law, provides dispensing of medication periodically on an individualized basis. Naltrexone can be prescribed in any setting by any clinician with prescribing privileges. The most appropriate setting and choice of therapy largely depends on patient preference, their psychosocial situation, concomitant disorders, and risk of diversion. All factors are considered in order to make treatment as successful as possible.

Goals for maintenance therapy include improvement in health and ability to work, decreased use of contaminated needles and risk for HIV or Hepatitis C infection, reduced opioid cravings, decreased use of illicit opioids, and crime reduction.[6] Long-acting opioids methadone and buprenorphine are the most studied. Methadone and buprenorphine have similar efficacy in patients with opioid use disorder when outcomes like self-reported opioid use, positive opioid urine drug screens, and patient retention in opioid treatment programs were studied.[8] Overall rates of adverse events between methadone and buprenorphine also appear to be similar when used for maintenance treatment.[8] Oral and extended-release injectable naltrexone formulations are also approved by the U.S. Food and Drug Administration (FDA) for opioid dependence in patients who can abstain from all opioids. Formulations approved for opioid use disorder are listed in Table 2.

Table 2. Drugs FDA-Approved for Patients with Opioid Use Disorder.

Drug	Proprietary Name	Formulation	AAAC for 30-day supply
Buprenorphine/ Naloxone	Buprenorphine/ Naloxone	SL Tablet	$47
	Suboxone®	SL Film/Buccal	$227
	Zubsolv®	SL Tablet	$233
	Bunavail®	Buccal Film	$229
Buprenorphine	Buprenorphine	SL Tablet	$22
	Probuphine®	Implant Device‡	$5940*
Methadone	Methadone	Tablet, Solution	$7
	Dolophine®	Tablet, Solution	$67*
Naltrexone	Naltrexone	Tablet	$15
	Vivitrol®	ER Injection	$1571*

Key: AAAC = average actual acquisition cost; ER = extended–release; SL = sublingual
‡Available as a 6-month implant; *Prices from Lexicomp Database. Accessed 4/24/17.

Methadone

Methadone is a mu-opioid agonist and an N-methyl-D-aspartate (NMDA) antagonist. The recommended initial dose ranges from 10 to 30 mg for

management of withdrawal, with reassessment every 3 to 4 hours.[5] Federal law mandates that the initial dose cannot exceed 30 mg. Methadone has a high potential for misuse and diversion. As maintenance therapy, it is recommended for patients who could benefit from single daily dosing and supervision provided in an opioid treatment program.[5] Opioid treatment programs have strict guidelines for dosing, supervised treatment and associated services. Doses can usually be anywhere from 60 to 120 mg per day.[5] There is no recommended limit to duration of maintenance therapy.

Methadone has strong evidence to support reducing mortality and substance abuse, improving physical and mental health outcomes, reducing criminal activity and reducing risk for HIV and risk behaviors.[8] However, methadone is not without risk for harm. Patients with cardiac or respiratory disease should avoid methadone. Adverse effects may include prolongation of the QT-interval which rarely may result in Torsade de pointes, a fatal arrhythmia. Respiratory depression can occur when the drug is titrated too quickly due to drug accumulation and methadone's complicated pharmacokinetic profile. Depending on clinical response, dose increases of 5 to 10 mg increments should occur no more frequently than every 7 days.[5]

Buprenorphine

Buprenorphine is a partial opioid agonist with lower intrinsic activity at the mu-opioid receptor than a full agonist, but due to its very high affinity for the receptor, buprenorphine possesses antagonist properties that can block the effects of other opioids if used concurrently. Buprenorphine (C-III) is not as highly controlled as methadone (C-II) and can be provided in clinician offices. Qualifying physicians, nurse practitioners (NP), or physician assistants (PA) must have a waiver from the Substance Abuse and Mental Health Services Administration (SAMSHA), completed the required buprenorphine training, and obtained a unique Drug Enforcement Administration (DEA) number. Physicians may provide care for up to 275 patients and NPs and PAs may care for up to 30 patients.[1]

Buprenorphine is formulated alone or with naloxone in a 4:1 ratio to discourage injection of the drug. The low dose of naloxone does not precipitate withdrawal symptoms unless it is injected. Buprenorphine has poor oral bioavailability due to extensive first-pass metabolism so formulations are dissolved against the tongue and buccal mucosa.

Buprenorphine reduces self-reported opioid use, reduces positive opioid urine drug screens, improves treatment retention, and has similar evidence for survival benefit as methadone.[8] Buprenorphine is safer than methadone due to its limited effects on the respiratory system, fewer drug interactions, and more predictable pharmacokinetics. However, buprenorphine is not the best option for everyone. Office-based treatment with buprenorphine may not be suitable for patients who regularly use alcohol or sedatives.[5] Physicians can reduce risk of diversion with buprenorphine with frequent office visits, urine drug testing, and recall visits for pill counts.[5] Another consideration is cost. Buprenorphine is more expensive than methadone, and private office charges for buprenorphine might exceed the usual costs of a methadone clinic.[7]

Opioid-dependent patients should wait until they are experiencing mild to moderate withdrawal before starting buprenorphine at a dose of 2 to 4 mg.[5] Doses can be increased in increments of 2 to 4 mg until it is determined to be well tolerated.[5] Maintenance therapy with buprenorphine should exceed 8 mg per day but no more than 24 mg per day.[5] Higher doses are not more effective but can increase risk of diversion. Buprenorphine taper and discontinuation is a slow process, without a defined duration, but can take several months. Close monitoring is advised even after buprenorphine is stopped. Accessing the Oregon Prescription Drug Monitoring Program (PDMP) data can be helpful to know what other controlled substances, if any, are being prescribed.

Naltrexone

Extended-release injectable opioid antagonist naltrexone can also be successfully used to treat opioid use disorder as evidenced by one randomized, placebo-controlled trial.[9] The long-acting formulation is given intramuscularly every 4 weeks. Success with oral naltrexone is often adversely affected by poor medication adherence because it requires a highly motivated patient. Oral naltrexone has not consistently demonstrated superiority to control groups at treatment retention or opioid consumption because of high attrition in clinical trials and so there is insufficient evidence to recommend it routinely in patients at this time.[4] Patients who initiate parenteral or oral naltrexone treatment or switch from methadone or buprenorphine must be free of opioid dependence (7-14 days without acute withdrawal symptoms), which can be confirmed with an opioid-free urine sample and a naloxone challenge (intramuscular or intravenous administration of 0.8 to 1.6 mg of naloxone; or alternatively, 50 mg of oral naloxone with no subsequent withdrawal symptoms).[7] Length of treatment with oral or extended-release injectable naltrexone depends on clinical judgement, but there is no physical dependence and it can be stopped abruptly without withdrawal symptoms.[5]

Guideline Resources

Cost of therapy, concomitant medical and psychiatric conditions, availability of methadone clinics, clinicians trained in administering buprenorphine or naltrexone, and risk of diversion are all factors that play a role in considering which drug is appropriate for an individual patient. Both the American Society of Addiction Medicine and the U.S. Department of Veteran Affairs and Department of Defense have published helpful guidelines that describe the nuances for each drug therapy.[4,5] Importantly, the guidelines emphasize that drug therapy alone is insufficient. Concomitant psychosocial interventions are described which should be applied to address the psychological and social circumstances that often hinder treatment from being successful.[4,5]

Peer Reviewed by: Andy Antoniskis, MD, FASAM, former Internist and Associate Medical Director of the Providence Portland Chemical Dependency Program and Laura De Simone, MS, RPh, Clinical Pharmacy Specialist for Pain Management, Kaiser Permanente

References:

1. The 114th Congress (2015-2016): Comprehensive Addiction and Recovery Act of 2016. Library of Congress. https://www.congress.gov/bill/114th-congress/senate-bill/524/text. Accessed August 3, 2016.
2. Oregon Health Plan Pharmacy and Therapeutics Committee; January 2017 Meeting Minutes. Available at http://www.oregon.gov/oha/healthplan/Pages/pt-committee.aspx. Accessed March 31, 2017.
3. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 5th Ed*. Washington, DC: American Psychiatric Association; 2015.
4. Clinical Practice Guideline for Substance Use Disorders (2015). U.S. *Department of Veterans Affairs/Department of Defense*. http://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf. Accessed July 25, 2016.
5. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *J Addict Med*. 2015;9(5):358-367. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4605275/pdf/adm-9-358.pdf. Accessed April 24, 2017.
6. The Opioid Crisis among the Privately Insured: The Opioid Abuse Epidemic as Documented in Private Claims Data. A FAIR Health White Paper; July 2016. http://www.fairhealth.org/servlet/servlet.FileDownload?file=01532000001nwD2. Accessed August 3, 2016.
7. Schuckit MA. Treatment of Opioid-Use Disorders. *N Engl J Med*. 2016;375:357-368.Available at http://www.nejm.org/doi/pdf/10.1056/NEJMra1604339. Accessed April 24, 2017.
8. Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane Database Syst Rev*. 2016;(5):CD011117. doi:10.1002/14651858.CD011117.pub2.
9. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet*. 2011;377:1506-13. doi: 10.1016/S0140-6736(11)60358-9.

HERC Review of Novel Treatments

Issue: At its March 9, 2017 HERC adopted changes to the Prioritized List that address novel treatments with marginal clinical benefit, low cost-effectiveness, and/or very high cost

Background: Many novel treatments emerge that may be high cost without necessarily offering much incremental benefit over existing treatments. Some novel treatments may not meet clinically important effectiveness criteria that would justify having a treatment be prioritized very high on the Prioritized List. There is precedent for the Prioritized List to have some treatments for conditions both above and below the funding line (e.g. surgical treatments and medical treatment for back pain).

Identifying novel treatments which may have marginal benefit

HERC's process for identifying novel treatments which may be candidates for evaluation as having a marginal benefit or low cost-effectiveness would be similar to any other topic; a HERC medical director may initiate such a review or a stakeholder could also submit it for consideration. The Pharmacy and Therapeutics Committee or its staff may also identify novel prescription drugs for which these new lines/guidelines may be applicable. Experimental treatments will continue to be left off of the Prioritized List as such treatments are not to be covered per Medicaid regulations.

Mechanisms for prioritizing treatments with marginal benefit on appropriate lines

Professional services of marginal benefit that can be identified by a CPT or HCPCS code (such as surgeries and physician-administered drugs) can be managed using pairings on a low prioritized line. If the diagnosis code does not already appear on an appropriately low prioritized line, both the diagnosis code and procedure code can be added to the new lines, lines for conditions with minimally effective treatments or no treatment necessary (Lines 653-665) or other lines created for such cases. A limited number of ancillary (e.g., durable medical equipment and supplies, adjunctive procedures) and diagnostic services (e.g., labs, imaging) have been addressed with ancillary and diagnostic guideline notes.

In order to better indicate the priority of outpatient prescription drugs, durable medical equipment and supplies, adjunctive procedures and condition-treatment pairings that would otherwise not appear on the Prioritized List, HERC has created two new lines, each paired with a new guideline note.

In the case of outpatient prescription drugs, as HERC is statutorily prohibited from conducting drug class evidence reviews or medical technology assessments solely of a prescription drug, HERC needs to rely on reports developed by other groups. As many novel treatments are prescription drugs, HERC can rely on drug class reviews conducted by Oregon's Pharmacy and Therapeutics Committee or other reputable sources. These reviews would speak to the appropriate indications for the medications and describe their effects, including the magnitude of the effect. Based on the clinical importance of the effects/cost-effectiveness of the drugs in question, HERC can now attach them to the new lines prioritized low on the list, if appropriate.

Approved changes to the Prioritized List effective January 1, 2018:

Create a new statement of intent as follows:

STATEMENT OF INTENT 3, HEATH SERVICES WITH LOW IMPORTANCE

It is the intent of the Commission that therapies that exhibit one or more of the following characteristics generally be given low priority on the Prioritized List:

i. Marginal clinical benefit
ii. No clinically important benefit
iii. Harms that outweigh benefits
iv. Very high cost in which the cost does not justify the benefit
v. Significantly greater cost compared to alternate therapies when both have similar benefit
vi. Significant budget impact that could affect the overall Prioritized List funding level

Where possible, the Commission prioritizes pairings of condition and treatment codes to reflect this lower priority, or simply does not pair a procedure code with one or more conditions if it exhibits one of these characteristics.

As codes for prescription drugs, durable medical equipment & supplies, certain adjunctive procedures and other ancillary services are not typically included on the Prioritized List and are not always billed in conjunction with diagnosis codes, it is more difficult to indicate the importance of these services through the prioritization process. Based on evidence reviews conducted by one of its subcommittees, the Pharmacy and Therapeutics Committee, or other reputable sources, HERC prioritizes such services regarded as having low importance when prescribed for certain conditions on Line XXX, CONDITIONS FOR WHICH CERTAIN TREATMENTS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS, or Line YYY, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS, and lists the relevant condition/treatment pairings in Guideline Notes AAA, TREATMENTS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS, or BBB, TREATMENTS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS.

Create two new lines as follows:

Line XXX
CONDITION: CONDITIONS FOR WHICH CERTAIN TREATMENTS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
TREATMENT: MEDICAL AND SURGICAL TREATMENT

Ranking: There are many scenarios which may place different condition/treatment pairings on this line, so this line would need to be hand-ranked as opposed to being able to come up with a composite line score. Staff suggests that this new line be ranked around Line 500.

Line YYY
CONDITION: CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
TREATMENT: MEDICAL AND SURGICAL TREATMENT

Ranking: If there is evidence indicating there is no clinical benefit to the treatment or harms outweigh benefits, staff suggests that this new line be ranked as the last line on the list.

Create two new guideline notes as follows:

GUIDELINE NOTE AAA, TREATMENTS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

The following treatments are prioritized on Line XXX for the conditions listed here:

CONDITION	PRESCRIPTION DRUG
e.g., Obesity	All prescription drugs
e.g., Cancer of the liver, lung or prostate; hemangiomas	Proton beam therapy
Various	e.g., Treatments previously review by HERC that were found to be no more effective that treatments prioritized higher on the list but cost significantly more

GUIDELINE NOTE BBB, TREATMENTS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following treatments are prioritized on Line YYY, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS, for the conditions listed here:

CONDITION	TREATMENT
e.g., Obstructive sleep apnea	Tongue base suspension surgery (CPT 41512)
e.g., All conditions except Pompeii's disease	Enzyme replacement therapy
Various	e.g., Treatments previously reviewed by HERC that were found to have insufficient evidence of effectiveness

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

OREGON HEALTH AUTHORITY

DRUG USE REVIEW BOARD/PHARMACY AND THERAPEUTICS COMMITTEE (P&T)

High Cost and Marginal Benefit (HCMB) Therapies Policy

GOAL:
To collaborate with and assist the Health Evidence Review Commission (HERC) to evaluate available evidence with a transparent process to encourage safe and financially sustainable policies that maximize access to high value medications for patients served by the Oregon Health Plan (OHP).

PROCEDURES:

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

    a. The reviews are made in public with opportunity and consideration of public comment and input.

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

3. The P&T may elect to recommend the HERC consider adding drugs that exhibit one or more of the following characteristics to the new Lines on the Prioritized List:

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

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

Policy Evaluation: Metabolic Monitoring of Antipsychotics in Children

Purpose: In October 2012, Oregon implemented a RetroDUR policy to improve metabolic monitoring for pediatric Medicaid patients who are on an antipsychotic drug. Faxed reminders were sent to physicians regarding annual glucose monitoring for children on antipsychotic drugs without claims for metabolic monitoring in the previous 12 months.[1] Providers also received a report card which compared their monitoring rates to other providers in the state.[1] The purpose of this review is to examine the impact of this RetroDUR policy on rates of metabolic monitoring for children taking antipsychotics and to identify areas for potential policy change.

Research Questions:

1. After implementation of the RetroDUR, was there a change in the proportion of children on antipsychotics who received yearly glucose monitoring (blood glucose or hemoglobin A1c [HbA1c])?
2. After implementation of the RetroDUR, was there any change in monitoring of other metabolic laboratory parameters, including triglycerides or high density lipoprotein (HDL)?
3. Was there any change in the rate of new diabetes diagnoses after implementation of the RetroDUR?
4. Were there any subgroups of patients based on drug therapy (i.e. drug, dose, or duration), patient characteristics (i.e. age or mental health diagnosis), or prescriber characteristics (i.e. provider specialty) who receive more routine metabolic glucose monitoring?

Conclusions:

- After implementation of the RetroDUR, there was only a modest change in glucose monitoring (Figure 2). In the year following implementation of the policy, approximately 50.3% of patients lacked glucose monitoring compared to 54.1% of patients without monitoring before implementation of the policy (mean difference=4.2%).
- There was no difference in monitoring rate of other metabolic laboratory parameters or in the rate of new diabetes diagnoses before or after implementation of the RetroDUR.
- Rates of glucose monitoring in subgroup populations based on drug therapy, patient, or prescriber characteristics were also similar before and after implementation of the RetroDUR.

Recommendations:

- Because there was minimal change in metabolic monitoring rates detected after implementation of the RetroDUR, discontinue the policy.

Author: Sarah Servid, Pharm.D.

Date: May 2017

Background:

Metabolic adverse effects including hyperglycemia, dyslipidemia, and weight gain are commonly associated with first- and second-generation antipsychotics. Second-generation antipsychotics carry labeling warnings from the U.S. Food and Drug Administration (FDA) for metabolic changes which may be associated with increased long-term risk for type 2 diabetes mellitus and cardiovascular and cerebrovascular diseases.[1,2] In 2004, the American Diabetes Association (ADA) and American Psychiatric Association (APA) released a consensus statement that recommends periodic metabolic monitoring for all patients on antipsychotic medications.[2] Upon initiation or modification of an antipsychotic regimen, baseline assessments of personal and family history of obesity, weight or body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose and fasting lipid profile are recommended.[2] Further evaluation of fasting plasma glucose is recommended at 12 weeks and annually thereafter.[2] Lipid assessment is recommended at 12 weeks followed by an assessment every 5 years. However, in children less than 10 years of age, there is no established criteria to define lipid abnormalities in young children, and as a result, lipid monitoring is not used regularly.[3] In children, more frequent metabolic monitoring is recommended if weight gain exceeds the 90th percentile for BMI or waist circumference for their age.[3,4] More frequent monitoring may also be necessary in patients at high risk for metabolic side effects or those who have worsening hyperglycemia or dyslipidemia while on therapy.[2]

However, despite these known risks, monitoring of metabolic adverse events remains low.[5,6] Data from a large cohort of Medicaid patients in 2012 demonstrated that monitoring in pediatric patients on an antipsychotic was lower than rates for adults for glucose (OR 0.41, 95% CI 0.38 to 0.44) and lipids (OR 0.56, 95% CI 0.52 to 0.61) .[7] Similarly, in 2011, a large nationwide cohort (n=52,407) demonstrated that rates of glucose testing and HbA1c testing in pediatric patients (ages 5-18) after initiation of an antipsychotic was suboptimal with rates of 15.6% and 1.6%, respectively.[8] In a population of pediatric Medicaid patients from California, Missouri and Oregon (n=5,370), 2 years following the release of the consensus guidelines, glucose screening was performed in only 31.6% of patients (95% CI 30.4% to 32.9%) and lipid testing was performed in 13.4% of patients (95% CI 12.5% to 14.4%).[6] Overall, patients in Oregon were less likely to have glucose testing (adjusted odds ratio [AOR] 0.81, 95% CI 0.65 to 1.02) and lipid testing (AOR 0.57, 95% CI 0.42 to 0.77) performed compared to children in California.[6]

In an effort to increase monitoring rates, several states have implemented programs to evaluate physician monitoring of their pediatric patients on antipsychotic therapy. In 2009, one state mental health authority began an initiative to improve metabolic monitoring rates by conducting education for prescribers, initiating audits on metabolic monitoring, and providing feedback to mental health center leaders regarding their monitoring.[9] Provider education included access to lectures by experts, discussions about improving monitoring, access to articles on antipsychotic monitoring, yearly data summaries on monitoring and prescribing practices, and quarterly letters describing the quality initiative.[9] The program included 10 community mental health centers with over 15,000 patients.[9] Data were collected on a random sample of 595 adults and 310 children over the course of 2 years.[9] Rates of yearly monitoring for glucose, lipids, weight, and waist circumference varied significantly between centers but did not demonstrate an overall improvement over the course of the study.[9] Another quality improvement program, conducted in the United Kingdom, utilized a yearly audit-based targeted screening program with feedback for providers regarding data on their relative and absolute performance compared to practice standards.[10] Each individual mental health Trust participating in the program developed a local action plan.[10] Resources provided to the centers included reference documents with information about testing results and resources for staff related to aspects of physical health, diet, exercise and smoking cessation.[10] Data were collected from a sample of patients each year on monitoring of 4 parameters: blood pressure, obesity or BMI, plasma glucose and lipids.[10] Over the course of the study, patients without monitoring for any of these parameters decreased from 46% to 14%.[10] Rates of patients with documented monitoring of all 4 parameters increased from 11% to 34%.[10] Patients with a known diagnosis of diabetes or dyslipidemia were more likely to have monitoring in all 4 categories.[10]

In October 2012, Oregon implemented a RetroDUR policy for metabolic monitoring in pediatric Medicaid patients who are on an antipsychotic drug. A detailed description of the program is available at the following website: http://www.orpdl.org/drugs.[1] The goal of this program is to improve monitoring rates in children taking an antipsychotic. For children on antipsychotic drugs without claims for metabolic monitoring in the previous 12 months, reminders were sent to physicians regarding annual glucose monitoring.[1] Providers also received a report card which compared their monitoring rates to other providers in the state.[1] The purpose of this review is to examine the impact of this RetroDUR policy on rates of metabolic monitoring for children taking antipsychotics and to identify areas for potential policy change.

Methods:

This observational before-and-after analysis compared patients in a historical control group before the implementation of the RetroDUR from October 2011 to September 2012 to patients after implementation of the policy from October 2012 to September 2013. Patients included in the study were in the FFS population, 18 years of age or less, and had at least one paid pharmacy claim for an antipsychotic with a minimum 5 days' supply (identified as the index event). Included members could be enrolled in a Coordinated Care Organization (CCO), but were required to be enrolled in Medicaid for at least 75% of the time in the year prior to the index event. If a patient had multiple claims for an antipsychotic within this time frame, the index event was defined as the earliest paid pharmacy claim during this time with a minimum 5 days' supply. Antipsychotics included in the program are listed in Table A1 and include both first- and second-generation antipsychotic medications. With implementation of the RetroDUR policy, this index event would trigger a report sent to the provider if there was no claim for of metabolic monitoring within the previous 12 months. In order to examine the impact of this policy, information was collected on metabolic monitoring in the 12 months prior to the index event in the historical control and compared to metabolic monitoring rates after implementation of the policy. Metabolic monitoring in these patients was identified via CPT code (Table A2).

Patients were excluded from the study if they had Medicare part D coverage (identified via benefit packages BMM, BMD, MND, or MED) or a prior diagnosis of diabetes. Antipsychotics or formulations brought to market after implementation of the RetroDUR were not included in subgroup analyses. Diagnosis of diabetes was identified via pharmacy claims for diabetic medications in the 1 year prior to the index event or medical claims indicating a diabetes diagnosis in the 2 years prior to the index event. Pharmacy claims data included patients who received insulin or oral hypoglycemic/antihyperglycemics (with the exception of metformin) during 1 year prior to the index event.[1] See Table A3 for a list of included medications. Medical claims indicating a diabetes diagnosis included patients with at least 2 face-to-face encounters in an outpatient setting or non-acute inpatient setting, on different dates of service, with a diagnosis of diabetes or one face-to-face encounter in an acute inpatient or ED during the 2 years prior to the index event.[1] ICD codes used to identify diabetes diagnosis are listed in Table A4 and CPT codes for encounter data are listed in Table A5.

Data assessed at the index event included baseline demographics (age, gender and ethnicity), prescribing provider specialty, mental health diagnoses, and type of medication. Diagnoses were identified by ICD-9 and ICD-10 codes (Table A6) and assessed within 12 months before or 3 months after the index event. Provider specialty was identified using the National Provider Identifier (NPI) number and the associated taxonomy. Subgroup analyses included patients stratified by dose and duration of therapy. Duration of therapy was defined as the proportion of days covered (PDC) by at least 1 antipsychotic prescription over the course of 365 days. Short-term therapy corresponds to a PDC of 33% (120 days) or less, intermittent therapy corresponds to a PDC of 34-80% (121-292 days), and long-term therapy corresponds to a PDC greater than 80% (>293 days). Intermittent therapy may indicate therapy of medium duration or low adherence to continuously prescribed therapy. Additional subgroup analyses will include stratification by medication type, provider specialty, and diagnoses. Differences in dose were identified based on FDA approved doses. Medications prescribed above the maximum FDA approved dose were defined as high dose and medications within the FDA dosing range were classified as standard doses (See Table A2). Maximum approved doses for pediatric use are often dependent

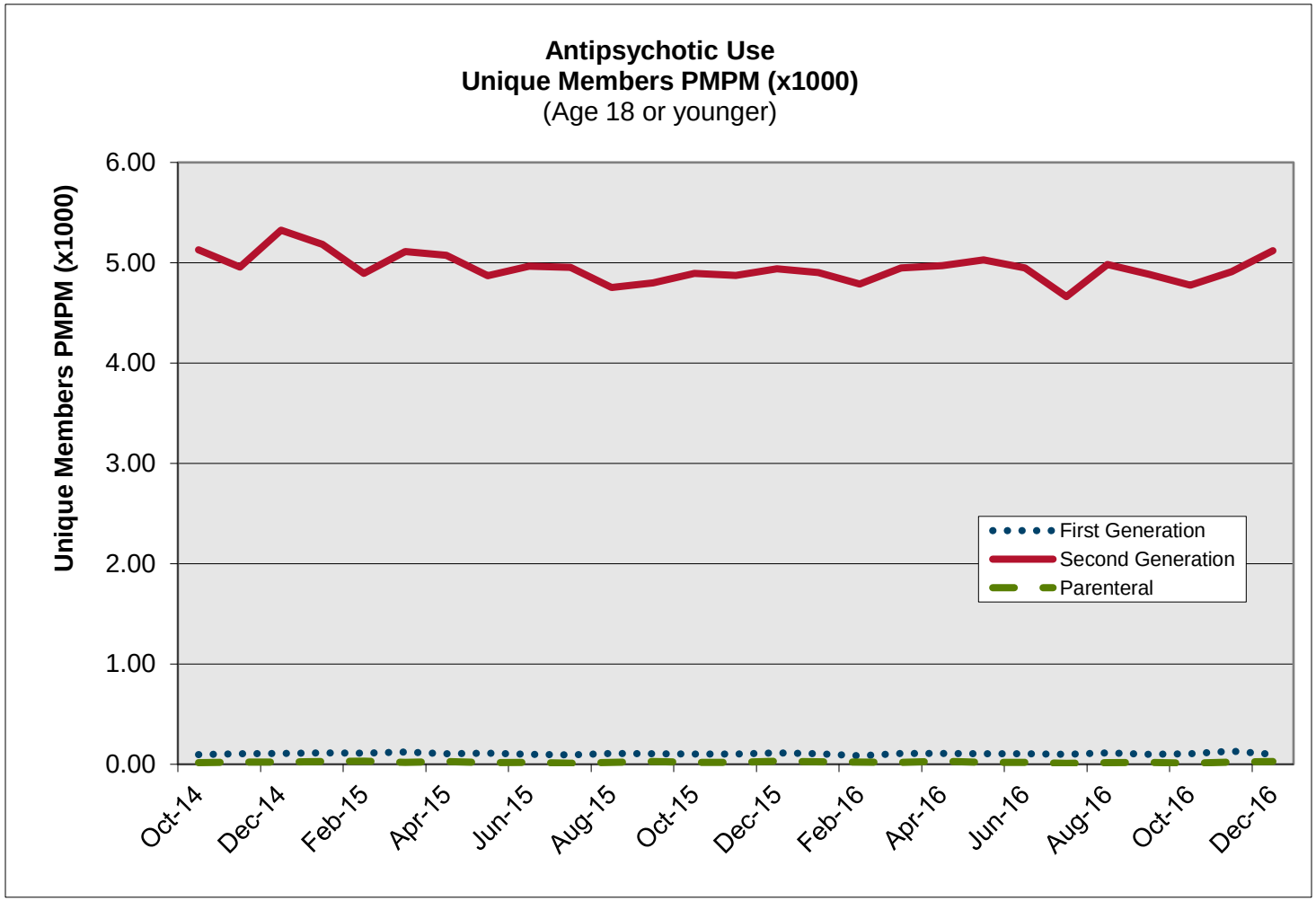
on weight, age of the child, or indication. In the case of indication-specific dosing, the highest approved for a particular age was used. If there is no established dose in pediatric patients, maximum adult doses are referenced.

Results:

Utilization

Figure 1 shows the recent utilization of antipsychotic medications by unique members from October 2014 through October 2016. Data is stratified by first generation antipsychotics, second generation antipsychotics, and parenteral antipsychotics. These medications are carve out medications and represent all pediatric members with FFS coverage regardless of CCO enrollment. Overall, use of second generation antipsychotics is more frequent than first generation or parenteral forms. Use of these medications over time has remained consistent.

Figure 1: Unique patient count of children (age ≤18 years) who utilized antipsychotics (PMPM) from October 2014 to present stratified by PDL class (first generation, second generation, and parenteral antipsychotics).



Patient demographics

Table 1 shows demographics of Medicaid members with a claim for an antipsychotic in the year prior to and following implementation of the RetroDUR. There was a total of 4132 patients with an index event in the year before implementation of the RetroDUR and 3838 patients in the following year. Patient demographics were similar in both groups. The mean age was approximately 13 years, 33% were female, and 63-65% of the population was white. Based on the proportion of days covered, 42-45% of patients were taking antipsychotics long-term and 33% of patients were taking antipsychotics intermittently. Less than 5% of the population received prescriptions for antipsychotics at doses greater than the maximum amount recommended by the FDA. The most common diagnoses for these patients are listed in Table 2. The majority of patients had multiple mental health diagnoses.

Evaluation of Monitoring Rates

After implementation of the RetroDUR, there was only a modest change in glucose monitoring (Figure 2). In the year following implementation of the policy, approximately 50.3% of patients lacked glucose monitoring compared to 54.1% of patients without monitoring before implementation of the policy (mean difference=4.2%). Similarly, there was no apparent change in the rates of newly diagnosed diabetes over time or in monitoring of lipid parameters (Figure 2). To evaluate changes in glucose monitoring for specific subpopulations claims were stratified by drug therapy (i.e. drug, dose, or duration), patient characteristics (i.e. age or mental health diagnosis), or prescriber characteristics (i.e. provider specialty). For the majority of subgroups rates were similar before and after implementation of the RetroDUR (Tables 1-4).

Prior studies indicate that interventions including academic detailing and education for providers may increase metabolic monitoring rates for patients on antipsychotics. However, in our patient population, monitoring rates were only slightly improved upon initiation of this RetroDUR. The policy included yearly reminders sent to physicians about pediatric patients whose claims history indicated they did not have metabolic monitoring within 1 year. The reminder included information about recommended standards of care and compared their monitoring rates to other providers in the state. Other types of interventions may have a greater potential to influence monitoring rates in this population. More intensive academic detailing, provider education, and audits may provide limited improvement. However, the costs of intensive and detailed interventions must be weighed against their potential benefit.

Figure 2. Change in glucose monitoring, lipid monitoring, and rates of newly diagnosed type 2 diabetes over time, described as the percent of patients without monitoring within 12 months after an antipsychotic claim. Patients with dual eligibility and prior evidence of diabetes were excluded.

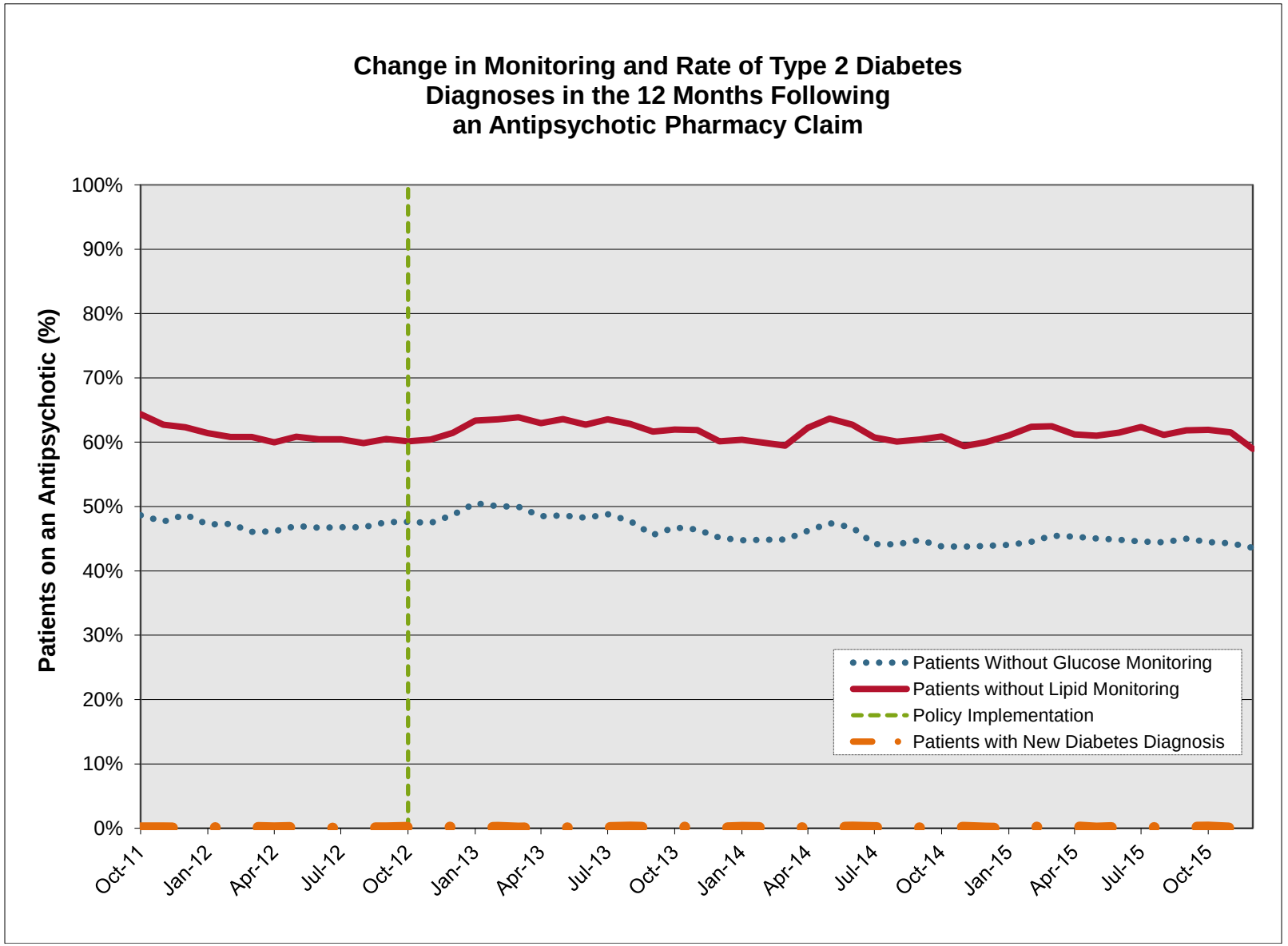


Table 1. Subgroup analysis of glucose or HbA1c monitoring rates categorized by baseline demographics.

Author: Servid

Date: May 2017

	Before Program				After Program				
	Population Characteristics		Population Without Monitoring		Population Characteristics		Population Without Monitoring		Change in Monitoring Rates
N=	**4,132**		**2,237**	54.1%	**3,838**		**1,929**	50.3%	4.2%
Mean age (range)	12.7	(1-18)	11.9	(1-18)	12.8	(2-18)	12.1	(3-18)	
0-5	143	3.5%	114	79.7%	114	3.0%	81	71.1%	8.7%
6-9	802	19.4%	535	66.7%	708	18.4%	470	66.4%	0.3%
10-15	2,002	48.5%	1,100	54.9%	1,936	50.4%	939	48.5%	6.4%
16-18	1,185	28.7%	488	41.2%	1,080	28.1%	439	40.6%	0.5%
Female	1,353	32.7%	643	47.5%	1,266	33.0%	564	44.5%	3.0%
White	2,698	65.3%	1,481	54.9%	2,423	63.1%	1,229	50.7%	4.2%
Duration									
Short-term (PDC <33%)	905	21.9%	521	57.6%	881	23.0%	470	53.3%	4.2%
Intermittent (PDC 33-80%)	1,357	32.8%	763	56.2%	1,282	33.4%	693	54.1%	2.2%
Long-term (PDC >80%)	1,870	45.3%	953	51.0%	1,675	43.6%	766	45.7%	5.2%
High dose (> maximum FDA approved dose)	177	4.3%	85	48.0%	182	4.7%	75	41.2%	6.8%

Note: Max dose and age range calculations taken on index claim only

Table 2. Subgroup analysis of glucose or HbA1c monitoring rates categorized by diagnosis. Patients may have more than one diagnoses.

	Before Program				After Program				
	Population Characteristics		Population Without Monitoring		Population Characteristics		Population Without Monitoring		Change in Monitoring Rates
N=	4,132		2,237	54.1%	3,838		1,929	50.3%	4.2%
ADHD	4,190	101.4%	2,358	56.3%	3,905	101.7%	1,947	49.9%	6.4%
Adjustment and Acute Reactions	3,096	74.9%	1,535	49.6%	2,698	70.3%	1,273	47.2%	2.4%
Affective Disorders, Excluding Bipolar	3,252	78.7%	1,376	42.3%	3,429	89.3%	1,385	40.4%	1.9%
Autism Spectrum Disorders	1,025	24.8%	539	52.6%	1,287	33.5%	646	50.2%	2.4%
Bipolar	213	5.2%	60	28.2%	205	5.3%	56	27.3%	0.9%
Developmental Disorders	1,384	33.5%	733	53.0%	1,269	33.1%	599	47.2%	5.8%

Disruptive Behavior Disorders	1,457	35.3%	702	48.2%	1,390	36.2%	608	43.7%	4.4%
Other Mental Health Diagnosis	973	23.5%	291	29.9%	1,121	29.2%	329	29.3%	0.6%
Other Psychotic Disorders	3,040	73.6%	1,273	41.9%	2,972	77.4%	1,176	39.6%	2.3%
Personality Disorders	223	5.4%	77	34.5%	347	9.0%	123	35.4%	-0.9%
PTSD	2,139	51.8%	933	43.6%	2,012	52.4%	744	37.0%	6.6%
Schizophrenia	338	8.2%	94	27.8%	308	8.0%	107	34.7%	-6.9%
Sleep Disorders	285	6.9%	159	55.8%	309	8.1%	154	49.8%	6.0%

Table 3. Subgroup analysis of glucose or HbA1c monitoring rates categorized by medications.

	Before Program				After Program				
	Population Characteristics		Population Without Monitoring		Population Characteristics		Population Without Monitoring		Change in Monitoring Rates
N=	4,132		2,237	54.1%	3,838		1,929	50.3%	4.2%
Antipsychotics, 1st Gen	31	0.8%	14	45.2%	47	1.2%	18	38.3%	6.9%
Antipsychotics, 2nd Gen									
ARIPIPRAZOLE	1,299	31.4%	635	48.9%	1,178	30.7%	532	45.2%	3.7%
OLANZAPINE	223	5.4%	82	36.8%	249	6.5%	85	34.1%	2.6%
QUETIAPINE FUMARATE	569	13.8%	259	45.5%	455	11.9%	208	45.7%	-0.2%
RISPERIDONE	1,808	43.8%	1,172	64.8%	1,710	44.6%	1,004	58.7%	6.1%
ZIPRASIDONE HCL	147	3.6%	54	36.7%	126	3.3%	51	40.5%	-3.7%
OTHER	51	1.2%	19	37.3%	65	1.7%	25	38.5%	-1.2%
Antipsychotics, Parenteral	4	0.1%	2	50.0%	8	0.2%	6	75.0%	-25.0%

Table 4. Provider specialty subgroup analyses of glucose or HbA1c monitoring rates after implementation of the RetroDUR.

	Before Program				After Program				
	Population Characteristics		Population Without Monitoring		Population Characteristics		Population Without Monitoring		Change in Monitoring Rates
N=	4,132		2,237	54.1%	3,838		1,929	50.3%	4.2%
Physician-psychiatric/neurology	1,584	38.3%	728	46.0%	1,449	37.8%	672	46.4%	-0.4%
NP-psychiatry/mental health	306	7.4%	173	56.5%	398	10.4%	178	44.7%	11.8%
Physician-family medicine	207	5.0%	126	60.9%	206	5.4%	110	53.4%	7.5%
NP-family	92	2.2%	53	57.6%	70	1.8%	33	47.1%	10.5%

Facility-mental health/pediatric	21	0.5%	12	57.1%	65	1.7%	32	49.2%	7.9%
Facility-mental health	5	0.1%	1	20.0%	6	0.2%	1	16.7%	3.3%
Other	138	3.3%	83	60.1%	142	3.7%	84	59.2%	1.0%
Unavailable	1,779	43.1%	1,061	59.6%	1,502	39.1%	819	54.5%	5.1%

Limitations:

Several limitations exist as a result of the retrospective nature of this study. First, data is based on claims history which may not accurately reflect true patient diagnoses or correlate with actual medication adherence. Use of proportion of days covered attempts to estimate the frequency which a patient takes a prescription, but accuracy of this method has not been validated. Second, provider specialization was identified using the National Provider Identifier (NPI) number and the associated taxonomy which may be inaccurate, out-of-date, or incomplete for some providers. The retrospective nature of the study also does not allow for potential unknown confounders which may influence results of the analysis. Potential confounders include changes in the population over time or changes in the general monitoring patterns of providers. It is unclear whether the small change observed after implementation of the policy was a result of the policy or simply a gradual change in practice over time. Estimates of maximum pediatric dose were made based on approved FDA dosing. However, many antipsychotics don't have data supporting dose in pediatric patients. If data are available, doses are often based on weight or age. If pediatric dosing data was lacking, the maximum adult dose was used which may not be appropriate for all children and may result in overestimated maximum doses.

References:

1. Drug Use Research and Management Program. Metabolic Monitoring of Antipsychotics in Children. 2013; http://www.orpdl.org/drugs/drugclass.php?cid=1074. Accessed September 21, 2016.
2. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care.* 2004;27(2):596-601.
3. Zimmet P, Alberti KGMM, Kaufman F, et al. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatr Diabetes.* 2007;8(5):299-306.
4. American Academy of Child and Adolescent Psychiatry. Practice Parameter for the use of atypical antipsychotic medications in children and adolescents. 2011; http://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx. Accessed October 18, 2016.
5. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic Screening After the American Diabetes Association's Consensus Statement on Antipsychotic Drugs and Diabetes. *Diabetes Care.* 2009;32(6):1037-1042.
6. Morrato EH, Nicol GE, Maahs D, et al. Metabolic screening in children receiving antipsychotic drug treatment. *Arch Pediatr Adolesc Med.* 2010;164(4):344-351.
7. Edelsohn GA, Parthasarathy M, Terhorst L, Karpov IO, Schuster J. Measurement of Metabolic Monitoring in Youth and Adult Medicaid Recipients Prescribed Antipsychotics. *J Manag Care Spec Pharm.* 2015;21(9):769-777, 777a-777cc.
8. Connolly JG, Toomey TJ, Schneeweiss MC. Metabolic monitoring for youths initiating use of second-generation antipsychotics, 2003-2011. *Psychiatr Serv.* 2015;66(6):604-609.
9. Cotes RO, de Nesnera A, Kelly M, et al. Antipsychotic Cardiometabolic Side Effect Monitoring in a State Community Mental Health System. *Community Ment Health J.* 2015;51(6):685-694.
10. Barnes TR, Bhatti SF, Adroer R, Paton C. Screening for the metabolic side effects of antipsychotic medication: findings of a 6-year quality improvement programme in the UK. *BMJ Open.* 2015;5(10):e007633.

Table A1: Antipsychotics included in the RetroDUR grouped by PDL class. If pediatric dosing was unavailable, maximum dose in adults was used.

Medication	Maximum FDA approved dose
1st Generation	
- Chlorpromazine HCl	500 mg/day
- Fluphenazine HCl	40 mg/day
- Haloperidol	15 mg/day
- Haloperidol lactate	15 mg/day
- Loxapine	250 mg/day
- Loxapine succinate	250 mg/day
- Perphenazine	8 mg/day
- Pimozide	10 mg/day
- Thioridazine HCl	800 mg/day
- Thiothixene	60 mg/day
- Trifluroperazine HCl	15 mg/day 40 mg/day
2nd Generation	
- Asenapine maleate	20 mg/day
- Aripiprazole	20 mg/day
- Brexpiprazole	4 mg/day
- Cariprazine HCl	6 mg/day
- Clozapine	900 mg/day
- Iloperidone	24 mg/day
- Lurasidone HCl	160 mg/day
- Olanzapine	20 mg/day
- Paliperidone	12 mg/day
- Quetiapine fumarate	800 mg/day
- Risperidone	3 mg/day
- Ziprasidone	160 mg/day
Parenteral Antipsychotics	
- Aripiprazole	30 mg/day, 400 mg/month
- Aripiprazole lauroxil	882 mg/month
- Chlorpromazine HCl	40 mg/day (Age <5 years), 75 mg/day (Age 5-12 years), 500 mg/day (Age > 12 years)
- Fluphenazine decanoate	100 mg/month
- Fluphenazine HCl	10 mg/day

- Haloperidol Decanoate	450 mg/month
- Haloperidol lactate	20 mg/day
- Olanzapine	30 mg/day
- Olanzapine pamoate	300 mg every 2 weeks, 405 mg/month
- Paliperidone palmitate	234 mg/month
- Risperidone microspheres	50 mg every 2 weeks
- Ziprasidone mesylate	40 mg/day
Miscellaneous Classes	
- Molindone HCl	225 mg/day
- Olanzapine/fluoxetine	12/50 mg/day
- Perphenazine/amitriptyline	12 mg/day perphenazine
- Prochlorperazine	25 mg/day

Table A2. CPT codes used to identify metabolic screening

Description	CPT
Glucose tests	80047 basic metabolic panel w/calcium, ionized 80048 basic metabolic panel w/calcium, total 80050 general health panel 80053 comprehensive metabolic panel 80069 renal function panel 82947 glucose assay 82948 reagent strip/blood glucose 82950 glucose test 82951 glucose tolerance test 82952 glucose tolerance test –added samples 82962 glucose test (home use)
HbA1c	83036 A1c 83037 A1c home use
Lipid tests	84478 triglycerides 82465 serum cholesterol 80061 lipid panel 83718 direct lipoprotein (HDL) 83704 lipoprotein bld, by NMR 83701 lipoportein bld, high resolution fractionation 83700 lipoprotein bld, electrophoretic 83721 LDL cholesterol 83719 blood lipoprotein (VLDL)

Table A3. Diabetic medications included in the RetroDUR to evaluate diagnosis of diabetes mellitus

DPP-4 inhibitors
- SITAGLIPTIN PHOS/METFORMIN HCL

- SITAGLIPTIN PHOSPHATE
- ALOGLIPTIN BENZ/METFORMIN HCL
- ALOGLIPTIN BENZ/PIOGLITAZONE
- ALOGLIPTIN BENZOATE
- LINAGLIPTIN
- LINAGLIPTIN/METFORMIN HCL
- SAXAGLIPTIN HCL
- SAXAGLIPTIN HCL/METFORMIN HCL
- SITAGLIPTIN PHOS/METFORMIN HCL

GLP-1 receptor agonists
- EXENATIDE
- ALBIGLUTIDE
- DULAGLUTIDE
- EXENATIDE MICROSPHERES
- LIRAGLUTIDE

Insulins
- INSULIN ASPART
- INSULIN ASPART PROT/INSULN ASP
- INSULIN DETEMIR
- INSULIN GLARGINE,HUM.REC.ANLOG
- INSULIN LISPRO
- INSULIN LISPRO PROTAMIN/LISPRO
- INSULIN NPH HUM/REG INSULIN HM
- INSULIN NPH HUMAN ISOPHANE
- INSULIN REGULAR, HUMAN
- INSULIN ZINC HUMAN RECOMBINANT
- INSULIN DEGLUDEC
- INSULIN DETEMIR
- INSULIN GLARGINE,HUM.REC.ANLOG
- INSULIN GLULISINE

SGLT-2 Inhibitors
- CANAGLIFLOZIN
- CANAGLIFLOZIN/METFORMIN HCL
- DAPAGLIFLOZIN PROPANEDIOL
- DAPAGLIFLOZIN/METFORMIN HCL
- EMPAGLIFLOZIN
- EMPAGLIFLOZIN/LINAGLIPTIN
- EMPAGLIFLOZIN/METFORMIN HCL

Sulfonylureas
- GLIMEPIRIDE
- GLIPIZIDE
- GLYBURIDE
- CHLORPROPAMIDE
- GLYBURIDE,MICRONIZED
- TOLAZAMIDE
- TOLBUTAMIDE

Thiazolidinediones - PIOGLITAZONE HCL - PIOGLITAZONE HCL/GLIMEPIRIDE - PIOGLITAZONE HCL/METFORMIN HCL - ROSIGLITAZONE MALEATE
Miscellaneous Antidiabetic Agents - ACARBOSE - GLIPIZIDE/METFORMIN HCL - GLYBURIDE/METFORMIN HCL - MIGLITOL - NATEGLINIDE - PRAMLINTIDE ACETATE - REPAGLINIDE - REPAGLINIDE/METFORMIN HCL

Table A4. ICD codes to identify diabetes

Category	ICD Version	Code	Description
Diabetes Mellitus	9	357.2	Polyneuropathy in diabetes
Diabetes Mellitus	9	250.x	Diabetes mellitus
Diabetes Mellitus	9	249.x	Secondary diabetes mellitus
Diabetes Mellitus	9	790.2x	Abnormal glucose
Diabetes Mellitus	9	648.0x	Diabetes mellitus complicating pregnancy childbirth or the puerperium
Diabetes Mellitus	9	648.8x	Abnormal glucose tolerance of mother complicating pregnancy childbirth or the puerperium
Diabetes Mellitus	9	362.0x	Diabetic retinopathy
Diabetes Mellitus	10	E09.x	Drug or chemical induced diabetes mellitus
Diabetes Mellitus	10	E11.x	Type 2 diabetes mellitus
Diabetes Mellitus	10	E13.x	Other specified diabetes mellitus
Diabetes Mellitus	10	O24.x	Diabetes mellitus in pregnancy, childbirth and the puerperium (Type 1 and 2)

Table A5. Claim/encounter data used to identify visit type

Description	CPT code	UB Revenue
Outpatient visit	99201-99205, 99211-99215, 99217-99220, 99241-99245, 99341-99345, 99347-99350, 99384-99387, 99394-99397, 99401-99404, 99411, 99412, 99420, 99429, 99455, 99456	051x, 0520-0523, 0526-0529, 057x-059x, 082x-085x, 088x, 0982, 0983
Nonacute inpatient visit	99304-99310, 99315, 99316, 99318, 99324-99328, 99334-99337	0118, 0128, 0138, 0148, 0158, 019x, 0524, 0525, 055x, 066x
Acute inpatient visit	99221-99223, 99231-99233, 99238, 99239, 99251-99255, 99291	010x, 0110-0114, 0119, 0120-0124, 0129, 0130-0134, 0139, 0140-0144, 0149, 0150-0154, 0159, 016x, 020x,021x, 072x, 080x, 0987
ED visit	99281-99285	045x, 0981

Table A6. Diagnosis codes used to identify mental health disorders.

Category	ICD-9 Code	Description
ADHD	3140	Attention deficit disorder of childhood
ADHD	31400	Attention deficit disorder without mention of hyperactivity
ADHD	31401	Attention deficit disorder with hyperactivity
ADHD	3149	Unspecified hyperkinetic syndrome
Adjustment and Acute Reactions	308	Acute reaction to stress
Adjustment and Acute Reactions	3080	Predominant disturbance of emotions
Adjustment and Acute Reactions	3081	Predominant disturbance of consciousness
Adjustment and Acute Reactions	3082	Predominant psychomotor disturbance
Adjustment and Acute Reactions	3083	Other acute reactions to stress
Adjustment and Acute Reactions	30830	DSM other acute reactions to stress
Adjustment and Acute Reactions	3084	Mixed disorders as reaction to stress
Adjustment and Acute Reactions	3089	Unspecified acute reaction to stress
Adjustment and Acute Reactions	309	Adjustment reaction
Adjustment and Acute Reactions	3090	Adjustment disorder with depressed mood
Adjustment and Acute Reactions	30900	DSM brief depressive reaction
Adjustment and Acute Reactions	3091	Prolonged depressive reaction
Adjustment and Acute Reactions	3092	Predominant disturbance other emotions as adjustment reaction
Adjustment and Acute Reactions	30921	Separation anxiety disorder
Adjustment and Acute Reactions	30922	Emancipation disorder of adolescence and early adult life
Adjustment and Acute Reactions	30923	Specific academic or work inhibition
Adjustment and Acute Reactions	30924	Adjustment disorder with anxiety
Adjustment and Acute Reactions	30928	Adjustment disorder with mixed anxiety and depressed mood
Adjustment and Acute Reactions	30929	Other adjustment reactions with predominant disturbance of other emotions
Adjustment and Acute Reactions	3093	Adjustment disorder with disturbance of conduct
Adjustment and Acute Reactions	30930	DSM adjustment reaction disorder
Adjustment and Acute Reactions	3094	Adjustment disorder with mixed disturbance of emotions and conduct
Adjustment and Acute Reactions	30940	DSM adjustment reaction disorder
Adjustment and Acute Reactions	3098	Other specified adjustment reactions
Adjustment and Acute Reactions	30982	Adjustment reaction with physical symptoms
Adjustment and Acute Reactions	30983	Adjustment reaction with withdrawal
Adjustment and Acute Reactions	30989	Other specified adjustment reactions
Adjustment and Acute Reactions	3099	Unspecified adjustment reaction
Adjustment and Acute Reactions	30990	DSM unspecified adjustment reaction
Adjustment and Acute Reactions	313	Disturbance emotions specific to childhood & adolescence
Adjustment and Acute Reactions	3130	Overanxious disorder specific to childhood & adolescence
Adjustment and Acute Reactions	31300	DSM overanxious disorder of childhood & adolescence
Adjustment and Acute Reactions	3131	Misery and unhappiness disorder specific to childhood and adolescence
Adjustment and Acute Reactions	3132	Sensitivity shyness & social withdrawal disorder
Adjustment and Acute Reactions	31321	Shyness disorder of childhood
Adjustment and Acute Reactions	31322	Introverted disorder of childhood
Adjustment and Acute Reactions	31323	Selective mutism

Adjustment and Acute Reactions	3133	Relationship problems specific to childhood and adolescence
Adjustment and Acute Reactions	3138	Other/mixed emotional disturb child/adolescence
Adjustment and Acute Reactions	31381	Oppositional defiant disorder
Adjustment and Acute Reactions	31382	Identity disorder of childhood or adolescence
Adjustment and Acute Reactions	31383	Academic underachievement disorder of childhood or adolescence
Adjustment and Acute Reactions	31389	Other emotional disturbances of childhood or adolescence
Adjustment and Acute Reactions	3139	Unspecified emotional disturbance of childhood or adolescence
Affective Disorders, Excluding Bipolar	2962	Major depressive disorder single episode
Affective Disorders, Excluding Bipolar	29620	Major depressive affective disorder, single episode, unspecified
Affective Disorders, Excluding Bipolar	29621	Major depressive affective disorder, single episode, mild
Affective Disorders, Excluding Bipolar	29622	Major depressive affective disorder, single episode, moderate
Affective Disorders, Excluding Bipolar	29623	Major depressive affective disorder, single episode, severe, without mention of psychotic behavior
Affective Disorders, Excluding Bipolar	29624	Major depressive affective disorder, single episode, severe, specified as with psychotic behavior
Affective Disorders, Excluding Bipolar	29625	Major depressive affective disorder, single episode, in partial or unspecified remission
Affective Disorders, Excluding Bipolar	29626	Major depressive affective disorder, single episode, in full remission
Affective Disorders, Excluding Bipolar	2963	Major depressive disorder recurrent episode
Affective Disorders, Excluding Bipolar	29630	Major depressive affective disorder, recurrent episode, unspecified
Affective Disorders, Excluding Bipolar	29631	Major depressive affective disorder, recurrent episode, mild
Affective Disorders, Excluding Bipolar	29632	Major depressive affective disorder, recurrent episode, moderate
Affective Disorders, Excluding Bipolar	29633	Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior
Affective Disorders, Excluding Bipolar	29634	Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior
Affective Disorders, Excluding Bipolar	29635	Major depressive affective disorder, recurrent episode, in partial or unspecified remission
Affective Disorders, Excluding Bipolar	29636	Major depressive affective disorder, recurrent episode, in full remission
Affective Disorders, Excluding Bipolar	2980	Depressive type psychosis
Affective Disorders, Excluding Bipolar	30000	Anxiety state, unspecified
Affective Disorders, Excluding Bipolar	30001	Panic disorder without agoraphobia
Affective Disorders, Excluding Bipolar	30002	Generalized anxiety disorder
Affective Disorders, Excluding Bipolar	30009	Other anxiety states
Affective Disorders, Excluding Bipolar	3004	Dysthymic disorder
Affective Disorders, Excluding Bipolar	30040	DSM neurotic depression
Affective Disorders, Excluding Bipolar	30113	Cyclothymic disorder
Affective Disorders, Excluding Bipolar	311	Depressive disorder, not elsewhere classified
Autism Spectrum Disorders	2990	Autistic disorder
Autism Spectrum Disorders	29900	Autistic disorder, current or active state
Autism Spectrum Disorders	29901	Autistic disorder, residual state
Bipolar	2960	Bipolar I disorder single manic episode
Bipolar	2961	Manic disorder, recurrent episode
Bipolar	2964	Bipolar I disorder most recent episode manic
Bipolar	2965	Bipolar I disorder most recent episode depressed
Bipolar	2966	Bipolar I disorder most recent episode mixed
Bipolar	2967	Bipolar I disorder, most recent episode (or current) unspecified
Bipolar	2968	Other and unspecified bipolar disorders
Developmental Disorders	315	Specific delays in development
Developmental Disorders	3150	Specific developmental reading disorder

Developmental Disorders	31500	Developmental reading disorder, unspecified
Developmental Disorders	31501	Alexia
Developmental Disorders	31502	Developmental dyslexia
Developmental Disorders	31509	Other specific developmental reading disorder
Developmental Disorders	3151	Mathematics disorder
Developmental Disorders	31510	DSM specific arithmetic disorder
Developmental Disorders	3152	Other specific developmental learning difficulties
Developmental Disorders	3153	Developmental speech or language disorder
Developmental Disorders	31531	Expressive language disorder
Developmental Disorders	31532	Mixed receptive-expressive language disorder
Developmental Disorders	31534	Speech and language developmental delay due to hearing loss
Developmental Disorders	31535	Childhood onset fluency disorder
Developmental Disorders	31539	Other developmental speech or language disorder
Developmental Disorders	3154	Developmental coordination disorder
Developmental Disorders	3155	Mixed development disorder
Developmental Disorders	31550	DSM mixed specific develop dis
Developmental Disorders	3158	Other specified delays in development
Developmental Disorders	3159	Unspecified delay in development
Developmental Disorders	31590	DSM unspecified delays in development
Developmental Disorders	316	Psychic factors associated with diseases classified elsewhere
Developmental Disorders	3160	Psychic factors associated with diseases classified elsewhere
Developmental Disorders	31600	DSM psychic factors associated with diseases classified elsewhere
Developmental Disorders	317	Mild intellectual disabilities
Developmental Disorders	318	Other specified mental retardation
Developmental Disorders	3180	Moderate intellectual disabilities
Developmental Disorders	31800	DSM moderate mental retardation
Developmental Disorders	3181	Severe intellectual disabilities
Developmental Disorders	31810	DSM severe mental retardation
Developmental Disorders	3182	Profound intellectual disabilities
Developmental Disorders	31820	DSM profound mental retardation
Developmental Disorders	319	Unspecified intellectual disabilities
Disruptive Behavior Disorders	3120	Undersocialized conduct disorder aggressive type
Disruptive Behavior Disorders	31200	Undersocialized conduct disorder, aggressive type, unspecified
Disruptive Behavior Disorders	31201	Undersocialized conduct disorder, aggressive type, mild
Disruptive Behavior Disorders	31202	Undersocialized conduct disorder, aggressive type, moderate
Disruptive Behavior Disorders	31203	Undersocialized conduct disorder, aggressive type, severe
Disruptive Behavior Disorders	3121	Undersocialized conduct disorder unaggressive
Disruptive Behavior Disorders	31210	Undersocialized conduct disorder, unaggressive type, unspecified
Disruptive Behavior Disorders	31211	Undersocialized conduct disorder, unaggressive type, mild
Disruptive Behavior Disorders	31212	Undersocialized conduct disorder, unaggressive type, moderate
Disruptive Behavior Disorders	31213	Undersocialized conduct disorder, unaggressive type, severe
Disruptive Behavior Disorders	3122	Socialized conduct disorder
Disruptive Behavior Disorders	31220	Socialized conduct disorder, unspecified
Disruptive Behavior Disorders	31221	Socialized conduct disorder, mild

Disruptive Behavior Disorders	31222	Socialized conduct disorder, moderate
Disruptive Behavior Disorders	31223	Socialized conduct disorder, severe
Disruptive Behavior Disorders	3123	Disorders of impulse control NEC
Disruptive Behavior Disorders	31230	Impulse control disorder, unspecified
Disruptive Behavior Disorders	31231	Pathological gambling
Disruptive Behavior Disorders	31232	Kleptomania
Disruptive Behavior Disorders	31233	Pyromania
Disruptive Behavior Disorders	31234	Intermittent explosive disorder
Disruptive Behavior Disorders	31235	Isolated explosive disorder
Disruptive Behavior Disorders	31239	Other disorders of impulse control
Disruptive Behavior Disorders	3124	Mixed disturbance of conduct and emotions
Disruptive Behavior Disorders	3128	Other specified disturbances of conduct NEC
Disruptive Behavior Disorders	31281	Conduct disorder, childhood onset type
Disruptive Behavior Disorders	31282	Conduct disorder, adolescent onset type
Disruptive Behavior Disorders	31289	Other conduct disorder
Disruptive Behavior Disorders	3129	Unspecified disturbance of conduct
Disruptive Behavior Disorders	V40	Mental and behavioral problems
Disruptive Behavior Disorders	V403	Other behavioral problems
Disruptive Behavior Disorders	V4039	Other specified behavioral problem
Disruptive Behavior Disorders	V409	Unspecified mental or behavioral problem
Other Mental Health Diagnosis	2930	Delirium due to conditions classified elsewhere
Other Mental Health Diagnosis	2931	Subacute delirium
Other Mental Health Diagnosis	3003	Obsessive-compulsive disorders
Other Mental Health Diagnosis	30081	Somatization disorder
Other Mental Health Diagnosis	30082	Undifferentiated somatoform disorder
Other Mental Health Diagnosis	3009	Unspecified nonpsychotic mental disorder
Other Mental Health Diagnosis	3014	Obsessive-compulsive personality disorder
Other Mental Health Diagnosis	306	Physiological malfunction arise from mental factors
Other Mental Health Diagnosis	3060	Musculoskeletal malfunction arising from mental factors
Other Mental Health Diagnosis	3061	Respiratory malfunction arising from mental factors
Other Mental Health Diagnosis	3062	Cardiovascular malfunction arising from mental factors
Other Mental Health Diagnosis	3063	Skin disorder arising from mental factors
Other Mental Health Diagnosis	3064	Gastrointestinal malfunction arising from mental factors
Other Mental Health Diagnosis	3066	Endocrine disorder arising from mental factors
Other Mental Health Diagnosis	3067	Disorder of organs of special sense arising from mental factors
Other Mental Health Diagnosis	3068	Other specified psychophysiological malfunction
Other Mental Health Diagnosis	3069	Unspecified psychophysiological malfunction
Other Mental Health Diagnosis	3071	Anorexia nervosa
Other Mental Health Diagnosis	30751	Bulimia nervosa
Other Mental Health Diagnosis	3077	Encopresis
Other Mental Health Diagnosis	V6284	Suicidal ideation
Other Psychotic Disorders	2938	Other spec transient mental d/o due conditions classified elsewhere
Other Psychotic Disorders	29381	Psychotic disorder with delusions in conditions classified elsewhere
Other Psychotic Disorders	29382	Psychotic disorder with hallucinations in conditions classified elsewhere

Other Psychotic Disorders	29383	Mood disorder in conditions classified elsewhere
Other Psychotic Disorders	29384	Anxiety disorder in conditions classified elsewhere
Other Psychotic Disorders	29389	Other specified transient mental disorders due to conditions classified elsewhere, other
Other Psychotic Disorders	2969	Other and unspecified episodic mood disorder
Other Psychotic Disorders	29690	Unspecified episodic mood disorder
Other Psychotic Disorders	29699	Other specified episodic mood disorder
Other Psychotic Disorders	2971	Delusional disorder
Other Psychotic Disorders	2973	Shared psychotic disorder
Other Psychotic Disorders	2978	Other specified paranoid states
Other Psychotic Disorders	2979	Unspecified paranoid state
Other Psychotic Disorders	2981	Excitative type psychosis
Other Psychotic Disorders	2983	Acute paranoid reaction
Other Psychotic Disorders	2988	Other and unspecified reactive psychosis
Other Psychotic Disorders	2989	Unspecified psychosis
Other Psychotic Disorders	29890	DSM unspecified atypical psychosis
Other Psychotic Disorders	29910	Childhood disintegrative disorder, current or active state
Other Psychotic Disorders	2998	Other spec pervasive developmental disorders
Other Psychotic Disorders	29980	Other specified pervasive developmental disorders, current or active state
Other Psychotic Disorders	29981	Other specified pervasive developmental disorders, residual state
Other Psychotic Disorders	29990	Unspecified pervasive developmental disorder, current or active state
Other Psychotic Disorders	29991	Unspecified pervasive developmental disorder, residual state
Other Psychotic Disorders	3108	Other nonpsychotic mental disorder following organic brain damage
Other Psychotic Disorders	3109	Unspecified nonpsychotic mental disorder following organic brain damage
Personality Disorders	3010	Paranoid personality disorder
Personality Disorders	30110	Affective personality disorder, unspecified
Personality Disorders	30112	Chronic depressive personality disorder
Personality Disorders	3013	Explosive personality disorder
Personality Disorders	30150	Histrionic personality disorder, unspecified
Personality Disorders	30159	Other histrionic personality disorder
Personality Disorders	3016	Dependent personality disorder
Personality Disorders	3017	Antisocial personality disorder
Personality Disorders	3018	Other personality disorders
Personality Disorders	30181	Narcissistic personality disorder
Personality Disorders	30182	Avoidant personality disorder
Personality Disorders	30183	Borderline personality disorder
Personality Disorders	30184	Passive-aggressive personality
Personality Disorders	30189	Other personality disorders
Personality Disorders	3019	Unspecified personality disorder
PTSD	30981	Posttraumatic stress disorder
Schizophrenia	295	Schizophrenic disorders
Schizophrenia	2950	Simple type schizophrenia
Schizophrenia	29500	Simple type schizophrenia, unspecified
Schizophrenia	29501	Simple type schizophrenia, subchronic
Schizophrenia	29502	Simple type schizophrenia, chronic

Schizophrenia	29503	Simple type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29504	Simple type schizophrenia, chronic with acute exacerbation
Schizophrenia	29505	Simple type schizophrenia, in remission
Schizophrenia	2951	Disorganized type schizophrenia
Schizophrenia	29510	Disorganized type schizophrenia, unspecified
Schizophrenia	29511	Disorganized type schizophrenia, subchronic
Schizophrenia	29512	Disorganized type schizophrenia, chronic
Schizophrenia	29513	Disorganized type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29514	Disorganized type schizophrenia, chronic with acute exacerbation
Schizophrenia	29515	Disorganized type schizophrenia, in remission
Schizophrenia	2952	Catatonic type schizophrenia
Schizophrenia	29520	Catatonic type schizophrenia, unspecified
Schizophrenia	29521	Catatonic type schizophrenia, subchronic
Schizophrenia	29522	Catatonic type schizophrenia, chronic
Schizophrenia	29523	Catatonic type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29524	Catatonic type schizophrenia, chronic with acute exacerbation
Schizophrenia	29525	Catatonic type schizophrenia, in remission
Schizophrenia	2953	Paranoid type schizophrenia
Schizophrenia	29530	Paranoid type schizophrenia, unspecified
Schizophrenia	29531	Paranoid type schizophrenia, subchronic
Schizophrenia	29532	Paranoid type schizophrenia, chronic
Schizophrenia	29533	Paranoid type schizophrenia, subchronic with acute exacerbation
Schizophrenia	29534	Paranoid type schizophrenia, chronic with acute exacerbation
Schizophrenia	29535	Paranoid type schizophrenia, in remission
Schizophrenia	2954	Schizophreniform disorder
Schizophrenia	29540	Schizophreniform disorder, unspecified
Schizophrenia	29541	Schizophreniform disorder, subchronic
Schizophrenia	29542	Schizophreniform disorder, chronic
Schizophrenia	29543	Schizophreniform disorder, subchronic with acute exacerbation
Schizophrenia	29544	Schizophreniform disorder, chronic with acute exacerbation
Schizophrenia	29545	Schizophreniform disorder, in remission
Schizophrenia	2955	Latent schizophrenia
Schizophrenia	29550	Latent schizophrenia, unspecified
Schizophrenia	29551	Latent schizophrenia, subchronic
Schizophrenia	29552	Latent schizophrenia, chronic
Schizophrenia	29553	Latent schizophrenia, subchronic with acute exacerbation
Schizophrenia	29554	Latent schizophrenia, chronic with acute exacerbation
Schizophrenia	29555	Latent schizophrenia, in remission
Schizophrenia	2956	Schizophrenic disorders residual type
Schizophrenia	29560	Schizophrenic disorders, residual type, unspecified
Schizophrenia	29561	Schizophrenic disorders, residual type, subchronic
Schizophrenia	29562	Schizophrenic disorders, residual type, chronic
Schizophrenia	29563	Schizophrenic disorders, residual type, subchronic with acute exacerbation
Schizophrenia	29564	Schizophrenic disorders, residual type, chronic with acute exacerbation

Schizophrenia	29565	Schizophrenic disorders, residual type, in remission
Schizophrenia	2957	Schizoaffective disorder
Schizophrenia	29570	Schizoaffective disorder, unspecified
Schizophrenia	29571	Schizoaffective disorder, subchronic
Schizophrenia	29572	Schizoaffective disorder, chronic
Schizophrenia	29573	Schizoaffective disorder, subchronic with acute exacerbation
Schizophrenia	29574	Schizoaffective disorder, chronic with acute exacerbation
Schizophrenia	29575	Schizoaffective disorder, in remission
Schizophrenia	2958	Other specified types of schizophrenia
Schizophrenia	29580	Other specified types of schizophrenia, unspecified
Schizophrenia	29581	Other specified types of schizophrenia, subchronic
Schizophrenia	29582	Other specified types of schizophrenia, chronic
Schizophrenia	29583	Other specified types of schizophrenia, subchronic with acute exacerbation
Schizophrenia	29584	Other specified types of schizophrenia, chronic with acute exacerbation
Schizophrenia	29585	Other specified types of schizophrenia, in remission
Schizophrenia	2959	Unspecified schizophrenia
Schizophrenia	29590	Unspecified schizophrenia, unspecified
Schizophrenia	29591	Unspecified schizophrenia, subchronic
Schizophrenia	29592	Unspecified schizophrenia, chronic
Schizophrenia	29593	Unspecified schizophrenia, subchronic with acute exacerbation
Schizophrenia	29594	Unspecified schizophrenia, chronic with acute exacerbation
Schizophrenia	29595	Unspecified schizophrenia, in remission
Sleep Disorders	3074	Specific disorders of sleep of nonorganic origin
Sleep Disorders	30740	Nonorganic sleep disorder, unspecified
Sleep Disorders	30741	Transient disorder of initiating or maintaining sleep
Sleep Disorders	30742	Persistent disorder of initiating or maintaining sleep
Sleep Disorders	30745	Circadian rhythm sleep disorder of nonorganic origin
Sleep Disorders	30746	Sleep arousal disorder
Sleep Disorders	30747	Other dysfunctions of sleep stages or arousal from sleep
Sleep Disorders	30748	Repetitive intrusions of sleep
Sleep Disorders	30749	Other specific disorders of sleep of nonorganic origin
Sleep Disorders	327	Organic sleep disorders
Sleep Disorders	3270	Organic disorders initiating & maintaining sleep
Sleep Disorders	32730	Circadian rhythm sleep disorder, unspecified
Sleep Disorders	32731	Circadian rhythm sleep disorder, delayed sleep phase type
Sleep Disorders	32732	Circadian rhythm sleep disorder, advanced sleep phase type
Sleep Disorders	32733	Circadian rhythm sleep disorder, irregular sleep-wake type
Sleep Disorders	32734	Circadian rhythm sleep disorder, free-running type
Sleep Disorders	32735	Circadian rhythm sleep disorder, jet lag type
Sleep Disorders	32737	Circadian rhythm sleep disorder in conditions classified elsewhere
Sleep Disorders	32739	Other circadian rhythm sleep disorder
Sleep Disorders	7805	Sleep disturbances
Sleep Disorders	78050	Sleep disturbance, unspecified
Sleep Disorders	V694	Lack of adequate sleep

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 Literature Scan: Anticoagulants (oral, injectable)

Date of Review: May 2017

Date of Last Review: March 2015
(Direct-acting Oral Anticoagulants, July 2016)
Literature Search: 01/16/17 – 03/01/17

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

Conclusions:

- Since the last review additional anticoagulation evidence has become available with the publication of 5 new guidelines[1–5], 8 new systematic reviews and meta-analyses[6–13], 5 randomized controlled trials[14–18] and 2 Food and Drug Administration (FDA) labeling changes.[19,20] Evidence directly comparing individual NOACs is insufficient. Recent literature refers to factor Xa inhibitors and direct thrombin inhibitors as non-vitamin K antagonist oral anticoagulants (NOACs) in place of previous direct acting oral anticoagulants (DOACs) nomenclature.
- Consistent with previous findings, low-molecular-weight heparins (LMWH) have the most evidence for venous thromboembolism (VTE) prevention in patients with cancer. A high quality systematic review of anticoagulant use for primary prophylaxis of VTE in patients with cancer receiving chemotherapy found that patients treated for a median of 10 months with LMWH had a reduced incidence of symptomatic deep vein thrombosis (DVT) compared to placebo/no treatment, 2.8% vs. 6%, respectively (ARR 3.2%; NNTB 30).[6] The results were not dependent upon LMWH used, type of cancer, dosage or treatment duration. Risk of major bleeds were not significantly different between groups (RR 1.44; 95% CI, 0.98 to 2.11; p= 0.07). In a second analysis, NOACs were found to have similar efficacy to conventional therapy (LMWH and vitamin K antagonists (VKAs)) for VTE reoccurrence in patients with cancer and VTE with an incidence rate of 3.9% and 6.0%, respectively.[7] Major bleeding occurred in 3.2% of NOAC treated patients and 4.2% of conventional therapy patients, which was not statistically different.
- In an analysis of the safety and efficacy of anticoagulants in patients undergoing orthopedic surgery, fondaparinux, rivaroxaban, and edoxaban had the highest efficacy in VTE prevention with 3.1 -5.1% less risk of VTE compared to enoxaparin (NNT 20 -40).[8] Apixaban and dabigatran were associated with the lowest risk of bleeding and fondaparinux had an 11-fold relative risk (RR) of major bleeding compared to enoxaparin, based on one trial. Limitations to this analysis include varied doses of enoxaparin and shorter duration of enoxaparin exposure versus oral comparators. These factors may bias the results in favor of enoxaparin comparators.
- In patients requiring extended (beyond 3 months) anticoagulation treatment for VTE, NOACs and VKAs were associated with VTE recurrence or death due to VTE in 1.3% of patients compared to 8.0% for placebo (RR 0.17; 95% CI, 0.12 to 0.24; p=0.0001; ARR 7%, NNT = 14). Major bleeding rates were similar in both treatment groups.[9]
- NOACs undergo anywhere from 27-80% renal excretion and are used with caution in patients with renal failure. Additionally, trials often exclude patients with renal failure limiting the evidence available in this population. A systematic review and meta-analysis found that in patients with reduced renal function

(estimated glomerular filtration rate [eGFR] < 80 mL/min) taking anticoagulants for NVAF had 1.3 times the risk of stroke and systemic embolism and 1.8 times the risk of major bleeds compared to patients with normal renal function (eGFR > 80 mL/min), regardless of anticoagulant used.[10] For patients with mild renal impairment (eCrCl >50 ml/min - 80 ml/min) NOACs were found to have a 2.7% incidence of stroke/systemic embolism compared to 3.9% incidence with warfarin (RR of 0.71; 95% CI, 0.62 to 0.81; ARR 1.2%; NNTB 83) and for moderate renal impairment (eCrCl < 50 ml/min) a 3.8% incidence of stroke/systemic embolism compared to 4.8% with warfarin (RR of 0.79; 95% CI, 0.66 to 0.94; ARR 1%; NNTB 100). Major bleeds occurred in 5.7% patients taking NOACs compared to 6.4% of warfarin treated patients with mild renal impairment (RR 0.88; 95% CI, 0.80 to 0.97) and in 7.2% of NOAC treated patients compared to 9.0% of warfarin treated patients who had moderate renal impairment (RR 0.80; 95% CI, 0.70 to 0.91).[10]

- The risk of major bleeding is a potential risk associated with the use of all anticoagulants. A systematic review and meta-analysis of patients receiving anticoagulation for non-valvular atrial fibrillation (NVAF) or VTE found NOACs to be associated with less risk of major bleeds than VKAs in patients with an eCrCl of > 50 - < 80 mL/min with an incidence of 6.6% vs. 7.6%, respectively (ARR 1.0%; NNH 100) when followed for 0.25 to 2.8 years. Major bleeding was not significantly different between the groups in patients with an eCrCl of < 50 ml/min. An indirect comparison found apixaban to have the lowest major bleeding risk in comparison to other NOACs in patients with an eCrCl of < 50 mL/min. Less risk of hemorrhagic stroke was demonstrated in patients with an eCrCl > 50 mL/min and < 80 mL/min with an incidence rate of 0.5% in patients treated with NOACs compared to 1.05% of patients treated with a VKA (RR 0.43; 95% CI, 0.33 to 0.56) .[11] In patients with an eCrCl of < 50 ml/min hemorrhagic stroke rates occurred in 1.0% of patients treated with NOACs compared to 1.5% of patients treated with a VKAs (RR 0.42; 95% CI, 30 -61; p < 0.00001). In a second analysis of patients with NVAF or VTE the risk of major bleed-related fatalities was reduced by 1-3 patients per 1000 with NOACs compared to VKAs (with or without initial LMWH) in a period of 1.0-2.8 years; however, studies were found to have a high risk of bias for this outcome.[12]
- A moderate quality systematic review and meta-analysis found NOACs to have less risk of mortality related to major bleeds, compared to warfarin, in patients treated for NVAF or VTE (RR 0.53; 95% CI, 0.43 to 0.64).[13] The case-fatality rate was 7.57% for NOACs compared to 11.05% for warfarin.
- The CHEST guidelines recommend NOACs over VKAs for acute DVT or PE treatment in patients without cancer.[1] LMWHs are recommended over NOACs and VKAs for the treatment of DVT or PE in patients with cancer.
- The National Institute for Health and Care Excellence (NICE) issued guidance on the use of edoxaban.[2,3] NICE recommends that edoxaban be considered as an option for the treatment of DVT or PE and for stroke prevention in patients with NVAF.
- Two new guidelines recommend rivaroxaban as an option in patients with non-ST-elevation acute coronary syndrome (ACS), who are also receiving aspirin and clopidogrel, based on evidence from one trial.[4,5] Patients should have no prior stroke or transient ischemic attack (TIA) history and have a low bleeding risk.
- There was insufficient evidence on subgroup populations, including evidence specifically related to Medicaid patients.

Recommendations:

- Literature evaluated in this review supports the current preferred drug list (PDL) status of therapies in the anticoagulant class.
- No further review or research is needed at this time. Evaluate comparative drug costs in executive session.

Previous Conclusions (from July 2016 direct-acting oral anticoagulants [DOACs] summary review)**:**

- There is insufficient evidence for direct comparisons of DOACs. All DOAC efficacy and safety outcome comparisons were based on indirect data.
- There is low strength of evidence that there were no differences in all-cause mortality risks between the DOACs when used in patients with non-valvular atrial fibrillation (NVAF) and in patients undergoing hip or knee replacement surgery. There was insufficient evidence to develop conclusions on all-cause mortality risk between the DOACs when used for VTE prevention during extended treatment. Mortality was not assessed in DOAC treatment for VTE.

- For the composite outcome of VTE and mortality in orthopedic patients undergoing hip or knee surgery, there is low-strength of evidence that apixaban and rivaroxaban were associated with the lowest risk when compared to once daily dabigatran based on low strength evidence. There is low strength evidence that apixaban 2.5 mg twice daily was associated with less major bleeding than rivaroxaban 10 mg daily (OR 0.35; 95% CI, 0.13 to 0.91).
- In patients with NVAF there is low strength evidence that edoxaban 30 mg is associated with a higher risk of the composite outcome of stroke or systemic embolism compared to apixaban 5 mg and dabigatran 150 mg (OR 1.38 and OR 1.64, respectively) twice daily. Rivaroxaban 20 mg daily was found to have a higher risk of stroke and systemic embolism than dabigatran twice daily (OR 1.32, 95% CI, 1.01 to 1.74) based on low strength of evidence. Apixaban and edoxaban were associated with the lowest risk of major bleeds overall compared to the other DOACs.
- For the treatment of VTE there were no differences found for DOAC comparisons based on insufficient evidence for the following outcomes: VTE recurrence, DVT and PE. There is low strength of evidence in this population that major bleeding was less with apixaban compared to edoxaban and dabigatran.
- No differences were found in VTE recurrence, all-cause mortality, acute coronary syndrome, or major bleeding when comparing apixaban, rivaroxaban and dabigatran in patients treated for prevention of recurrent VTE for an extended period (insufficient evidence). Apixaban was associated with less major bleeding than rivaroxaban and dabigatran.
- The evidence of superior efficacy or harms in patient subgroups was insufficient, preventing meaningful conclusions.

Previous Recommendations:
- Evidence supports our current PDL and no changes are recommended.
- Recommend to continue access to all DOACs without prior authorization criteria.

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

<u>Safety and Efficacy of NOACs in VTE prevention after Orthopedic Surgery</u>
The efficacy and safety of NOACs in the prevention of VTE after hip and knee arthroplasty was evaluated in a systematic review and meta-analysis.[8] Eighteen trials met the inclusion criteria of being double-blind, RCTs enrolling adult patients scheduled for hip or knee surgery and prescribed anticoagulants. All trials were graded and rated 4-5 on the Jadad scale for quality assessment, indicating high-quality. All trials were funded by the manufacturers. Included trials

evaluated apixaban, dabigatran, rivaroxaban, edoxaban or fondaparinux which were compared to enoxaparin, dosed at 40 mg once daily in most studies. The primary efficacy outcome was VTE occurrence and the primary safety outcome was the composite of major and clinically relevant bleeding.

There was insufficient evidence to perform a meta-analysis to determine mortality differences between anticoagulants due to a low incidence of death. The incidence of VTE was 4.7% with apixaban compared to 7.2% for enoxaparin (RR 0.71; 95% CI, 0.52 to 0.96; p = 0.026); however, there was significantly heterogeneity between the trials due to different dosing regimens for enoxaparin.[8] For the composite bleeding endpoint, the incidence of major/clinically relevant bleeding was 3.8% in the apixaban group compared to 4.6% in the enoxaparin group (RR 0.84; 95% CI, 0.70 to 0.99; p = 0.043). Based on data from four trials, dabigatran was found to have a similar incidence of recurrent VTE as enoxaparin. In comparisons between dabigatran 150 mg daily and enoxaparin the incidence of recurrent VTE was 18% and 15%, respectively (RR 1.19; 95% CI, 0.98 to 1.44). Recurrent VTE was 13% for both groups when dabigatran 220 mg daily was compared to enoxaparin (RR 1.04; 95% CI, 0.87 to 1.24). Incidence of the composite of major and clinically relevant bleeding and major bleeding were similar between groups. Fondaparinux was compared to enoxaparin in four trials. The risk of VTE with fondaparinux was 5% compared to 10.1% for enoxaparin (RR 0.53; 95% CI, 0.45 to 0.63; p < 0.001). No data was available for the composite analysis for bleeding but the incidence of major bleeds was 2.6% in the fondaparinux group compared to 1.71% for enoxaparin (RR 1.64; 95% CI, 0.24 to 11.2; p = 0.62).[6] Four trials were available for the rivaroxaban analysis. Different anticoagulant treatment durations were utilized in the rivaroxaban trials; 31-39 days for rivaroxaban and 10-14 days for enoxaparin. Rivaroxaban was found to have a lower incidence of VTE with a recurrence rate of 3.1% compared to 6.2% for enoxaparin (RR 0.55; 95% CI 0.46 to 0.66; p < 0.001).[8] Risk of major/clinically relevant bleeds was 3.1% for rivaroxaban compared to 2.5% for enoxaparin. Two studies provided data for edoxaban, taking place in Japan and Taiwan, so reduced dosages were used and are less applicable to the US Medicaid population. Edoxaban was shown to decrease risk of VTE compared to enoxaparin in this population.

Primary Prophylaxis of VTE in Patients with Cancer

In a 2016 Cochrane review and meta-analysis the effects of primary prophylaxis for VTE in patients with cancer, any age, and undergoing chemotherapy were studied. Five new studies were identified since the last update in 2012.[6] Therefore, a total of 26 RCTs (n=12,352) were included in the current review. Treatments included in the review were the following: semuloparin (not available in the US), LMWH (dalteparin, enoxaparin, certoparin, nadroparin, bemiparin – the last 3 treatments unavailable in the US), UFH, warfarin, antithrombin or apixaban (phase II trial). Eighteen of the studies were comparisons involving LMWH to either placebo/no prophylaxis (n=16), aspirin (n=1) or warfarin (n=1). Doses of LMWH were prophylactic in 16 trials, intermediate in one trial and therapeutic in one trial. The majority of patients had a diagnosis of locally advanced or metastatic cancer and were being treated in an ambulatory care setting. The main outcome was symptomatic VTE, objectively verified DVT or PE.

High quality evidence found thromboprophylaxis with LMWH to reduce the risk of symptomatic VTE with an incidence rate of 2.8% compared to a VTE rate of 6% with placebo/no prophylaxis (RR 0.54; 95% CI, 0.38 to 0.75; p = 0.0003; ARR 3.2%; NNTB 30), based on a pooled analysis of 9 trials with a median follow up of 10 months.[6] Funnel plot analysis found no evidence of bias. Major bleeding was not significantly different between LMWH compared to placebo/no prophylaxis based on low quality evidence (RR 1.44; 95% CI, 0.98 to 2.11; p= 0.07).[4] In an active treatment comparison of LMWH (enoxaparin 40 mg daily) versus warfarin (low dose of 1.25 mg daily) in patients with multiple myeloma, LMWH was found to reduce the risk of VTE more than warfarin (RR 0.33; 95% CI, 0.14 to 0.83).[6] LMWH and warfarin were not associated with any major bleeding. In pooled comparisons between enoxaparin 40 mg daily versus aspirin 100 mg daily, median treatment duration of 18.5 months, there was moderate evidence that enoxaparin decreased VTE more than aspirin (RR 0.51, 95% CI, 0.22 to 1.17). Results were not significantly different and precision was low as indicated by wide confidence intervals. Patients taking aspirin had less than 1% incidence of major bleeds and there were no major bleeds in the enoxaparin group. In one, small (n=328) placebo controlled trial, warfarin (INR of at least 1.5) was found to reduce the risk of symptomatic VTE more than placebo but results were not statistically significant, based on low quality evidence (RR 0.15; 95% CI, 0.02 to 1.2). A trial of semuloparin

was found to reduce the risk of symptomatic VTE compared to placebo (RR 0.36; 95% CI, 0.22 to 0.60) with no increased risk of major bleeding. Subgroup analysis suggests a decreased incidence of VTE in patients with pancreatic or lung cancer without an increased risk of bleeding. Limitations to this analysis is a small number of trials in patients treated with VKAS and doses used for prophylaxis are of unknown efficacy.

NOACs in Patients with VTE and Cancer

A recent systematic review and meta-analysis evaluated the efficacy of NOACs in patients with cancer and VTE.[7] Six studies involving 1,132 patients were included in the meta-analysis. Trial data was available for edoxaban, rivaroxaban, dabigatran and apixaban. The comparator was warfarin for all trials (with initial LMWH). Trial quality was assessed and risk of bias was reported as low (based on analysis of funnel plot inspection). The primary outcome was VTE reoccurrence based on subgroup analysis of patients with cancer that were included in original trials used for approval. This population represented 2.5% to 9.4% of total patients from original trials.

In a pooled analysis of VTE reoccurrence, NOACs were associated with 23 (3.9%) events compared to 32 (6.0%) events with conventional therapy (OR 0.63; 95% CI, 0.37 to 1.10; p = 0.10).[7] Major bleeding risk was 3.2% (n=19/587) for NOACs compared to 4.2% (n=22/527) for vitamin K comparators. Clinical relevant bleeding was seen in 85 (14.5%) patients treated with NOACs compared to 87 (16.5%) patients treated with VKAs. Patients with active cancer at higher risk of VTE may have been treated with LMWH, which represents standard therapy, which may limit the application of this analysis. Additional evidence comparing NOACs to LMWH would help to delineate the optimal treatment for VTE prevention in patients with cancer.

Extended Use of Anticoagulants for VTE

The efficacy and safety of using NOACs in patients with unprovoked VTE was the focus of a systematic review and meta-analysis.[9] Six trials met the criteria for extended anticoagulation. Included treatments were dabigatran, rivaroxaban, apixaban and warfarin. NOACs were compared to placebo (4 trials); warfarin (1 trial of dabigatran compared to warfarin); or treatment discontinuation (warfarin trial). Patients were required to receive at least 6 months of anticoagulation with a NOAC or warfarin, with trial durations lasting 6-36 months. All patients received at least 3 months of previous anticoagulation treatment. Recurrent VTE or deaths related to recurrent VTE was the primary efficacy outcome.

In placebo controlled comparisons, NOACs and warfarin decreased recurrent VTE or death due to VTE compared to placebo, with a reoccurrence rate of 1.3% compared to 8% for placebo (RR 0.17; 95% CI, 0.12 to 0.24).[9] Warfarin and dabigatran were associated with the lowest risk of VTE reoccurrence or death, 0.03 and 0.08, respectively. Risk of major bleeding was not significantly different with NOACs or warfarin compared to placebo (RR 1.15; 95% CI, 0.40 to 3.31); however, non-major clinically relevant bleeding (NMCRB) was higher in patients treated with NOACs or warfarin compared to placebo (RR 2.12; 95% CI, 1.55 to 2.90).[9] Overall study bias was deemed to be low.

Renal Function Status on Safety and Efficacy of NOACs in Patients with AF

Efficacy and safety data for the use of NOACs in patients with mild to moderate renal dysfunction taking anticoagulants for stroke prevention in patients with NVAF was studied.[10] Patients were divided into 3 groups; normal renal function (eGFR of > 80 mL/min), mild impairment (eGFR 50-80 mL/min) and moderate impairment (eGFR < 50 mL/min). Patients were over the age of 65 years with a CHADS2 score of 2.1 to 3.5. Patients treated with warfarin experienced time in therapeutic range 58-68% of the time. All comparisons were to warfarin and all US approved NOACs (apixaban, dabigatran, edoxaban and rivaroxaban) were included. Four RCTs (58,338 patients) were identified for inclusion. Trials had low degree of bias and were considered high quality. The primary efficacy endpoint was stroke or systemic embolism and the primary safety outcome was major bleeds.

Patients with reduced renal function experienced 1.3 times the risk of stroke/systemic embolism and 1.8 times the risk of major bleeds compared to patients with normal renal function, irrespective of anticoagulant used.[10] Efficacy endpoints were similar for all anticoagulants in patients with normal renal function with an incidence rate of 2% for NOACs and 2.2% for warfarin (risk ratio [RR 0.96; 95% CI, 0.81 to 1.15; p = 0.69); however, NOACs were associated with less major bleeds compared to warfarin, 3.7% vs. 4.3%, respectively (RR 0.86; 95% CI, 0.75 to 0.98; p = 0.03).[8] NOACs were found to have a reduced risk of stroke/systemic embolism compared to warfarin in patients with moderate renal dysfunction, 3.8% and 4.8%, respectively (RR 0.79; 95% CI, 0.66 to 0.94; p = 0.008). The risk of stroke/systemic embolism for patients with mild renal impairment was 2.7% for patients taking NOACs compared to 3.9% for patients taking warfarin (RR 0.71; 95% CI, 0.62 to 0.81; p < 0.00001).[10] Major bleed risk was reduced with NOAC therapy compared to warfarin in patients with mild renal impairment, 5.7% vs. 6.4%, respectively (RR 0.87; 95% CI, 0.79 to 0.95; p = 0.01) and in patients with moderate renal dysfunction with an incidence of 7.2% in the NOAC group compared to 9% in the warfarin group (RR 0.80; 95% CI, 0.71 to 0.91; p = 0.0005). Limitations to the data include high heterogeneity in studies evaluating the risk of major bleeds which can decrease the reliability of the results.

Safety

NOACs and Major Bleeding and Hemorrhagic Stroke in Patients with Renal Failure

The use of NOACs in patients with renal failure has not been extensively studied.[11] This systematic review and meta-analysis evaluated the risk of major bleeding and hemorrhagic stroke in patients with renal failure who were treated with NOACs for NVAF or VTE. Nine RCTS with 94,879 patients that were followed for 0.25 to 2.8 years were included. NOACs included in the analysis were: apixaban, edoxaban, rivaroxaban and dabigatran. All comparisons were to VKAs (warfarin). Patients were analyzed dependent upon renal function; normal renal function (estimated CrCl [eCrCl] > 80 mL/min), eCrCl > 50-< 80 mL/min or eCrCl < 50mL/min. Nine trials were identified which included 94,879 patients. Fifty-eight percent had an estimated CrCl of < 80 mL/min.

In patients with an eCrCl of > 50 mL/min and < 80 mL/min, the NOACs were associated with a decreased risk of major bleeds compared to VKAs. The incidence of major bleeds was 6.6% in the NOAC group compared to 7.6% in the warfarin group (RR 0.87; 95% CI, 0.81 to 0.93; p = 0.0001).[11] Apixaban and edoxaban were the only NOACs associated with this reduced risk in a subgroup analysis. In patients with an estimated CrCl of < 50 mL/min, NOACs were also found to be associated with less risk of major bleeding compared to VKAs with major bleeding occurring in 8.3% and 9.7%, respectively (RR 0.83; 95% CI, 0.68 to 1.02; p = 0.08). Subgroup analysis found that dabigatran and rivaroxaban were not associated with a reduced risk. In patients with an estimated CrCl of < 50 mL/min apixaban was found to have a reduced risk of major bleeding compared with other NOACs.[11] In patients with NVAF there was more risk reduction in major bleeding in patients treated with NOACs compared to VKAs in patients with an estimated CrCl of > 50 mL/min and < 80 mL/min compared to patients with an estimated CrCl of < 50 mL/min. In patients with VTE more benefit was seen with NOACs compared to VKAs in patients with an estimated CrCl of < 50 mL/min compared to patients with an estimated CrCl of > 50 and < 80 mL/min.

Hemorrhagic stroke was reduced in patients taking NOACs compared to VKAs. The incidence of hemorrhagic stroke was 0.5% in patients treated with NOACs compared to 1.1% in patients treated with VKAs in patients with an eCrCl of < 50 to > 80 mL/min (RR 0.43; 95% CI, 0.33 to 0.56; p < 0.00001; ARR 0.6%; NNH 166). Hemorrhagic stroke rates were 1% in patients treated with NOACs and 1.5% of patients treated with VKAs in patients who had an eCrCl of < 50 mL/min (RR 0.42; 95% CI, 0.30 to 0.61; p < 0.00001; ARR 0.5%; NNH 200).[11] The overall risk of bias was low for all included trials; however, there was a high degree of heterogeneity.

NOACs and Major Bleeding Fatalities

In a systematic review and meta-analysis, the risk of major bleeding-related fatalities associated with NOACs compared to VKAs (with or without initial LMWH therapy) was studied.[12] Eleven, phase 3 trials were identified in patients with AF (5 trials) and VTE (6 trials). These types of trials were chosen so that medium-term

to long-term anticoagulation could be accessed. Longer treatment durations are required due to low rates of fatal events. All US approved NOACs were included (dabigatran, apixaban, edoxaban and rivaroxaban). A majority (73%) of patients had an AF diagnosis. The mean age was 71 years for AF patients and 56 for VTE patients. The primary outcome was overall mortality associated with major bleeding events.

Major bleeding fatalities occurred in 121 patients with AF taking NOACs compared to 152 taking VKAs (OR 0.53; 95% CI, 0.42 to 0.68; 3 events avoided per 1000 patients treated over 1-2.8 years).[12] In patients with VTE, the incidence rate of fatalities for NOACs was 7 compared to 22 for VKAs (OR 0.36; 95% CI, 0.15 to 0.85; 1 event avoided per 1000 patients over 6 months). Overall, trials were found to have a low to moderate risk of bias, except for adjusted estimates for fatal bleeding, in which all trials were considered to have a high risk of bias.

Mortality Outcomes with NOACs

A second meta-analysis and systematic review focused on mortality comparisons between NOACS and VKAs.[13] Thirteen trials in patients with NVAF and VTE were included in the analysis. NOAC treatments included: apixaban, dabigatran, edoxaban and rivaroxaban. Trial durations ranged from 6-30 months and 8 were designated as high quality. All trials were at low risk of publication bias based on funnel plot analysis. The primary outcome was case-fatality rate. The case-fatality rate is calculated by the number of fatal bleeds divided by the number of major bleeds expressed as a percentage.

NOACs were associated with a major bleeding case-fatality rate of 7.57% compared to 11.05% for patients taking warfarin based on 12 trials. Fatal bleeding comparisons between NOACS and warfarin demonstrated less fatal bleeds in the NOAC group (RR 0.53; 95% CI, 0.43 to 0.64).[13] Limitations to this analysis include conflicts of interest between the authors and pharmaceutical manufacturers.

New Guidelines:

CHEST Guideline: Antithrombotic Therapy for VTE

The 9th edition of antithrombotic therapy and VTE published by CHEST was updated in 2016. Recommendations are considered strong (Grade 1) or weak (Grade 2) based on the evidence quality, delineated as high (Grade A), moderate (Grade B) or low (Grade C).[1] Recommendations regarding treatment selection and duration of treatment are presented in Table 1.

Table 1. Treatment Recommendations for VTE[1]

Indication	Recommendation	Grade
- Acute proximal DVT or PE and no cancer requiring long-term (first 3 months) anticoagulant therapy	- Dabigatran, rivaroxaban, apixaban or edoxaban over vitamin K antagonists*	Grade 2B
- Proximal DVT or PE and no cancer not treated with dabigatran, rivaroxaban, apixaban, or edoxaban	- Vitamin K antagonists over LMWH*	Grade 2C
- Proximal DVT or PE and cancer requiring long-term (first 3 months) anticoagulant therapy	- LMWH over VKA therapy, dabigatran, rivaroxaban, apixaban or edoxaban*	Grade 2C

- Proximal DVT or PE who receive extended therapy	- Continue current anticoagulant	Grade 2C
- Proximal DVT or PE provoked by surgery	- Treatment for 3 months over treatment for a shorter duration - Treatment over a longer time-limited† period - Extended therapy (no scheduled stop date)	Grade 1B Grade 1B Grade 1B
- Proximal DVT or PE provoked by nonsurgical transient risk factor	- Treatment for 3 months over treatment for a shorter duration - Treatment over a longer time-limited† period - Treatment for 3 months versus a longer time-limited† period if there is a low or moderate bleeding risk - Treatment for 3 months versus extended treatment if there is a high bleeding risk	Grade 1B Grade 1B Grade 2B Grade 1B
- Distal DVT provoked by surgery or by nonsurgical transient risk factor	- Treatment for 3 months over treatment for a shorter duration - Treatment for 3 months over a longer time-limited† period - Treatment for 3 months over extended therapy (no scheduled stop date)	Grade 2C Grade 1B Grade 1B
- Unprovoked DVT (isolated proximal or distal) or PE	- Treatment for at least 3 months over a shorter duration - Treatment for 3 months over treatment of a longer time-limited† duration	Grade 1B Grade 1B
- First VTE that is an unprovoked proximal DVT of the leg or PE	- If low or moderate bleeding risk, extended anticoagulation therapy is recommended - If high bleeding risk, 3 months of anticoagulation therapy over extended therapy	Grade 2B Grade 1B
- Second unprovoked VTE	- If low bleeding risk, extended anticoagulant therapy versus 3 months of therapy - If moderate bleeding risk, extended anticoagulant therapy over 3 months of therapy - High bleeding risk, 3 months of anticoagulant therapy over extended therapy	Grade 1B Grade 2B Grade 2B
- Patients with DVT or PE with active cancer	- If bleeding risk is not high, extended anticoagulation therapy over 3 months of anticoagulation - If high bleeding risk, extended anticoagulation over 3 months of therapy	Grade 1B Grade 2B
- Unprovoked proximal DVT or PE who are stopping anticoagulant therapy	- Aspirin therapy over no therapy if no contraindications to aspirin are present	Grade 2B
- Acute isolated distal DVT without severe symptoms	- Serial imaging of the deep veins for 2 weeks over anticoagulation - Anticoagulation over serial imaging if severe symptoms or risk factors for extension	Grade 2C Grade 2C

- Acute isolated distal DVT who are managed with anticoagulation	- Same treatment as for acute proximal DVT (outlined above)	Grade 1B
- Acute isolated distal DVT managed with serial imaging	- No anticoagulation if thrombus does not extend - Anticoagulation therapy if thrombus extends but remains confined to distal veins - Anticoagulation therapy if thrombus extends into the proximal veins	Grade 1B Grade 2C Grade 1B
- Subsegmental PE	- Clinical surveillance over anticoagulation if no involvement of proximal pulmonary arteries and no proximal DVT and low risk for recurrent VTE - High risk for recurrent VTE then anticoagulation is recommended over clinical surveillance	Grade 2C Grade 2C
- Upper extremity DVT	- Anticoagulation therapy over thrombolysis	Grade 2C
- Recurrent VTE on VKA or on dabigatran, apixaban, edoxaban or rivaroxaban	- Switch to LMWH at least temporarily	Grade 2C
- Recurrent VTE on LMWH	- Increase dose by one-quarter to one-third	Grade 2C
* Initial parenteral anticoagulation is given before dabigatran and edoxaban but not before rivaroxaban and apixaban and overlapped with VKA therapy. † Time-limited period: 6, 12 or 24 months Abbreviations: LMWH = low-molecular weight heparin;		

NICE: Edoxaban for DVT and PE

NICE reviewed the literature for edoxaban in the treatment of DVT and PE to make a guidance recommendation related to its use.[3] One good quality study found edoxaban associated symptomatic recurrent VTE in 3.2% of patients compared to 3.5% of warfarin treated patients, demonstrating non-inferiority ($p < 0.0001$). NICE recommends edoxaban as an option for the treatment and prevention of DVT and PE in adults.

NICE: Edoxaban for Stroke

The use of edoxaban for the prevention of stroke in patients with NVAF was evaluated for a NICE guidance.[2] Edoxaban is recommended for patients after a discussion on the benefits and risks of such treatment compared with warfarin, apixaban, dabigatran and rivaroxaban. For patients taking warfarin that are considering switching to edoxaban, the benefits and risks as well as the history of INR control should be evaluated.

NICE: Rivaroxaban for ACS

The evidence for the use of rivaroxaban in patients with ACS was reviewed by NICE.[4] After analysis of data from one multi-center, double-blind, manufacturer funded, RCT in over 15,000 patients, guidance recommendations were issued. Rivaroxaban was recommended for the prevention of atherothrombotic events in patients with ACS and elevated biomarkers. Rivaroxaban should be used in this patient population as part of a regimen containing aspirin or aspirin plus clopidogrel.

ESC: Guidelines for the Management of ACS

The ESC provided guidance on managing patients who present with ACS without persistent ST-segment elevation.[5] Evidence level and strength of the recommendation of management strategies were weighed and graded. The recommendation was assigned a class of recommendation with the following: Class I (is recommended and indicated), Class II (conflicting evidence – refer to Class IIa or IIb), Class IIa (should be considered), Class IIb (may be considered), and Class III (is not recommended). The levels of evidence ranged from A (randomized controlled trials or meta-analysis, highest level), B (single RCT or large non-randomized trial) to C (consensus of opinion, lowest level). The Task Force responsible for guideline development did not receive funding from the healthcare industry. The recommendations pertaining to anticoagulation management following the acute phase will be presented below.

ESC recommends the use of rivaroxaban 2.5 mg as an option in patients with non-ST-elevation ACS with no prior stroke or TIA history that are at high risk for ischemia and low risk of bleeding who are also receiving aspirin and clopidogrel (class IIb, level B). Patients should have parenteral anticoagulation discontinued before initiation of rivaroxaban.[5]

New Formulations:

No new formulations identified.

New FDA Safety Alerts:

Apixaban

In July of 2016 the lack of reversal agent for apixaban was noted in the warnings and precautions section.[20] In patients with NVAF, dosing in specific populations was modified to include the dosing regimen of 2.5 mg twice daily in patients with at least two of the following risk factors: age of 80 years or older, body weight of 60 kg or less and serum creatinine of 1.5 mg/dL or less. Recommendations for dosing in patients with end-stage renal disease (ESRD) on dialysis are the same as in patients without ESRD based on pharmacodynamics data. No patients with ESRD, with or without dialysis have been studied. In patients being treated for DVT and PE prevention following hip or knee replacement surgery should not receive a dose adjustment if they have renal impairment or ESRD on dialysis based on pharmacokinetic data. In June of 2015 recommendations for dosing apixaban in patients for renal impairment alone, including those with ESRD on dialysis were updated. Patients should receive the recommended dose without reductions unless they are being treated with NVAF and meet the criteria for dosage reduction. No dose adjustment is required for patients with mild hepatic impairment. Dosing in moderate hepatic impairment has not been studied and therefore dosing cannot be recommended. Apixaban is not recommended in patients with severe hepatic impairment.

Rivaroxaban

Labeling was updated that the use of rivaroxaban with selective serotonin inhibitors and norepinephrine reuptake inhibitors as this combination has the potential to interact and increase the risk of bleeding.[19] Periodic assessment of renal function is also recommended in patients taking rivaroxaban. Patients who have ESRD on dialysis were not included in the rivaroxaban studies. Rivaroxaban doses of 15 mg daily should produce similar concentrations to those included in the ROCKET AF study.

References:

1. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):454S-545S. doi:10.1378/chest.08-0658.

2. National Institute for Health and Care Excellence. Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. *Technology Appraisal Guidance*. 2015; September. Available at: http://www.nice.org.uk/guidance/ta355. Accessed March 1, 2017.

3. National Institute for Health and Care Excellence. Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism. *Technology Appraisal Guidance*. 2015; August. Available at: http://www.nice.org.uk/guidance/ta354. Accessed March 1, 2017.

4. National Institute for Health and Care Excellence. Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. *Technology Appraisal Guidance*. 2015; March. 82602549055429. Available at: https://www.nice.org.uk/guidance/ta335. Accessed March 1, 2017.

5. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevationTask Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315. doi:10.1093/eurheartj/ehv320.

6. Di Nisio, M, Porreca E, Candeloro M. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receving chemotherapy (Review). *Cochrane Database of Systematic Reviews*. 2016;(12):Art. No.: CD008500. doi:10.1002/14651858.

7. Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer. *Chest*. 2015;147(2):475-483. doi:10.1378/chest.14-0402.

8. Venker BT, Ganti BR, Lin H, et al. Safety and efficacy of new anticoagulants for the prevention of venous thromboembolism after hip and knee arthroplasty: A Meta-Analysis. *J Arthroplasty*. 2017;32(2):645-652. doi:10.1016/j.arth.2016.09.033.

9. Sindet-Pedersen C, Pallisgaard JL, Olesen JB, et al. Safety and efficacy of direct oral anticoagulants compared to warfarin for extended treatment of venous thromboembolism -a systematic review and meta-analysis. *Thrombosis Research*. 2015;136(4):732-738. doi:10.1016/j.thromres.2015.07.022.

10. Del-Carpio Munoz F, Gharacholou SM, Munger TM, et al. Meta-Analysis of renal function on the safety and efficacy of novel oral anticoagulants for atrial fibrillation. *Am J Cardiol*. 2016;117(1):69-75. doi:10.1016/j.amjcard.2015.09.046.

11. Raccah BH, Perlman A, Danenberg HD, et al. Major bleeding and hemorrhagic stroke with direct oral anticoagulants in patients with renal failure: systematic review and meta-analysis of randomized trials. *Chest*. 2016;149(6):1516-1524. doi:10.1016/j.chest.2015.12.029.

12. Caldeira D, Rodrigues FB, Barra M, et al. Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis. [Review]. *Heart*. 2015;101(15):1204-1211. doi:10.1136/heartjnl-2015-307489.

13. Chai-Adisaksopha C, Hillis C, Isayama T, et al. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2015;13(11):2012-2020. doi:10.1111/jth.13139.

14. Lee AYY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA*. 2015;314(7):677-686. doi:10.1001/jama.2015.9243.

15. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *The Lancet*. 2016;388(10055):1995-2003. doi:10.1016/S0140-6736(16)31474-X.

16. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222. doi:10.1056/NEJMoa1700518.

17. Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. *N Engl J Med*. March 2017. doi:10.1056/NEJMoa1701005.

18. Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet*. March 2017. doi:10.1016/S0140-6736(17)30751-1.

19. Food and Drug Administration. Safety Information - Xarelto (Rivaroxaban) Tablets. May 2016. Available at: https://www.fda.gov/safety/medwatch/safetyinformation/ucm367392.htm. Accessed February 23, 2017.

20. Food and Drug Administration. Safety Information - Eliquis (apixaban) Tablets. July 2016. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm384790.htm. Accessed February 23, 2017.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	PRADAXA	DABIGATRAN ETEXILATE MESYLATE	Y
ORAL	TAB DS PK	XARELTO	RIVAROXABAN	Y
ORAL	TABLET	COUMADIN	WARFARIN SODIUM	Y
ORAL	TABLET	ELIQUIS	APIXABAN	Y
ORAL	TABLET	JANTOVEN	WARFARIN SODIUM	Y
ORAL	TABLET	SAVAYSA	EDOXABAN TOSYLATE	Y
ORAL	TABLET	WARFARIN SODIUM	WARFARIN SODIUM	Y
ORAL	TABLET	XARELTO	RIVAROXABAN	Y
SUB-Q	SYRINGE	ENOXAPARIN SODIUM	ENOXAPARIN SODIUM	Y
SUB-Q	SYRINGE	FRAGMIN	DALTEPARIN SODIUM,PORCINE	Y
SUB-Q	SYRINGE	LOVENOX	ENOXAPARIN SODIUM	Y
SUB-Q	VIAL	ENOXAPARIN SODIUM	ENOXAPARIN SODIUM	Y
SUB-Q	VIAL	LOVENOX	ENOXAPARIN SODIUM	Y
SUB-Q	SYRINGE	ARIXTRA	FONDAPARINUX SODIUM	N
SUB-Q	SYRINGE	FONDAPARINUX SODIUM	FONDAPARINUX SODIUM	N
SUB-Q	VIAL	FRAGMIN	DALTEPARIN SODIUM,PORCINE	N

Appendix 2: New Comparative Clinical Trials

A total of 449 citations were manually reviewed from the initial literature search. After further review, 444 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 5 randomized controlled trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Goette, et al[15] RCT, OL, MC	Edoxaban 60 mg* daily vs. Enoxaparin-warfarin (INR 2.0-3.0) 28-days post procedure	Patients with NVAF undergoing electrical cardioversion N= 2199	Incidence of stroke, systemic embolic event, myocardial infarction and cardiovascular mortality	Edoxaban: 5 (<1%) Enoxaparin-warfarin: 11 (1%) OR 0.46; 95% CI, 0.12 to 1.43
Lee, et al[14] RCT, OL, MC	Tinzaparin (175 IU/kg) vs. Tinzaparin (175 IU/kg)/warfarin (INR 2.0-3.0) 6 months	Patients with active cancer and documented PE or DVT N=900	Recurrent DVT, fatal or nonfatal PE and incidental VTE	Tinzaparin: 31 (7.2%) Tinzaparin/warfarin: 45 (10.5%) HR 0.65; 95% CI, 0.41 to 1.03) P = 0.07
Calkins, et al[17] RCT, OL, MC	Dabigatran 150 mg twice daily vs. Warfarin (INR 2.0 to 3.0) 4-8 weeks pre-procedure and 8 weeks post-procedure	Patients undergoing catheter ablation of atrial fibrillation N = 704	Major bleeding events	Dabigatran: 5 (1.6%) Warfarin: 22 (6.9%) ARR -5.3%; 95% CI, -8.4 to -2.2 P<0.001
Weitz, et al[16] RCT, DB, MC	Rivaroxaban 20 mg or 10 mg daily vs. Aspirin 100 mg daily 12 months	Patients with VTE with a prior 6-12 months of anticoagulation and were equipoise for the need for	Symptomatic recurrent fatal or nonfatal venous thromboembolism	Rivaroxaban 20 mg: 17 (1.5%) Rivaroxaban 10 mg: 13 (1.2%) Aspirin: 50 (4.4%) Rivaroxaban 20 mg vs. Aspirin: HR 0.34; 95% CI, 0.20 to 0.59 P<0.001

		continuing anticoagulation N = 3365		Rivaroxaban 10 mg vs. Aspirin: HR 0.26; 95% CI, 0.14 to 0.47 P<0.001
Ohman, et al[18] RCT, DB, MC	Rivaroxaban 2.5 mg twice daily† vs. Aspirin 100 mg daily† 291 days	Patients with ACS	Thrombolysis in myocardial infarction clinically significant bleeding (not related to coronary artery bypass graft) up to day 390	Rivaroxaban: 80 (5%) Aspirin: 74 (5%) HR 1.09; 95% CI, 0.80 to 1.50 P = 0.5840
* Edoxaban dose was reduced to 30 mg daily if one or more of the following: CrCl 15-50 mL/min, low body weight (≤ 60 kg) or concomitant use of P-glycoprotein inhibitors † Patients also received clopidogrel or ticagrelor				

Abbreviations: ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; MC = multi-center; OL = open label; OR = odds-ratio; RCT = randomized clinical trial

Appendix 3: Abstracts of Comparative Clinical Trials

Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial
Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY; ENSURE-AF investigators

BACKGROUND:
Edoxaban, an oral factor Xa inhibitor, is non-inferior for prevention of stroke and systemic embolism in patients with atrial fibrillation and is associated with less bleeding than well controlled warfarin therapy. Few safety data about edoxaban in patients undergoing electrical cardioversion are available.
METHODS:
We did a multicenter, prospective, randomised, open-label, blinded-endpoint evaluation trial in 19 countries with 239 sites comparing edoxaban 60 mg per day with enoxaparin-warfarin in patients undergoing electrical cardioversion of non-valvular atrial fibrillation. The dose of edoxaban was reduced to 30 mg per day if one or more factors (creatinine clearance 15-50 mL/min, low bodyweight [≤60 kg], or concomitant use of P-glycoprotein inhibitors) were present. Block randomisation (block size four)-stratified by cardioversion approach (transoesophageal echocardiography [TEE] or not), anticoagulant experience, selected edoxaban dose, and region-was done through a voice-web system. The primary efficacy endpoint was a composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality, analysed by intention to treat. The primary safety endpoint was major and clinically relevant non-major (CRNM) bleeding in patients who received at least one dose of study drug. Follow-up was 28 days on study drug after cardioversion plus 30 days to assess safety. This trial is registered with ClinicalTrials.gov, number NCT02072434.
FINDINGS:
Between March 25, 2014, and Oct 28, 2015, 2199 patients were enrolled and randomly assigned to receive edoxaban (n=1095) or enoxaparin-warfarin (n=1104). The mean age was 64 years (SD 10·54) and mean CHA_2DS_2-VASc score was 2·6 (SD 1·4). Mean time in therapeutic range on warfarin was 70·8% (SD 27·4). The primary efficacy endpoint occurred in five (<1%) patients in the edoxaban group versus 11 (1%) in the enoxaparin-warfarin group (odds ratio [OR] 0·46, 95% CI 0·12-1·43). The primary safety endpoint occurred in 16 (1%) of 1067 patients given edoxaban versus 11 (1%) of 1082 patients given enoxaparin-warfarin (OR 1·48, 95% CI 0·64-3·55). The results were independent of the TEE-guided strategy and anticoagulation status.
INTERPRETATION:
ENSURE-AF is the largest prospective randomised clinical trial of anticoagulation for cardioversion of patients with non-valvular atrial fibrillation. Rates of major and CRNM bleeding and thromboembolism were low in the two treatment groups.

Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial
Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA; CATCH Investigators

IMPORTANCE:
Low-molecular-weight heparin is recommended over warfarin for the treatment of acute venous thromboembolism (VTE) in patients with active cancer largely based on results of a single, large trial.
OBJECTIVE:
To study the efficacy and safety of tinzaparin vs warfarin for treatment of acute, symptomatic VTE in patients with active cancer.

DESIGN, SETTINGS, AND PARTICIPANTS:
A randomized, open-label study with blinded central adjudication of study outcomes enrolled patients in 164 centers in Asia, Africa, Europe, and North, Central, and South America between August 2010 and November 2013. Adult patients with active cancer (defined as histologic diagnosis of cancer and receiving anticancer therapy or diagnosed with, or received such therapy, within the previous 6 months) and objectively documented proximal deep vein thrombosis (DVT) or pulmonary embolism, with a life expectancy greater than 6 months and without contraindications for anticoagulation, were followed up for 180 days and for 30 days after the last study medication dose for collection of safety data.
INTERVENTIONS:
Tinzaparin (175 IU/kg) once daily for 6 months vs conventional therapy with tinzaparin (175 IU/kg) once daily for 5 to 10 days followed by warfarin at a dose adjusted to maintain the international normalized ratio within the therapeutic range (2.0-3.0) for 6 months.
MAIN OUTCOMES AND MEASURES:
Primary efficacy outcome was a composite of centrally adjudicated recurrent DVT, fatal or nonfatal pulmonary embolism, and incidental VTE. Safety outcomes included major bleeding, clinically relevant nonmajor bleeding, and overall mortality.
RESULTS:
Nine hundred patients were randomized and included in intention-to-treat efficacy and safety analyses. Recurrent VTE occurred in 31 of 449 patients treated with tinzaparin and 45 of 451 patients treated with warfarin (6-month cumulative incidence, 7.2% for tinzaparin vs 10.5% for warfarin; hazard ratio [HR], 0.65 [95% CI, 0.41-1.03]; P = .07). There were no differences in major bleeding (12 patients for tinzaparin vs 11 patients for warfarin; HR, 0.89 [95% CI, 0.40-1.99]; P = .77) or overall mortality (150 patients for tinzaparin vs 138 patients for warfarin; HR, 1.08 [95% CI, 0.85-1.36]; P = .54). A significant reduction in clinically relevant nonmajor bleeding was observed with tinzaparin (49 of 449 patients for tinzaparin vs 69 of 451 patients for warfarin; HR, 0.58 [95% CI, 0.40-0.84]; P = .004).
CONCLUSIONS AND RELEVANCE:
Among patients with active cancer and acute symptomatic VTE, the use of full-dose tinzaparin (175 IU/kg) daily compared with warfarin for 6 months did not significantly reduce the composite measure of recurrent VTE and was not associated with reductions in overall mortality or major bleeding, but was associated with a lower rate of clinically relevant nonmajor bleeding. Further studies are needed to assess whether the efficacy outcomes would be different in patients at higher risk of recurrent VTE.

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism.
Weitz JI, Lensing AW, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MC, Holberg G, Kakkar AK, Haskell L, van Bellen B, Pap AF, Berkowitz SD, Verhamme P, Wells PS, Prandoni P; EINSTEIN CHOICE Investigators

Background: Although many patients with venous thromboembolism require extended treatment, it is uncertain whether it is better to use full- or lower-intensity anticoagulation therapy or aspirin.

Methods: In this randomized, double-blind, phase 3 study, we assigned 3396 patients with venous thromboembolism to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal venous thromboembolism, and the principal safety outcome was major bleeding.

Results: A total of 3365 patients were included in the intention-to-treat analyses (median treatment duration, 351 days). The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant nonmajor bleeding were 2.7%, 2.0%, and 1.8%, respectively. The incidence of adverse events was similar in all three groups.

Conclusions: Among patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in bleeding rates. (Funded by Bayer Pharmaceuticals; EINSTEIN CHOICE ClinicalTrials.gov number, NCT02064439 .).

Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation
Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, Okumura K, Serota H, Nordaby M, Guiver K, Biss B, Brouwer MA, Grimaldi M; RE-CIRCUIT Investigators

Background: Catheter ablation of atrial fibrillation is typically performed with uninterrupted anticoagulation with warfarin or interrupted non-vitamin K antagonist oral anticoagulant therapy. Uninterrupted anticoagulation with a non-vitamin K antagonist oral anticoagulant, such as dabigatran, may be safer; however, controlled data are lacking. We investigated the safety of uninterrupted dabigatran versus warfarin in patients undergoing ablation of atrial fibrillation. Methods: In this randomized, open-label, multicenter, controlled trial with blinded adjudicated end-point assessments, we randomly assigned patients scheduled for catheter ablation of paroxysmal or persistent atrial fibrillation to receive either dabigatran (150 mg twice daily) or warfarin (target international normalized ratio, 2.0 to 3.0). Ablation was performed after 4 to 8 weeks of uninterrupted anticoagulation, which was continued during and for 8 weeks after ablation. The primary end point was the incidence of major bleeding events during and up to 8 weeks after ablation; secondary end points included thromboembolic and other bleeding events.

Results: The trial enrolled 704 patients across 104 sites; 635 patients underwent ablation. Baseline characteristics were balanced between treatment groups. The incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%]; absolute risk difference, -5.3 percentage points; 95% confidence interval, -8.4 to -2.2; P<0.001). Dabigatran was associated with fewer periprocedural pericardial tamponades and groin hematomas than warfarin. The two treatment groups had a similar incidence of minor bleeding events. One thromboembolic event occurred in the warfarin group.

Conclusions: In patients undergoing ablation for atrial fibrillation, anticoagulation with uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin. (Funded by Boehringer Ingelheim; RE-CIRCUIT ClinicalTrials.gov number, NCT02348723 .)

Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial.
Ohman EM, Roe MT, Steg PG, James SK, Povsic TJ, White J, Rockhold F, Plotnikov A, Mundl H, Strony J, Sun X, Husted S, Tendera M, Montalescot G, Bahit MC, Ardissino D, Bueno H, Claeys MJ, Nicolau JC, Cornel JH, Goto S, Kiss RG, Güray Ü, Park DW, Bode C, Welsh RC, Gibson CM

BACKGROUND:
Dual antiplatelet therapy (DAPT), aspirin plus a P2Y12 inhibitor, is the standard antithrombotic treatment following acute coronary syndromes. The factor Xa inhibitor rivaroxaban reduced mortality and ischaemic events when added to DAPT, but caused increased bleeding. The safety of a dual pathway antithrombotic therapy approach combining low-dose rivaroxaban (in place of aspirin) with a P2Y12 inhibitor has not been assessed in acute coronary syndromes. We aimed to assess rivaroxaban 2·5 mg twice daily versus aspirin 100 mg daily, in addition to clopidogrel or ticagrelor (chosen at investigator discretion before randomisation), for patients with acute coronary syndromes started within 10 days after presentation and continued for 6-12 months.
METHODS:
In this double-blind, multicentre, randomised trial (GEMINI-ACS-1) done at 371 clinical centres in 21 countries, eligible patients were older than 18 years with unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI), with positive cardiac biomarkers and either ischaemic electrocardiographic changes or an atherosclerotic culprit lesion identified during angiography. Participants were randomly assigned (1:1) within 10 days after admission for the index acute coronary syndromes event to either aspirin or rivaroxaban based on a computer-generated randomisation schedule. Randomisation was balanced by using randomly permuted blocks with size of four and was stratified based on the background P2Y12 inhibitor (clopidogrel or ticagrelor) intended to be used at the time of randomisation. Investigators and patients were masked to treatment assignment. Patients received a minimum of 180 days of double-blind treatment with rivaroxaban 2·5 mg twice daily or aspirin 100 mg daily. The choice of clopidogrel or ticagrelor during trial conduct was not randomised and was based on investigator preference. The primary endpoint was thrombolysis in myocardial infarction (TIMI) clinically significant bleeding not related to coronary artery bypass grafting (CABG; major, minor, or requiring medical attention) up to day 390. Primary analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT02293395.
FINDINGS:
Between April 22, 2015, and Oct 14, 2016, 3037 patients with acute coronary syndromes were randomly assigned; 1518 to receive aspirin and 1519 to receive rivaroxaban. 1704 patients (56%) were in the ticagrelor and 1333 (44%) in the clopidogrel strata. Median duration of treatment was 291 days (IQR 239-354). TIMI non-CABG clinically significant bleeding was similar with rivaroxaban versus aspirin therapy (total 154 patients [5%]; 80 participants [5%] of 1519 vs 74 participants [5%] of 1518; HR 1·09 [95% CI 0·80-1·50]; p=0·5840).
INTERPRETATION:
A dual pathway antithrombotic therapy approach combining low-dose rivaroxaban with a P2Y12 inhibitor for the treatment of patients with acute coronary syndromes had similar risk of clinically significant bleeding as aspirin and a P2Y12 inhibitor. A larger, adequately powered trial would be required to definitively assess the efficacy and safety of this approach.
FUNDING:
Janssen Research & Development and Bayer AG.

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2017
Search Strategy:

#	Searches	Results
1	apixaban.mp.	1427
2	rivaroxaban.mp. or Rivaroxaban/	2320
3	dabigatran.mp. or Dabigatran/	2736
4	edoxaban.mp.	515
5	warfarin.mp. or Warfarin/	17078
6	enoxaparin.mp. or Enoxaparin/	3830
7	dalteparin.mp. or Dalteparin/	1065
8	fondaparinux.mp.	1505
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	24153
10	limit 9 to (english language and humans and yr="2015 -Current")	2573
11	limit 10 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	457

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

Policy Evaluation: Removal of Prior Authorization on Non-Vitamin K Oral Anticoagulants (NOACS)

Research Questions:

1) Did the utilization of oral anticoagulants change after removal of the prior authorization (PA) criteria?
2) Did the use of non-vitamin K antagonists oral anticoagulants (NOACS) for FDA approved indications increase after removal of the PA criteria? Did use of the NOACS in the presence of contraindications or precautions increase since removal of the PA policy?
3) What are the adherence rates of NOACS compared to warfarin?
4) Did the number of patients encountering a denied claim for a NOAC decrease after removal of the PA?

Conclusions:

- Utilization for the NOACs increased after removal of the PA criteria (from 37 unique members per member per month [PMPM] to 64 unique members PMPM). However, utilization remains low overall and this increase in use is consistent with clinical practice patterns. The use of NOACS for FDA approved indications was slightly lower after removal of the PA criteria compared to the control group (60% vs. 79%). However, there were more patients with an unknown indication in the study group as well, which is a limitation of the analysis. There were no significant concerns regarding use of a NOAC in patients with a contraindication or precaution after removal of the PA policy.
- Adherence to NOACS was not found to be higher compared to warfarin (> 80%).
- There were no denied claims for a NOAC after removal of the PA. Therefore, removal of the PA decreased a barrier to treatment with oral anticoagulants that was observed in the previous policy evaluation.

Recommendations:

- Continue to allow open access to the NOACs.
- Continue to monitor appropriate use as utilization increases.

Previous recommendations:

1. Given the high risk to patients from anticoagulation disruption, the high incidence of disruption among patients encountering the prior authorization requirement and the apparent low use of the NOACS it is recommended the clinical PA for NOACS be discontinued.
2. It is recommended that a Retrospective DUR program be developed to monitor appropriate dosing and use in the presence of contraindications, as these remain a concern.
3. It is recommended the class utilization be reviewed again in one year given the evolving evidence and new drugs in the class.

Author: Kim Vo, PharmD and Megan Herink, PharmD Date: May 2017

Background:

Warfarin has been the preferred and only oral anticoagulant for many decades. However, with the approval and increasing use of NOACS, warfarin may be less favorable in particular patients due to many drug-drug and drug-food interactions, required lab monitoring, and complicated dosing regimens. Currently, there are four NOACS available on the United States market including dabigatran (Pradaxa™), rivaroxaban (Xarelto™), apixaban (Eliquis™), and edoxaban (Savaysa™). The NOACS are indicated for prevention and treatment of venous thromboembolism (VTE), for prevention of stroke in non-valvular atrial fibrillation (NVAF), and for VTE prophylaxis in those patients undergoing orthopedic surgery**. Table 1** outlines the approved FDA indications for all oral anticoagulants.

Table 1. Oral anticoagulants and FDA approved indications [1-3, 8]

			Indications		
HSN code	**Brand**	**Generic**	**Orthopedic VTE prophylaxis**	**VTE treatment**	**Stroke prevention in NVAF***
Warfarin					
002812	Coumadin	Warfarin	Yes	Yes	Yes
NOACS					
035604	Pradaxa®	Dabigatran	Yes	Yes	Yes
035915	Xarelto®	Rivaroxaban	Yes	Yes	Yes
037792	Eliquis®	Apixaban	Yes	Yes	Yes
041672	Savaysa®	Edoxaban	No	Yes	Yes

HSN Code = hierarchical ingredient code list (HICL) sequence number as reported by First DataBank™
Abbreviations: AF: atrial fibrillation; NVAF: non-valvular atrial fibrillation; VTE: venous thromboembolism
**NVAF is defined as:* AF in the absence of prosthetic mechanical heart valves or hemodynamically significant valve disease, referring to a valve lesion severe enough to warrant surgical or percutaneous intervention or would have an impact on survival

The American College of Chest Physicians (CHEST) guidelines for VTE issued an update in early 2016 recommending NOACS over warfarin for the initial and long-term treatment of VTE in patients without cancer. [4] Anticoagulation therapy in AF is supported by two American guidelines, the 2012 CHEST and the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines. Per the 2012 CHEST guidelines, chronic anticoagulation is recommended for those with a CHADS2 score of 1 or more. [5] The CHEST guideline recommends dabigatran 150 mg taken twice daily, the only FDA approved NOAC at the time, over a vitamin K antagonist (warfarin) for AF. The exception is for patients with valvular disease (mitral stenosis and prosthetic heart valves), in which warfarin is the only recommended oral anticoagulant. [5] According to the 2014 AHA/ACC/HRS guidelines for the management of patients with AF, warfarin is also the recommended oral anticoagulant for patients with valvular AF. [6] Generally, patients with mitral stenosis and prosthetic heart valves or valve repair were excluded from NOAC trials. The AHA/ACC/HRS guideline recommends either warfarin or a NOAC for those with NVAF and a CHA2DS2-VASc score of 2 or more. [6] In February 2017, AHA/ACC provided a focused update for managing patients with valvular heart disease. Warfarin is still indicated for patients with AF with rheumatic mitral stenosis and mechanical heart valves; these patients were excluded in studies with NOACS. [7] However, NOACS are reasonable alternatives for patients with AF and native aortic valve disease, tricuspid valve disease, or mitral regurgitation. [7]

Other clinical scenarios in which warfarin may still be recommended over a NOAC include in those with end-stage chronic kidney disease (CKD) (CrCl <15 ml/min) or on hemodialysis. [6] NOACs excluding edoxaban and dabigatran may be considered in moderate to severe CKD, however, safety and efficacy have not been established. [6] Utilization of edoxaban, the newest NOAC on the market, has been low in part due its unique dosing parameters, which recommend avoiding therapy in patients with creatinine clearance greater than 95 mL/min. [8] Additionally, safety and efficacy have not been established in obese patients with a BMI ≥ 40 or weight ≥ 120 kg.

A reversal agent, idarucizumab (Praxbind™), was approved for bleeding associated with the direct thrombin inhibitor, dabigatran use in October 2015, which provided an additional safety net in the event of adverse bleeding effects associated with dabigatran therapy. There are other agents in clinical trials for reversal of Xa agents (apixaban, edoxaban, and rivaroxaban). [9]

Another theorized benefit of NOACs is easier administration and improved adherence over warfarin. A systematic review examined dosing frequency and medication adherence in chronic diseases showed that patients are more adherent with once-daily dosing compared to more frequently scheduled doses.[10] Although the difference in once versus twice daily was not as clear cut as once daily versus more complicated regimens requiring three to four times a day drug administration. [10] In a retrospective cohort analysis that included nearly 65,000 patients with AF initiated on warfarin or a NOAC (dabigatran, rivaroxaban, apixaban), the proportion of days covered (PDC) after 1 year of follow-up showed that 47.5% of patients prescribed a NOAC had a PDC of 80% or above compared to only 40.2% in the warfarin group ($p < 0.001$). [11]

The Oregon Health Plan (OHP) fee-for-service (FFS) removed the prior authorization (PA) criteria for the use of NOACs in May 2015 to enhance patient access to anticoagulant therapy. Initially, the OHP developed PA criteria for NOACS to limit use for FDA approved indications in people who were not a candidate for warfarin. The results of a PA policy evaluation in 2015 showed that a PA was requested for only 54 patients (56.3%) after a denied claim. In addition, only 57.3% of those patients received subsequent anticoagulation therapy within 14 days of the denied claim. This resulted in removal of the PA criteria for overall safety concerns. [12] Another recommendation was to complete retrospective DUR to assess the safe and appropriate use of NOACS.

The purpose of this evaluation is to examine change in utilization of oral anticoagulants and assess the impact of removing PA criteria on patient access to oral anticoagulants. This review will determine if patients are receiving appropriate therapy based on approval for FDA indications and as evaluate safety by screening for contraindications or precautions. Additionally, adherence will be assessed by calculating PDC.

Methods:

Patients were identified if they had a new paid FFS pharmacy claim for any NOAC in **Table 1** from July 1, 2014 through June 30, 2015 (control group) or from July 1, 2015 through June 30, 2016 (study group). Patients were excluded if they had Medicare Part D coverage as indicated by benefit packages BMM, BMD, MED or MND. Only new starts were included and were defined as the first FFS pharmacy claim for a NOAC or warfarin in the control or study period, without any prior FFS or CCO pharmacy claim for a NOAC or warfarin in the 90 days prior. The first claim was designated the index event. Patients were excluded if they were found to have less than 75% of combined FFS or CCO eligibility in the 12 months prior to the index event, in order to insure complete medical records for their prior diagnoses. The list of ICD9 & 10 codes for these diagnoses are referenced in **Tables 2** and **3**.

Table 2. FDA labeled indications for NOACS

	ICD-9 Code	ICD-10 Code
Atrial Dysfunction		
Atrial fibrillation & atrial flutter, supraventricular premature beats	427.3x, 427.61	I4891, I4892, I491
Thromboembolic Events		
Phlebitis & thrombophlebitis	451.xx, 453.xx, V12.51, 415.1x, V12.55	I8000, Z86718, I2690, I2699, T800XXA, T81718A, T8172XA, T82817A, I2690, I2692, I2699, Z86711
Orthopedic Procedures		
Total knee arthroplasty, Total hip arthroplasty	81.54-81.55; V43.65, 81.51-81.53; V43.64, 820xx	Z96659, Z96649
Acute Coronary Syndrome		
Cardiac device in situ	V45.xx, V45.81, V45.82, 413.x, 410.xx	Z959, Z950, Z95810, Z95818, Z95.1, Z9861, I208, I201, I208, I209, I2109, I2119, I2111, I2129, I214, I213

Table 3. Contraindications or precautions for NOACS

	ICD-9 Code	ICD-10 Code
Valve Replacement		
Heart valve replaced by transplant , Heart valve replaced by other means	V42.2 , V43.3	Z953, Z952
Valvular Disease/Dysfunction		
Other congenital anomalies of heart	746.xx, 394.x, 397.x	Q2xx, I050, I051, I052, I058 , I060, I061, I062, I068, I069, I071, I072, I078, I080, I088, I089, I091, 10XXX, I0989
Cardiac		
Acute & subacute endocarditis, Aortic aneurysm & dissection	421.x, 441.xx	I330, I39, I339, I7100-17103, 1711-1719
Cranial Bleeding		
Subarachnoid hemorrhage, Intracerebral hemorrhage, Other & unspecified intracranial hemorrhage	430, 431, 432.x	I609, I619, I621, I6200, I629
Gastrointestinal		
Esophageal varices with bleeding, ulcers, hemorrhages	456.0, 456.20, 459.0, 530.21, 531.xx-535.xx, 578.x	I8501, I8511, R58, K2211, K25x-K29xx, K920-K922

Hematologic and Circulatory		
Hemorrhagic disorder due to intrinsic circulating anticoagulants, coagulation defects	286.5x, 790.0x, 790.92, 286.xx	D68311, D68312, D68318 , R710, R718, R791, D6x-D6xxx
Hepatic		
Chronic liver disease & cirrhosis	571.xx	K7XX-K7xxx
Kidney Disease		
Chronic kidney disease	585.x	N18x
Other		
Purpura & other hemorrhagic conditions	287.xx, 442.xx	D473, D69x-D69xx, I72x

Adherence with direct oral anticoagulants compared to warfarin

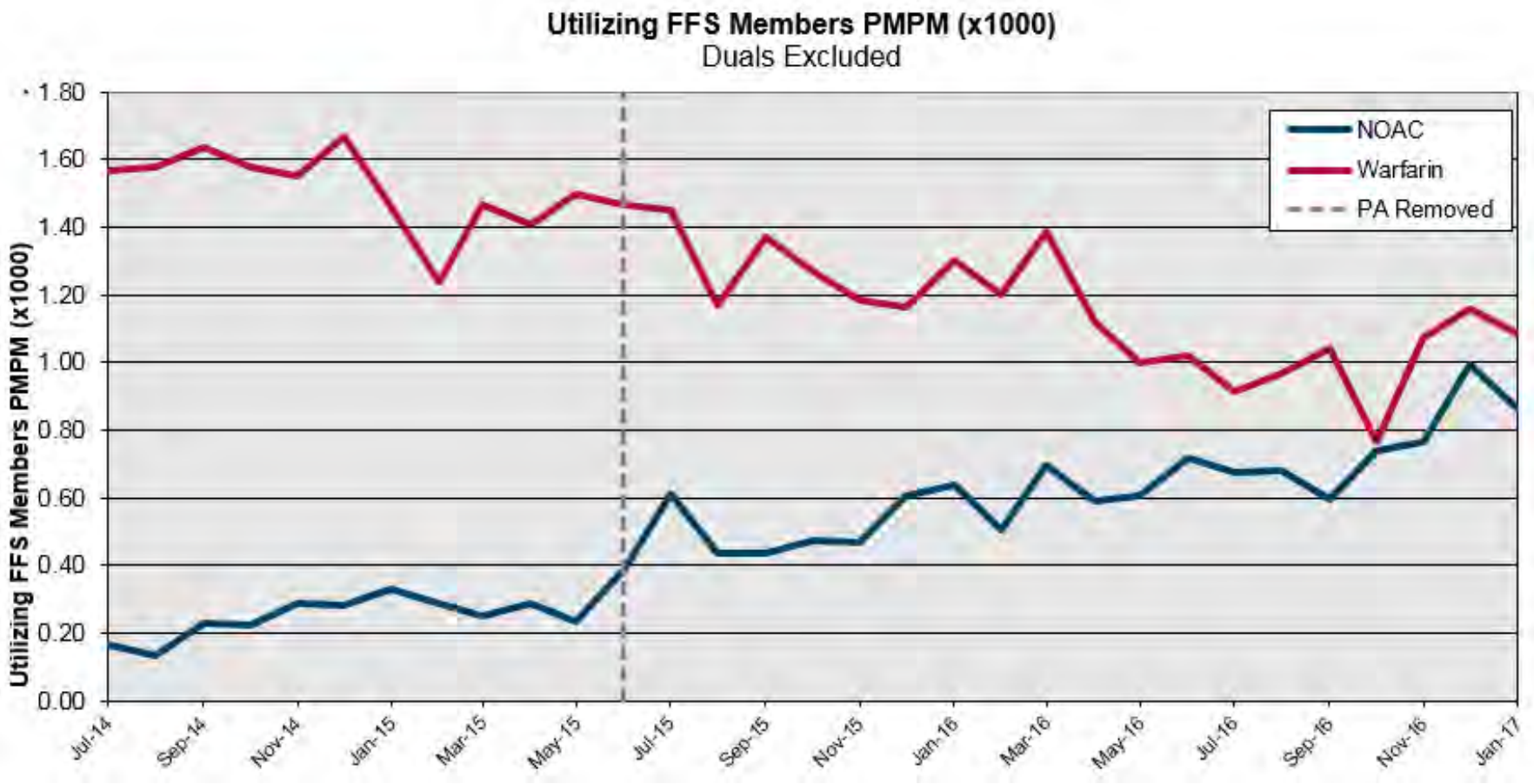
A different group of patients was selected using similar parameters to identify new therapy starts, but days' supply was an additional metric to assist with assessment of adherence. Patients were selected if they had a new start paid FFS pharmacy claim for any NOAC or warfarin listed in Table 1 from July 1, 2014 through June 30, 2015 (control group) or from July 1, 2015 through June 30, 2016 (study group). Patients were once again excluded if they had Medicare Part D coverage. New starts were defined as the first FFS pharmacy claim for a NOAC in the control or study period, without any prior FFS or CCO pharmacy claim for a NOAC in the 90 days prior. The first claim was designed the index event. Patients were then excluded if they were found to have less than 75% of combined FFS or CCO eligibility in the 3 months after the index event, in order to be sure of having complete records of their subsequent medications.

Finally, adherence in the form of PDC was calculated by adding the days' supply for all anticoagulant claims in the 90 days following the new start claim and dividing by 90. "All anticoagulants" means any anticoagulant from Table 1 and from any source, i.e. FFS or CCO.

Results:

Figure 1 depicts the trend of oral anticoagulant utilization per individual agent for the unique FFS patients with paid claims on a per-member-month (PMPM) basis. Each month the count of unique patients with a FFS claim for warfarin or NOAC was counted and divided by the number of total enrolled FFS patients in that month. Those with dual eligibility were excluded. Warfarin was the most utilized anticoagulant; ranging from 94 patients per 1000 FFS members to 187 patients per 1000 FFS members per month. Utilization of NOACS seemed to increase and warfarin decreased right around the time of removal of the PA criteria (June to July 2015). The difference in utilization between warfarin and the NOACS decreased substantially since 2014. The utilization for NOACS from June to July for the PMPM went from 37 to 64 patients. Note that the overall utilization remains low.

Figure 1. Utilization of oral anticoagulants



After excluding patients with <75% of days of combined FFS and coordinated care organization eligibility from 12 months prior to the index month to 3 months after the index month (for a total of 16 months), 155 patients with new-start FFS pharmacy claims for a NOAC were included in the study. Of these patients, there were no patients with a denied claim.

Table 4 displays the patient demographics. Patients (n = 44 in control and n = 111 in study groups) ranged in age from 19 to 64 years old. The mean age was 51.6 years old in the control group and 46.3 years old in the study group. There were more females (51.4%) in the study group compared to the control group (43.2%).

Table 4. Demographics of Study Population for NOACS

	Control Group		Study Group	
N=	44		111	
Mean age (range)	51.6	(25-64)	46.3	(21-64)
< 19		0.0%		0.0%
19-64	44	100.0%	111	100.0%
> 64		0.0%		0.0%
Female	19	43.2%	57	51.4%
White	25	56.8%	47	42.3%

Table 5 displays the diagnoses for the patients with paid NOAC index claims. The majority of patients in both the control and study groups had a FDA labeled indication. However, the overall percentage went down slightly after removal of the PA criteria (79.5% to 60.4%). There were also slightly fewer patients with a contraindication or precaution in the study group (36.9%) compared to the control group (43.2%). However, the percentage of patients who had valvular disease/dysfunction, cardiac, and gastrointestinal events were higher in the study group.

Table 5. Use of NOACS by Diagnosis in year prior and after index event

	Control Group		Study Group	
N=	44		111	
FDA Indications	**35**	**79.5%**	**67**	**60.4%**
Atrial Dysfunction (atrial fibrillation & flutter, etc)	20	45.5%	34	30.6%
Thromboembolic Events (phlebitis & thrombophlebitis)	12	27.3%	33	29.7%
Orthopedic Procedures (knee or total hip arthoplasty)	5	11.4%	4	3.6%
Acute Coronary Syndrome (cardiac device in situ)	9	20.5%	23	20.7%
Unknown indication	9	20.5%	44	39.6%
Contraindications and Precautions	**19**	**43.2%**	**41**	**36.9%**
Valve replacement	1	2.3%	1	0.9%
Valvular Disease/Dysfunction	2	4.5%	7	6.3%
Cardiac (eg acute & subacute endocarditis, aortic aneurysm, etc)		0.0%	1	0.9%
Cranial Bleeding (eg subarachnoid hemorrhage, intracerebral hemorrhage, etc)	2	4.5%	4	3.6%
Gastrointestinal (esophageal varices w/ bleeding, ulcers, hemorrhages)	3	6.8%	17	15.3%

*FDA Indications and Contraindications are not mutually-exclusive

The proportion of days covered (PDC) was characterized by index drug for both the control and study groups in **Table 6.** Among the control group, apixaban, dabigatran, and warfarin had an average PDC of 80-86%. For apixaban and warfarin, the adherence average in the study group were almost unchanged. Dabigatran adherence in the study group, however, had a difference of 15.6% lower average PDC compared to the control group. Rivaroxaban adherence was similar to both the control and study groups, but had the lowest average PDC among the oral anticoagulants. There were no claims for edoxaban.

Table 6. Adherence to oral anticoagulants (measured by the PDC)

	Control Group		Study Group	
	Patient Count	Avg PDC	Patient Count	Avg PDC
Index Drug N=	428		459	
APIXABAN	14	84.0%	61	82.3%
DABIGATRAN ETEXILATE MESYLATE	6	80.6%	8	64.4%
RIVAROXABAN	43	64.1%	114	63.0%
WARFARIN SODIUM	365	86.2%	276	83.4%

Denied claims

There were no denied claims identified for a PA or PDL denial after removal of the PA policy. This was the desired effect of removing the PA criteria.

Discussion:

This evaluation demonstrated an increase in utilization of the NOACS since removal of the NOAC PA. The increase in utilization was observed around the time the PA criteria was removed. Meanwhile, warfarin utilization trended downwards. Several changes in practice during the time frame of the study group selection may have contributed to increased utilization of NOACS. A reversal agent for dabigatran (idarucizumab) was approved and CHEST guidelines for VTE recommended NOACS over warfarin in non-cancer patients.[4] Because NOACS require minimal clinical monitoring, this may be an appealing factor for both the provider and the patient. There is also more data that the NOACs are associated with less severe bleeding compared to warfarin. As providers are becoming more comfortable with using these agents in a variety of patient populations, we would expect an increase in utilization consistent with clinical practice.

The majority of patients using NOACs seem to have an appropriate diagnosis for use. While the PA ensured that these medications were used for FDA approved diagnoses only, this does not seem to be a concern since the PA was removed. The main contraindications or precautions identified were gastrointestinal related (ulcers, previous gastrointestinal bleed, varices, etc.). While these are risk factors for bleeding, they are also a concern with the use of warfarin and there is not enough information from the data to fully capture the risk versus benefit of anticoagulation in each patient. Lastly, there were 7 patients on a NOAC with valvular disease. While, these agents are not preferred in valvular disease, trials excluded patients with significant mitral stenosis and prosthetic heart valves, but not necessarily those with other types of valvular heart disease.

Non-adherence is one factor that may impact overall utilization of oral anticoagulants. This study showed similar adherence rates between the control group and the study group for most of the oral anticoagulants, except for dabigatran. Compared to warfarin, apixaban had a similar adherence rate. One limitation with comparing NOACS to warfarin is that warfarin dosing is variable among individuals, which may skew the PDC in comparison to NOACS. The PDC of rivaroxaban remained low at about 64% despite removal of the PA policy, which was interesting since maintenance dosing of rivaroxaban is only once daily. The safety and bleeding data for apixaban may be a consideration when weighing the benefits of using a once or twice daily dosing NOAC such as rivaroxaban. Rivaroxaban has been noted in a previous study for use in patients with a history of medication non-adherence. [15] Perhaps the patients in this study continued to be non-adherent regardless if the medication was only once daily dosing, which accounted for the low adherence rate in **Table 6**.

Study Limitations:

Since this study was a retrospective analysis using claims data, there may be some inconsistencies in use of the coding system for indications. Also patients may have multiple indications identified within the timeframe of the study and there is no way to associate the use of anticoagulation for a particular indication. It is unclear what valvular disease a patient may have since mitral stenosis and mechanical heart valves were contraindicated, but other valvular diseases were acceptable for NOAC use. . The validation of the measures using claims data such as demographics are considered reliable. The validation for PDC for adherence rates have some limitations; it was difficult to determine the exact reasons for each individual person without delving further into medical charts. The limitation of using PDC is that adherence data may be compromised if days supplied is incorrectly added or if other human errors were introduced. Also the PDC does not show if the patients actually consumed the medication. In terms of eligibility churn, by indicating inclusion with at least 75% coverage under an FFS or CCO, the data captured an appropriate sample for this study.

References:

1. DailyMed - PRADAXA- dabigatran etexilate mesylate capsule. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ba74e3cd-b06f-4145-b284-5fd6b84ff3c9. Accessed October 29, 2016.

2. DailyMed - ELIQUIS- apixaban tablet, film coated. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e9481622-7cc6-418a-acb6-c5450daae9b0. Accessed October 29, 2016.

3. DailyMed - XARELTO- rivaroxaban tablet, film coated XARELTO- rivaroxaban. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=10db92f9-2300-4a80-836b-673e1ae91610. Accessed October 29, 2016.

4. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for vte disease: Chest guideline and expert panel report. *Chest*. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026.

5. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2_suppl):e531S-e575S. doi:10.1378/chest.11-2304.

6. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol*. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021.

7. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. 2017;1-59. DOI:10.1161/CIR.0000000000000503.

8. DailyMed - SAVAYSA- edoxaban tosylate tablet, film coated. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e77d3400-56ad-11e3-949a-0800200c9a66. Accessed October 29, 2016.

9. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med*. 2016;375(12):1131-1141. doi:10.1056/NEJMoa1607887.

10. Dosing Frequency and Medication Adherence in Chronic Disease - jmcp.2012.18.7.527. http://www.jmcp.org/doi/pdf/10.18553/jmcp.2012.18.7.527. Accessed March 30, 2017.

11. Brown JD, Shewale AR, Talbert JC. Adherence to Rivaroxaban, Dabigatran, and Apixaban for Stroke Prevention in Incident, Treatment-Naïve Nonvalvular Atrial Fibrillation. *J Manag Care Spec Pharm*. 2016;22(11):1319-1329. doi:10.18553/jmcp.2016.22.11.1319.

12. Anticoagulant DERP Summary Report_archive - 2016_07_28_AnticoagulantDERPSummaryReport.pdf. http://www.orpdl.org/durm/meetings/meetingdocs/2016_07_28/archives/2016_07_28_AnticoagulantDERPSummaryReport.pdf. Accessed February 5, 2017.

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 Literature Scan: Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Date of Review: May 2017

Date of Last Review: March 2015
Literature Search: 02/27/17 – 03/03/17

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

Conclusions:

- A literature scan identified six systematic reviews and meta-analyses[1–7], three guidelines[8–10], one new formulation[11] and one expanded indication[11]. There were no specific studies on Medicaid programs. Evidence for subpopulations were identified for patients with cystic fibrosis (CF) and pregnant women.[5,6]
- In patients with functional dyspepsia (FD), proton pump inhibitor (PPI) therapy was associated with resolution of dyspepsia symptoms in 30% of patients compared to 25% of placebo treated patients based on the findings of a recent Cochrane Review (number needed to treat for an additional beneficial outcome [NNTB] was 13 over 2 to 8 weeks).[1] Treatment with PPIs were associated with 33% of patients reporting no symptoms of dyspepsia compared with 26% of H2 receptor antagonist (H2RA) treated patients with a NNTB of 13 based on 2 trials of 2 to 8 weeks duration.[1]
- For erosive esophagitis, one systematic review and meta-analysis found esomeprazole 40 mg and 20 mg to be more effective than omeprazole 20 mg, with NNTs of 17 and 30, respectively.[3] Helicobacter pylori (H. pylori) eradication rates, as part of combination therapy, were similar between esomeprazole 40 mg and 20 mg and omeprazole 20 mg.
- The role of H. pylori in gastric ulcers and cancer make it a target for therapeutic intervention. A high quality systematic review evaluated standard triple therapy (STT), which consists of a PPI, clarithromycin and amoxicillin, compared to non-bismuth quadruple sequential therapy (SEQ) of two phases, the first induction phase (amoxicillin and a PPI for 5 days) followed by a triple regimen phase (PPI, clarithromycin and metronidazole for 5 days).[2] The analysis found SEQ regimens to eradicate H. pylori 82% of the time compared to 75% in the STT group (RD 0.09; 95% CI, 0.06 to 0.11; $p < 0.001$; ARR 7%; NNT 14); however, when trials from 2008 and later were considered there was no longer a benefit of SEQ treatment over STT.[2]
- A comparison of esomeprazole and omeprazole for the treatment of GERD was done in a systematic review and meta-analysis of good quality.[4] Esophageal healing rates were found to be similar for esomeprazole and omeprazole when used at equivalent doses. Esomeprazole 40 mg was found to be more effective than omeprazole 20 mg on esophageal healing rates (ARR 6%; NNT 17). There was no evidence for comparisons between esomeprazole 40 mg and omeprazole 40 mg. Relief of GERD symptoms were similar between esomeprazole and omeprazole when used at equivalent doses.[4]
- Evidence for the use of PPIs and H2RAs in subpopulations were available for patients with CF and pregnant women.[5,6] There was insufficient evidence to suggest that therapies that lower gastric acidity have conclusive benefits in patients with CF.[5] Medical treatment with intramuscular (IM) prostigmine, magnesium sulfate, aluminum hydroxide, simethicone and sucralfate were found to relieve heartburn symptoms more than placebo in pregnant women.[6]

Author: Kathy Sentena, PharmD

- Guidelines from the American College of Gastroenterology on management of H. pylori support the use of a PPIs in H. pylori treatment regimens.[8] No preference of specific PPI was recommended.
- The National Institute for Health and Care Excellence (NICE) published a guidance on the management of infants, children and young people with GERD, in which PPI or H2RA therapy were recommended equally.[10] Choice of therapy should be based on age-appropriate formulation, patient or caregiver preference and cost.[10]
- Dexlansoprazole SoluTabs (Dexilant) was approved in January of 2016 based on evidence from previous studies of dexlansoprazole delayed-release capsules.[11]

Recommendations:
- Recommend adding dexlansoprazole SoluTabs to the current prior authorization (PA) criteria for PPIs. Clarify intent of the PPI PA criteria by making minor modifications to the wording. (Appendix 4)
- No further research is needed at this time. Evaluate comparative drug costs for both classes in executive session.

Previous Conclusions:
- There is high quality evidence that there is no difference in effectiveness between PPIs for healing and maintaining remission of erosive gastro-esophagitis based on endoscopy, relieving symptoms of heartburn for up to 8 weeks, or treatment of PUD or NSAID-induced ulcers.
- There is high quality evidence that there is no difference in efficacy between H2RAs for the management of gastro-esophageal reflux or GERD.
- There is moderate quality evidence that there are no differences in harms between different PPIs or between H2RAs. In general, long-term use of PPIs are associated with severe adverse effects that are not associated with H2RAs
    - No association between outpatient use of H2RAs and risk for *Clostridium difficile*-associated diarrhea was found; this evidence conflicts with previous evidence that suggested an association with chronic PPI use does exist.
    - Patients on long-term PPI therapy should receive an annual re-evaluation to determine need for continued therapy secondary to increased harms, including osteoporosis, *Clostridium difficile*–associated diarrhea and certain nutritional deficiencies. However, the accumulating evidence from better designed, prospective clinical studies cannot substantiate the initial concerns for adverse cardiovascular effects of PPI use in patients on clopidogrel originally seen in the retrospective cohort studies.
- There is high quality evidence that there is no difference between long-term treatment of PPIs and short-term treatment of PPIs for erosive gastro-esophagitis based on endoscopy.
- There is insufficient evidence for long-term treatment of PPIs for symptomatic GERD as most studies evaluating PPIs for the management of GERD are limited to 8 weeks' duration.
- There is insufficient evidence to suggest long-term PPI use significantly decreases incidence of esophageal adenocarcinoma and/or high-grade dysplasia in patients with Barrett's esophagus. The role of PPIs in Barrett's esophagus remains uncertain due to conflicting observational data.
- There is moderate quality evidence that there is no difference in safety or efficacy between PPIs in managing symptoms of reflux in the pediatric population aged 1 year and older. Evidence for use of H2RAs is limited to ranitidine. There is insufficient evidence for use of these agents in infants.
- Low quality evidence suggests PPIs and H2RAs in Cystic Fibrosis patients improves gastrointestinal symptoms and fat absorption but there is insufficient evidence of their effect on nutritional status, lung function, quality of life or mortality.

Previous Recommendations:

- Use current evidence and data presented in the PPI/H2RA Drug Use Evaluation to guide new PA criteria.
- Evaluate comparative drug costs for both classes in the executive session.

Methods:

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

Cochrane: PPIs for Functional Dyspepsia

A 2017 Cochrane Review focused on the evidence for the use of PPIs for the improvement in dyspepsia symptoms and quality of life when used in patients with functional dyspepsia (FD).[1] Comparators included placebo, H2RAs or prokinetics. Twenty-three randomized controlled trials in patients 16 years and older with a diagnosis of FD were included. Follow-up lasted from 2-8 weeks. Low and high dose PPIs had similar efficacy and therefore these groups were combined. Global symptoms of dyspepsia or epigastric pain/discomfort was the main outcome of interest.

PPI therapy was associated with no or minimal symptoms of dyspepsia in 30% percent of patients compared with 25% of patients taking placebo based on data from 16 trials (RR 0.88; 95% CI, 0.82 to 0.94; ARR 5%; NNT 13) (based on moderate quality of evidence).[1] The number needed to treat for an additional beneficial (NNTB) outcome was 13. When PPIs were compared to H2RAs, PPI treatment resulted in no symptoms in 33% of patients compared to 26% of placebo treated patients with a NNTB of 13, based on 2 studies (RR 0.88; 95% CI, 0.74 to 1.04).[1] Similar evidence was found for PPI and prokinetic comparisons, where PPIs were more effective (RR 0.90; 95% CI, 0.81 to 1.00). The combination regimen of PPI and prokinetics were more effective at reducing symptoms of dyspepsia compared to PPIs alone. The evidence ranged from low to moderate in quality.

Cochrane: Sequential vs. Standard Triple First-line Therapy for H. Pylori Eradication

The focus of this review is to compare standard triple therapy (STT) with a newly recommended non-bismuth quadruple sequential therapy (SEQ) on the eradication rates for H. pylori.[2] The STT regimen consists of a PPI, clarithromycin and amoxicillin compared to the SEQ regimen of two phases, the first induction phase (amoxicillin and a PPI for 5 days) followed by a triple regimen phase (PPI, clarithromycin and metronidazole for 5 days). Randomized controlled trials evaluating 10 days of SEQ to STT (of at least 7 days) in adults and children with an H. pylori diagnosis were included. Forty-four trials (n=12,284) were included.[2]

Trials found SEQ to eradicate H. pylori 82% of the time compared to 75% in the STT group (risk difference [RD] 0.09; 95% CI, 0.06 to 0.11; $p < 0.001$).[2] High heterogeneity ($I^2 = 75\%$) and no difference between treatment in 20 of the trials, weakens the strength of the evidence for this outcome. Subgroup analysis of studies from 2008 and later found no difference between SEQ and STT regimens. Use of STT regimens for 14 days produced equivalent outcomes to SEQ regimens. Very low quality evidence in patients with clarithromycin resistance found SEQ to be effective in 75% of patients compared to 43% with STT.[2] Adverse events occurred in 20.4% of patients taking SEQ compared with 19.5% taking STT (RD 0.00; 95% CI, -0.02 to 0.02). Overall evidence was limited by lack of trial methodology reporting. Both SEQ and STT failed to meet desired eradication rates of ≥ 90%.

Esomeprazole vs. Omeprazole for GERD, PUD and H. Pylori Eradication

A systematic review and meta-analysis analyzed RCTs that compared omeprazole to esomeprazole in adult patients (18 and over) with PUD, GERD or H. pylori infection. Fifteen RCTs were identified, 7 related to GERD and 8 related to H. Pylori.[3] In trials were the indication for PPI therapy was GERD, the mean age was 45 to 58 years old and the majority (73%) had grade B or C erosive esophagitis based on the Los Angeles classification system. Esomeprazole was given as 20 mg or 40 mg daily compared to omeprazole 20 mg daily. In the trials of H. pylori eradication, the mean age was 39 to 59 years old.[3] Esomeprazole doses in the H. pylori trials were 40 mg twice daily in 3 trials and 20 mg twice daily in 5 trials, with all comparisons to omeprazole 20 mg twice daily. The main outcomes were resolution of GERD-related symptoms, esophagitis healing, peptic ulcer healing, H. pylori eradication, quality of life and adverse effects.

Esomeprazole 40 mg was found to be 6% more effective than omeprazole 20 mg for the healing of esophagitis at week 8 of treatment with a NNT of 17 (RR 1.07; 95% CI, 1.02 to 1.12).[3] Comparisons between esomeprazole 20 mg and omeprazole 20 mg at week 8 also demonstrated 3.3% higher healing rates with esomeprazole (RR 1.04; 95% CI, 1.01 to 1.08; NNT 30). The rates of heartburn resolution were 64% to 68% for esomeprazole 40 mg and 57% to 63% for patients taking omeprazole 20 mg. The efficacy between esomeprazole 20 mg and omeprazole 20 mg for H. pylori eradication was similar (RR 1.01; 95% CI, 0.96 to 1.05) and for esomeprazole 40 mg compared to omeprazole 20 mg (RR 1.16; 95% CI, 1.01 to 1.32).[3] Eradication rates ranged from 70-96% for esomeprazole (20 mg and 40 mg doses) and 65-88% for omeprazole. A subgroup analysis found that esomeprazole 40 mg was not more effective than omeprazole 20 mg at week 8 in participants in eastern Asia. There was insufficient data on comparisons between omeprazole and esomeprazole in PUD. Adverse events were similar between treatments.

Comparative Efficacy and Tolerability Between Esomeprazole and Omeprazole for GERD

Esomeprazole and omeprazole are commonly used treatments for GERD. This systematic review and meta-analysis was done to evaluate the efficacy and tolerability of omeprazole when used for the treatment of GERD in adults (18 years and over).[4] Ten randomized controlled trials (n=10,286) graded as high quality were included. Main outcome measures were healing rate (determined by endoscopic evaluation), GERD related symptom relief and tolerability (defined by withdrawal rates). Patients who had secondary GERD due to asthma, chronic cough, or laryngitis or GERD due to laryngopharyngeal reflux disease and trials of duplicate or un-extractable data were not included.

Healing rates were 87% for esomeprazole (20 and 40 mg doses combined) compared to 82% for omeprazole with a RR of 1.0564 (95% CI, 1.0128 to 1.1018; p=0.01; ARR 5%, NNT=20).[4] Healing rate comparisons between esomeprazole 20 mg and omeprazole 20 mg were similar (RR 1.0363; 95% CI, 0.9997 to 1.0743). Esomeprazole 40 mg healed 88% of patients compared to 82% of those treated with omeprazole 20 mg (RR 1.0690; 95% CI, 1.0043 to 1.1380; p = 0.001; ARR 6%, NNT 17).[4] For symptoms relief only the comparison between esomeprazole 20 mg and omeprazole 40 mg demonstrated significant differences between groups. Esomeprazole 20 mg was associated with 46% of patients obtaining relief from GERD symptoms compared to 68% in the omeprazole 20 mg group (ARR 22%, NNT 5). Tolerability was found to be similar between esomeprazole and omeprazole (RR 1.07; 95% CI, 0.88 to 1.30; p = 0.47).[4] Overall, esophageal healing was increased when higher doses were used but not different at equivalent doses of therapy. Esomeprazole 40 mg had the highest healing rates but there were no comparisons

to omeprazole 40 mg. Relief of GERD symptoms did not mirror healing rates and the only difference was found when omeprazole was used at a higher dose than esomeprazole.

Cochrane: Deprescribing versus Continuation of Chronic Proton Pump Inhibitor Use in Adults

The effects of deprescribing long-term use of PPI treatment compared to chronic daily use, defined as 28 days or longer, was evaluated.[7] Deprescribing involves gradually reducing therapy or stopping treatment in an effort to reduce overutilization of medication that is no longer indicated. Trials enrolling patients over the age of 18 with a diagnosis of GERD, functional dyspepsia, PUD, H. pylori, esophageal stricture or Barrett's esophagus were included. Six RCTs (n=1758) were identified that met the inclusion criteria of PPI discontinuation or decreased dosage, with or without the addition of an H2RA. Five trials evaluated on-demand therapy and one trial abruptly discontinued PPI therapy.[7] Trial durations were 13 weeks to 6 months in length and included the following PPIs: pantoprazole 20 mg, rabeprazole 10 mg and 20 mg and esomeprazole 20 mg. The majority of patients were 48-57 years of age and one trial enrolled patients with a mean age of 73. Patients were diagnosed with nonerosive reflux disease or mild forms of esophagitis as indicated by LA grade A or B. None of the trials were conducted in the United States (US). Lack of symptom control (heartburn, regurgitation, dyspepsia, epigastric pain, nausea, bloating and belching) was the primary outcome.

Trials that evaluated continuous PPI use compared to on-demand PPI use found a 9.2% incidence of lack of symptom control in the continuous group compared to 16.3% of the participants in the on-demand group (RR 1.71; 95% CI, 1.31 to 2.21), based on low quality of evidence.[7] Moderate quality of evidence found the amount of PPI taken each week was less with those taking on-demand PPIs compared to continuous therapy (MD -3.79; 95% CI -4.73 to -2.84).[7] Adverse events were only reported in two trials. The incidence of esophagitis and relapse rates of esophagitis was higher in patients treated with the on-demand dosage regimen. Satisfaction with PPI therapy was lower in patients taking on-demand dosing compared to continuous dosing based on very low quality evidence. External validity is low since no patients were from US sites. Small sample sizes and unclear to high risk of bias in a majority of the trials prevents strong conclusions.

<u>Subpopulations</u>

Cochrane: Drug Therapies for Gastric Acid Reduction in People with Cystic Fibrosis

A 2016 Cochrane Review evaluated the effect of drug therapies that reduce gastric acidity in adults and children with cystic fibrosis (CF).[5] Thirteen trials included placebo comparisons to PPIs (6 trials) and H2RAs (7 trials). The other trials conducted the following comparisons: PPIs vs. H2RAs vs. placebo; pancrelipase vs. pancrelipase and misoprostol; misoporstil vs. placebo; enprostil (not available in the US) vs. ranitidine; sodium bicarbonate vs. placebo; sodium bicarbonate vs. calcium carbonate.[5] Outcomes of interest were: nutritional status, symptoms associated with gastric acidity, fat absorption, lung function, quality of life and survival. Seventeen trials were included but not enough data was provided for a meta-analysis. Risk of bias and study quality was not able to be accessed due to lack of trial methodology. Very limited evidence from one trial with misoprostol suggests improvement in symptoms of abdominal pain in patients with CF. Misoprostol, omeprazole, cimetidine, ranitidine and sodium bicarbonate were found to improve measures of fat malabsorption based on low quality evidence. Additional high-quality evidence is needed to determine the benefits of gastric acid reduction in patients with CF.

Cochrane: Interventions for Heartburn in Pregnancy

Interventions to treat heartburn in pregnancy were the focus of a Cochrane Review.[6] Randomized controlled trials of diet, lifestyle modifications, PPIs, H2RAs, antacids and promotility drugs were included. Evidence was available for the following pharmaceuticals: prostigmine, combination of magnesium sulfate, aluminum hydroxide and simethicone and sucralfate. The primary outcome was complete heartburn relief.

Four trials (n=358) were identified. Two trials evaluated the effects of pharmaceutical therapy, using IM prostigmine 0.5 mg compared to placebo and magnesium sulfate, aluminum hydroxide and simethicone combination compared to placebo.[6] Complete heartburn relief was more common in patients receiving medical

treatment versus placebo (RR 1.85; 95% CI, 1.36 to 2.50) (moderate quality evidence). Evidence on partial relief of heartburn and adverse events were found to be similar between groups and was based on very low quality of evidence. One small trial found sucralfate, 1 g three times daily, was found to be more effective than dietary and lifestyle interventions (not described) for complete heartburn relief (RR 2.41; 95% CI, 1.42 to 4.07).[6] There was insufficient evidence for the outcomes of miscarriage, preterm labor, material satisfaction, fetal abnormalities, intrauterine growth restriction or low birthweight.

New Guidelines:

American College of Gastroenterology: Treatment of H. Pylori

In a 2017 guideline update the *American College of Gastroenterology (ACG)* outlined recommendations for the treatment of H. pylori updating its 2007 recommendations.[8] The quality of the study was assessed according to the GRADE methodology (very low to high) and recommendations were considered strong or conditional based on this evidence. Table 1 outlines indication for treatment of H. pylori and Table 2 outlines treatment recommendations. History of antibiotic use should be obtained from the patients before recommending treatment regimen. Testing to prove eradication should be done after treatment or H. pylori with a urea breath test, fecal antigen test or biopsy-based testing at least 4 weeks after completion of antibiotic therapy and at least 1-2 weeks after withholding PPI treatment. If treatment with one of the first-line options fail, additional regimens should avoid containing antibiotics that have been taken previously by the patient (strong recommendation; moderate quality of evidence).[8] Local antimicrobial resistance patterns should be taken into account when recommending salvage regimens. Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred therapy for patients previously receiving a regimen containing clarithromycin. If the patient received bismuth quadruple therapy the recommendation is for clarithromycin or levofloxacin-containing salvage regimens. Clarithromycin triple therapy should not be used as salvage regimen. Table 3 outlines salvage regimen options.

Table 1. Indications for treatment of H. Pylori[8]

Indication	Strength of recommendation/ quality of evidence
Patients with known H. pylori infection based on gastric biopsy during upper endoscopy in patients with dyspepsia	Strong/ high
Patients with symptoms of GERD who test positive for H. pylori (effect on GERD symptoms are unpredictable)	Strong/ high
Patients taking long-term, low-dose aspirin therapy who test positive for H. pylori to reduce risk of ulcer bleeding	Conditional / moderate
Patients who will be starting chronic NSAIDs and test positive for H. pylori	Strong / moderate
Testing and treating patients for H. pylori who are already taking NSAIDs	Conditional / low
Patients with unexplained iron deficiency anemia and who test positive for H. pylori	Conditional / low
Adults with idiopathic thrombocytopenic purpura (ITP) and who test positive for H. pylori	Conditional / very low

Table 2. H. Pylori Treatment Recommendations[8]

First-line Treatment Options	Strength of recommendation / quality of evidence
Clarithromycin triple therapy – Clarithromycin, a PPI, and amoxicillin or metronidazole for 14 days*	Conditional / low (for duration of treatment: moderate)
Bismuth quadruple therapy – PPI, bismuth, tetracycline and a nitroimidazole for 10-14 days (good option for patients with a penicillin allergy and previous macrolide exposure)	Strong / low
Concomitant therapy - PPI, clarithromycin, amoxicillin and a nitroimidazole for 10-14 days	Strong / low (for duration of treatment: moderate)
Sequential therapy - PPI and amoxicillin for 5-7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5-7 days	Conditional / low (for duration of treatment: very low)
Hybrid therapy - PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin, and a nitroimidazole for 7 days	Conditional / low (for duration of treatment: very low)
Levofloxacin triple therapy – PPI, levofloxacin and amoxicillin for 10-14 days	Conditional / low (for duration of treatment: very low)
Fluoroquinolone sequential therapy – PPI and amoxicillin for 5-7 days followed by a PPI, fluoroquinolone and nitroimidazole for 5-7 days	Conditional / low (for duration of treatment: very low)
* In regions where resistance is low (< 15%) and in patients with no history of previous history of macrolide exposure for any reason	

Table 3. Salvage Treatment for First-line Therapy Failures[8]

Salvage Regimen	Strength of recommendation / quality of evidence
Bismuth quadruple therapy for 14 days	Strong / low
Levofloxacin triple regimen for 14 days	Strong / moderate (for treatment duration: low)
Concomitant therapy for 10-14 days	Conditional / very low
Rifabutin triple regimen – PPI, amoxicillin and rifabutin for 10 days	Conditional / moderate (for treatment duration: very low)
High-dose dual therapy – PPI and amoxicillin for 14 days	Conditional / low (for treatment duration: very low)

NICE: GERD in Children and Young People

In a 2015 update, NICE updated recommendations for the treatment for GERD in infants (less than 1 year), children (1-12 years) and young (12-18 years) people.[10] Guidelines do not recommend treatment of regurgitation with PPIs or H2RAs in infants and children if it occurs as an isolated symptom. Metoclopramide, droperidone or erythromycin should be used for gastro-esophageal reflux or GERD only after consultation with a specialist to weigh risks and benefits. A trial lasting 4 weeks of a PPI or H2RA should be considered in patients who are unable to verbalize symptoms who have overt regurgitation and one of the following:

- Unexplained feeding difficulties
- Distressed behavior
- Faltering growth

PPI and H2RAs can also be used for a 4-week trial in children and young people with persistent heartburn, retrosternal or epigastric pain.[10] Consultation with a specialist for a possible endoscopy should be considered for patients that continue to have symptoms after a 4-week trial or who have reoccurrence of symptoms after stopping treatment. Patients who have endoscopy proven reflux esophagitis should be considered for repeat endoscopic evaluation to guide future treatment. Choice of treatment between PPIs and H2RAs should be dependent upon the availability of age-appropriate preparations, the preference of patient or caregiver and cost.[10]

CHEST: Treatment of Unexplained Chronic Cough

A systematic review of randomized trials was done to provide recommendations for the management of unexplained chronic cough. Trials of patients twelve and older with a chronic cough lasting more than 8 weeks with no causative explanation were included. Trials were graded for quality and incorporated into guideline recommendations. For the purpose of this review, only recommendations pertaining to PPIs and H2RAs will be included. The evidence found no benefit of PPI therapy on cough severity or quality of life in adult patients without a history of acid gastroesophageal reflux disease based on one trial with high-dose esomeprazole (weak recommendation based on low to very-low quality of evidence).

New Formulations:

In January of 2016 a new form of dexlansoprozole, Dexilant SoluTab, was approved.[11] This delayed-release orally disintegrating tablet (DT) is indicated for the maintenance of healed erosive esophagitis (EE) and relief of heartburn and treatment of symptomatic non-erosive GERD in patients 12 and over. The dexlansoprozole SoluTab is not recommended for the healing of EE. The dose is given as one 30 mg SoluTab at least 30 minutes before a meal. Two 30 mg dexlansoprozole SoluTabs are not interchangeable with one 60 mg dexlansoprozole oral capsule and therefore there is no evidence for the efficacy of dexlansoprazole SoluTabs in EE healing and they are not recommended for this indication.

In July of 2016 dexlansoprazole capsules obtained the indication for use in pediatric patients 12-17 years old for healing all grades of EE.[11] Both dexlansoprazole capsules and dexlansoprazole DT received approval for use in pediatric patients 12-17 years for maintenance of healed EE and relief of heartburn and treatment of heartburn associated with symptomatic non-erosive GERD.

New FDA Safety Alerts: No new safety alerts identified.

References:

1. Pinto-Sanchez MI, Yuan Y, Bercik P, Moayyedi P. Proton pump inhibitors for functional dyspepsia. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2017. doi:10.1002/14651858.CD011194.pub2.

2. Nyssen OP, McNicholl AG, Megraud F, et al. Sequential versus standard triple first-line therapy for Helicobacter pylori eradication. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2016. doi:10.1002/14651858.CD009034.pub2.

3. Teng M, Khoo AL, Zhao YJ, et al. Meta-analysis of the effectiveness of esomeprazole in gastroesophageal reflux disease and Helicobacter pylori infection. *J Clin Pharm Ther*. 2015;40(4):368-375. doi:10.1111/jcpt.12277.

4. Qi Q, Wang R, Liu L, Zhao F, Wang S. Comparative effectiveness and tolerability of esomeprazole and omeprazole in gastro-esophageal reflux disease: A systematic review and meta-analysis. [Review]. *Journal of Clinical Pharmacology*. 2015;53(10):803-810. doi:10.5414/CP202396.

5. Ng SM, Moore HS. Drug therapies for reducing gastric acidity in people with cystic fibrosis. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2016. doi:10.1002/14651858.CD003424.pub4.

6. Phupong V, Hanprasertpong T. Interventions for heartburn in pregnancy. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2015. doi:10.1002/14651858.CD011379.pub2.

7. Boghossian T, Rashid F, Thompson W. Deprescribing versus continuation of chronic proton pump inhibitor use in adults (Review). *Cochrane Database of Systematic Reviews*. 2017. doi:10.1002/14651858.CD011969.pub2.

8. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am J Gastroenterol*. 2017;112(2):212-239. doi:10.1038/ajg.2016.563.

9. Gibson P, Wang G, McGarvey L, et al. Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. [Review]. *Chest*. 2016;149(1):27-44. doi:10.1378/chest.15-1496.

10. National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease in children and young people: diagnosis and management. 2015. nice.org.uk/guidance/ng1.

11. Dexilant (dexlansoprazole delayed-release capsules), Dexilant Solu Tabs (dexlansoprazole delayed-release orally disintegrating tablets). Takeda Pharmaceuticals America, Inc. Deerfield, IL.

Appendix 1: Current Preferred Drug List

Proton Pump Inhibitors:

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE DR	OMEPRAZOLE	OMEPRAZOLE	Y
ORAL	CAPSULE DR	PRILOSEC	OMEPRAZOLE	Y
ORAL	TABLET DR	PANTOPRAZOLE SODIUM	PANTOPRAZOLE SODIUM	Y
ORAL	TABLET DR	PROTONIX	PANTOPRAZOLE SODIUM	Y
ORAL	CAP DR BP	DEXILANT	DEXLANSOPRAZOLE	N
ORAL	CAP DR SPR	ACIPHEX SPRINKLE	RABEPRAZOLE SODIUM	N
ORAL	CAPSULE	OMEPRAZOLE-SODIUM BICARBONATE	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	CAPSULE	ZEGERID	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	CAPSULE	ZEGERID OTC	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	CAPSULE DR	ESOMEPRAZOLE MAGNESIUM	ESOMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	ESOMEPRAZOLE STRONTIUM	ESOMEPRAZOLE STRONTIUM	N
ORAL	CAPSULE DR	HEARTBURN TREATMENT 24 HOUR	LANSOPRAZOLE	N
ORAL	CAPSULE DR	LANSOPRAZOLE	LANSOPRAZOLE	N
ORAL	CAPSULE DR	NEXIUM	ESOMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	NEXIUM 24HR	ESOMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	OMEPRAZOLE MAGNESIUM	OMEPRAZOLE MAGNESIUM	N
ORAL	CAPSULE DR	PREVACID	LANSOPRAZOLE	N
ORAL	CAPSULE DR	PREVACID 24HR	LANSOPRAZOLE	N
ORAL	GRANPKT DR	PROTONIX	PANTOPRAZOLE SODIUM	N
ORAL	PACKET	OMEPRAZOLE-SODIUM BICARBONATE	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	PACKET	ZEGERID	OMEPRAZOLE/SODIUM BICARBONATE	N
ORAL	SUSPDR PKT	NEXIUM	ESOMEPRAZOLE MAGNESIUM	N
ORAL	SUSPDR PKT	PRILOSEC	OMEPRAZOLE MAGNESIUM	N
ORAL	TAB RAP DR	PREVACID	LANSOPRAZOLE	N
ORAL	TABLET DR	ACIPHEX	RABEPRAZOLE SODIUM	N
ORAL	TABLET DR	NEXIUM 24HR	ESOMEPRAZOLE MAGNESIUM	N
ORAL	TABLET DR	OMEPRAZOLE	OMEPRAZOLE	N
ORAL	TABLET DR	PRILOSEC OTC	OMEPRAZOLE MAGNESIUM	N
ORAL	TABLET DR	RABEPRAZOLE SODIUM	RABEPRAZOLE SODIUM	N

Histamine-2 Receptor Antagonists:

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	SYRUP	RANITIDINE HCL	RANITIDINE HCL	Y
ORAL	SYRUP	ZANTAC	RANITIDINE HCL	Y
ORAL	TABLET	ACID CONTROLLER	FAMOTIDINE	Y
ORAL	TABLET	ACID REDUCER	FAMOTIDINE	Y
ORAL	TABLET	ACID REDUCER	RANITIDINE HCL	Y
ORAL	TABLET	FAMOTIDINE	FAMOTIDINE	Y
ORAL	TABLET	HEARTBURN PREVENTION	FAMOTIDINE	Y
ORAL	TABLET	HEARTBURN RELIEF	FAMOTIDINE	Y
ORAL	TABLET	HEARTBURN RELIEF	RANITIDINE HCL	Y
ORAL	TABLET	PEPCID AC	FAMOTIDINE	Y
ORAL	TABLET	RANITIDINE	RANITIDINE HCL	Y
ORAL	TABLET	RANITIDINE HCL	RANITIDINE HCL	Y
ORAL	TABLET	WAL-ZAN 75	RANITIDINE HCL	Y
ORAL	TABLET	ZANTAC 75	RANITIDINE HCL	Y
ORAL	CAPSULE	AXID	NIZATIDINE	N
ORAL	CAPSULE	NIZATIDINE	NIZATIDINE	N
ORAL	CAPSULE	RANITIDINE HCL	RANITIDINE HCL	N
ORAL	ORAL SUSP	FAMOTIDINE	FAMOTIDINE	N
ORAL	ORAL SUSP	PEPCID	FAMOTIDINE	N
ORAL	SOLUTION	AXID	NIZATIDINE	N
ORAL	SOLUTION	CIMETIDINE	CIMETIDINE HCL	N
ORAL	SOLUTION	CIMETIDINE HCL	CIMETIDINE HCL	N
ORAL	SOLUTION	NIZATIDINE	NIZATIDINE	N
ORAL	TAB CHEW	ACID CONTROLLER COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	ACID REDUCER COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	DUAL ACTION	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	DUAL ACTION COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	DUO FUSION	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	PEPCID COMPLETE	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB CHEW	TUMS DUAL ACTION	FAMOTIDINE/CA CARB/MAG HYDROX	N
ORAL	TAB RAPDIS	PEPCID RPD	FAMOTIDINE	N
ORAL	TABLET	ACID CONTROL	FAMOTIDINE	N
ORAL	TABLET	ACID CONTROL	RANITIDINE HCL	N
ORAL	TABLET	ACID CONTROLLER	FAMOTIDINE	N
ORAL	TABLET	ACID REDUCER	CIMETIDINE	N

ORAL	TABLET	ACID REDUCER	FAMOTIDINE	N
ORAL	TABLET	ACID REDUCER	RANITIDINE HCL	N
ORAL	TABLET	ACID REDUCER 150	RANITIDINE HCL	N
ORAL	TABLET	CIMETIDINE	CIMETIDINE	N
ORAL	TABLET	FAMOTIDINE	FAMOTIDINE	N
ORAL	TABLET	HEARTBURN PREVENTION	FAMOTIDINE	N
ORAL	TABLET	HEARTBURN RELIEF	CIMETIDINE	N
ORAL	TABLET	HEARTBURN RELIEF	FAMOTIDINE	N
ORAL	TABLET	HEARTBURN RELIEF	RANITIDINE HCL	N
ORAL	TABLET	HEARTBURN RELIEF 150	RANITIDINE HCL	N
ORAL	TABLET	PEPCID	FAMOTIDINE	N
ORAL	TABLET	PEPCID AC	FAMOTIDINE	N
ORAL	TABLET	RANITIDINE HCL	RANITIDINE HCL	N
ORAL	TABLET	TAGAMET	CIMETIDINE	N
ORAL	TABLET	TAGAMET HB	CIMETIDINE	N
ORAL	TABLET	WAL-ZAN 150	RANITIDINE HCL	N
ORAL	TABLET	ZANTAC	RANITIDINE HCL	N

Appendix 2: New Comparative Clinical Trials

A total of 292 citations were manually reviewed from the initial literature search. After further review, 282 citations were excluded and no randomized trials were included because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2017
Search Strategy:

#	Searches	Results
1	ranitidine.mp. or Ranitidine/	2787
2	cimetidine.mp. or Cimetidine/	2540
3	famotidine.mp. or Famotidine/	1102
4	nizatidine.mp. or Nizatidine/	189
5	1 or 2 or 3 or 4	5904
6	limit 5 to (english language and humans and yr="2015 -Current")	121
7	limit 6 to (clinical trial or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews)	30
8	omeprazole.mp. or Omeprazole/	7600
9	pantoprozole.mp.	6
10	dexlansoprazole.mp. or Dexlansoprazole/	69
11	esomeprazole.mp. or Esomeprazole/	1126
12	lansoprazole.mp. or Lansoprazole/	2263
13	rabeprazole.mp. or Rabeprazole/	1062
14	8 or 9 or 10 or 11 or 12 or 13	9501
15	limit 14 to (english language and humans and yr="2015 -Current")	443
16	limit 15 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	171

Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions

Requires PA:

- Preferred PPIs beyond 68 days' duration
- Non-preferred PPIs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/
- Individual components for treatment of *H. pylori* that are preferred products

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a preferred PPI?	**Yes:** Go to #5	**No:** Go to #3
3. Is the treating diagnosis an OHP-funded condition (see **Table**)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by OHP.
4. Will the prescriber consider changing to a preferred PPI product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives.	**No:** Go to #5
5. Has the patient already received 68 days of PPI therapy for either of the following diagnoses: • Esophagitis or gastro-esophageal reflux disease with or without esophagitis (K20.0-K21.9); or • Current *H. pylori* infection?	**Yes:** Go to #6	**No:** Go to #7
6. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalizations?	**Yes:** Approve for 1 year	**No:** Go to #7
7. Does the patient have a history of gastrointestinal ulcer or bleed and have one or more of the following risk factors? • Age 65 years or older • Requires at least 3 months of continuous daily: i. Anticoagulant; ii. Aspirin or non-selective NSAID; or iii. Oral corticosteroid	**Yes:** Approve for 1 year	**No:** Go to #8

8. Are the indication, daily dose and duration of therapy consistent with criteria outlined in the **Table**? Message: OHP-funded conditions are listed in the **Table**.	**Yes:** Approve for recommended duration.	**No:** Pass to RPh. Deny; medical appropriateness or not funded by OHP Message: Patient may only receive 8 weeks of continuous PPI therapy. RPh may approve a quantity limit of 30 doses (not to exceed the GERD dose in the **Table**) over 90 days if time is needed to taper off PPI. Note: No specific PPI taper regimen has proven to be superior. H2RAs may be helpful during the taper. Preferred H2RAs are available without PA.

Table. Dosing and Duration of PPI Therapy for OHP Funded Conditions.

Funded OHP Conditions*	Maximum Duration	Maximum Daily Dose
GERD: Esophagitis (K20.0-K20.9) Esophageal reflux (K21.0-K21.9)	8 weeks* *Treatment beyond 8 weeks is not funded by OHP.	Dexlansoprazole 30 mg Dexlansoprazole Solu Tab 30 mg Esomeprazole 20 mg Lansoprazole 15 mg Omeprazole 20 mg Pantoprazole 40 mg Rabeprazole 20 mg
H. pylori Infection	2 weeks	
Achalasia and cardiospasm Barrett's esophagus with dysplasia Stricture and stenosis of esophagus Perforation of esophagus Dyskinesia of esophagus Gastroesophageal laceration-hemorrhage syndrome Esophageal hemorrhage Gastric ulcer Duodenal ulcer Peptic ulcer Gastrojejunal ulcer Gastritis and duodenitis Zollinger-Ellison Neoplasm of the thyroid or parathyroid gland Malignant mast cell tumors Multiple endocrine neoplasia [MEN] type I	1 year	Dexlansoprazole 60 mg Dexlansoprazole 30 mg† Esomeprazole 40 mg Lansoprazole 60 mg Omeprazole 40 mg Pantoprazole 80 mg Rabeprazole 40 mg

*A current list of funded conditions is available at: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

† Dexlansoprazole SoluTab 30 mg (given as 2 SoluTabs at once) are not recommended for healing of erosive esophagitis.

P&T / DUR Review: *5/17(KS); 1/16; 5/15; 3/15; 1/13; 2/12; 9/10; 3/10; 12/09; 5/09; 5/02; 2/02; 9/01, 9/98*
Implementation: *9/17;6/8/16; 4/15; 5/13; 5/12; 1/11; 4/10; 1/10; 9/06, 7/06, 10/04, 3/04*

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

Policy Evaluation: Proton Pump Inhibitors (PPIs)

Research Questions:

1. Has the utilization of proton pump inhibitors (PPIs) for unfunded diagnoses decreased since the implementation of prior authorization criteria? Has there been an increase in prescribing of PPIs for funded diagnoses?
2. Has the percent of patients on PPI therapy > 8 weeks decreased since implementation of the prior authorization criteria?
3. Has the PA resulted in an interruption in therapy for those with severe conditions?
4. Has the utilization rate of other acid-blocking agents [histamine-receptor antagonists (H2As) or antacids] changed since the PPI policy change?

Conclusions:

- Utilization of PPIs for unfunded diagnoses has decreased since the implementation of the prior authorization criteria. Before the criteria, 9.4% of claims were for unfunded diagnoses and after the criteria, only 2.7% of claims were for unfunded diagnoses.
- The prior authorization criteria did not result in an increase in prescribing for funded diagnoses.
- The PA criteria successfully limited the use of PPIs for this indication as illustrated by the decrease in PPI therapy for esophageal reflux and esophagitis for > 8 weeks between the control and study groups (7.9% vs. 0.4%).
- Of the identified index events without a paid claim, none of the claims in either group had a prior severe condition.
- There was a limited number of claims for H2As or antacids in the 90 days after the index event in both groups (30 claims in the control group versus 35 claims in the study group).

Recommendations:

- Maintain current PA policy for PPIs
- Future policy evaluation to evaluate additional safety concerns such as possible increase in hospitalization

Background:

Gastroesophageal reflux disease (GERD) is a common condition encountered in the Western World, with a prevalence of about 10 to 20 percent.[1] PPIs are the mainstay of treatment for erosive esophagitis due to GERD and other conditions such as Zollinger-Ellison syndrome, *Helicobacter pylori* (*H. pylori*) GI tract infection, duodenal ulcers, gastric ulcers and Crohn's disease related ulcers.[2] PPIs are commonly used long-term for acid suppression in patients with GERD; however, there is insufficient evidence to support the use of PPIs for greater than 8 weeks for the treatment of GERD.[3] Long-term use of PPIs may be associated with significant risks including *Clostridium difficile* infection, pneumonia, and bone fractures of the hip, wrist and spine.[4] Additional FDA safety alerts include nutritional deficiencies such as low magnesium levels and cyanocobalamin (vitamin B-12) deficiency with long-term PPI use.[3]

A recently published randomized controlled trial, that included 38,019 men and women aged 45 years and older, concluded that PPI use was associated with an increased risk of infectious gastroenteritis hospitalizations.[5] Additionally, they found that there is a dose response relationship, with higher doses being

associated with higher risk of hospitalization due to infectious gastroenteritis.[5] Preliminary, observational data presented at the American Heart Association's Scientific Sessions 2016, reported that PPI use increased overall ischemic stroke risk by 21% (relative risk).[6]

Due to safety concerns and limited long term efficacy of PPIs, the Health Evidence Review Committee (HERC) determined long-term (>8 weeks) treatment of GERD or esophagitis were no longer funded conditions.[7] A complete list of PPI indications, corresponding diagnosis codes, and the corresponding Oregon Health Plan (OHP) funding line are listed in **Appendix 2.** PPIs are also used for the treatment of dyspepsia and dyskinesia of the esophagus, which are also unfunded conditions. Other Food and Drug Administration (FDA) approved indications for PPIs and H2As remain funded conditions.

The symptoms of GERD or other GI related conditions may be non-specific and concerning, such as non-cardiac chest pain, which may prompt a visit to the ED. Other common symptoms include heartburn, epigastric or abdominal pain, bloating, nausea and vomiting.[1] Antacids and H2As are also used for the treatment of GERD and dyspepsia which remain unrestricted by OHP FFS.[3] Evidence shows there is no difference in the effectiveness of H2As for the treatment of GERD.[3]

The previous drug use evaluation performed by the Drug Use Research & Management Program in March 2015 found that PPI use >8 weeks occurred in approximately 75% of the Oregon Health Plan (OHP) Fee-for-Service (FFS) population. Prior authorization (PA) criteria was established and implemented on June 8, 2016 to restrict the use of PPIs for more than 60 days for unfunded diagnoses (**Appendix 3**). The goals of this review are to assess the impact of the PA criteria on the utilization and duration of PPIs, determine if the PA resulted in an unintended interruption in therapy for severe conditions, and its effect on the utilization of other acid-lowering agents.

Methods:
Patients were included in this analysis if they had a paid or denied FFS drug claim for a PPI in **Appendix 1** from 6/1/15 through 12/7/16.

This analysis used a pre- and post-observational cohort to compare utilization before and after the implementation of the PA criteria, which occurred on 6/8/16. Patients with a paid or denied FFS claim for PPIs defined in **Appendix 1** from 6/1/15 to 11/30/15 were defined as the control group; patients with a paid or denied FFS claim for PPIs defined in **Appendix 1** from 6/8/16 through 12/7/16 were defined as the study group. Denied claims were defined as claims with an Explanation of Benefit (EOB) Code 1056 ("PA Required") or 1059 ("Non-Preferred Drug") with no simultaneous EOB code of 0154 ("Bill Part D"), 0389 ("Bill Part B"), 1109 ("Drug Covered by Medicare Part D") or 2017 ("Bill Managed Care"). If patients were identified in both cohorts, they were excluded from both groups. The first PPI paid or denied claim per patient during the control and study periods was designated the index event (IE) and this was used to compare utilization between control and study group.

Patients were excluded if they had Medicare Part D coverage as indicated by benefit packages of BMM, BMD, MND or MED. Patients were also excluded if they had less than 75% days of combined FFS or coordinated care organization eligibility from 11 months prior to the index month to 2 months after the index month. Patients were excluded if they had a prior claim (FFS or CCO) for a PPI within the 90 days prior to the IE to capture new starts only. Baseline characteristics of age, gender, and ethnicity were assessed at the time of the IE. Patients with an IE for a PPI, paid FFS or CCO claims for an H2A or antacid listed in **Appendix 1** within 90 days of the IE, were identified.

Patients were categorized into groups based on any of the diagnoses of interest in **Appendix 2** during the 12 months prior to the index claim in either encounter or FFS claims. These groups are mutually exclusive; if a funded diagnosis was identified, an unfunded diagnosis was not included in the search. To compare PPI therapy > 8 weeks before and after the PA was implemented, patients with continuous PPI therapy (any drug in PPI class,) without a gap in therapy > 15 days

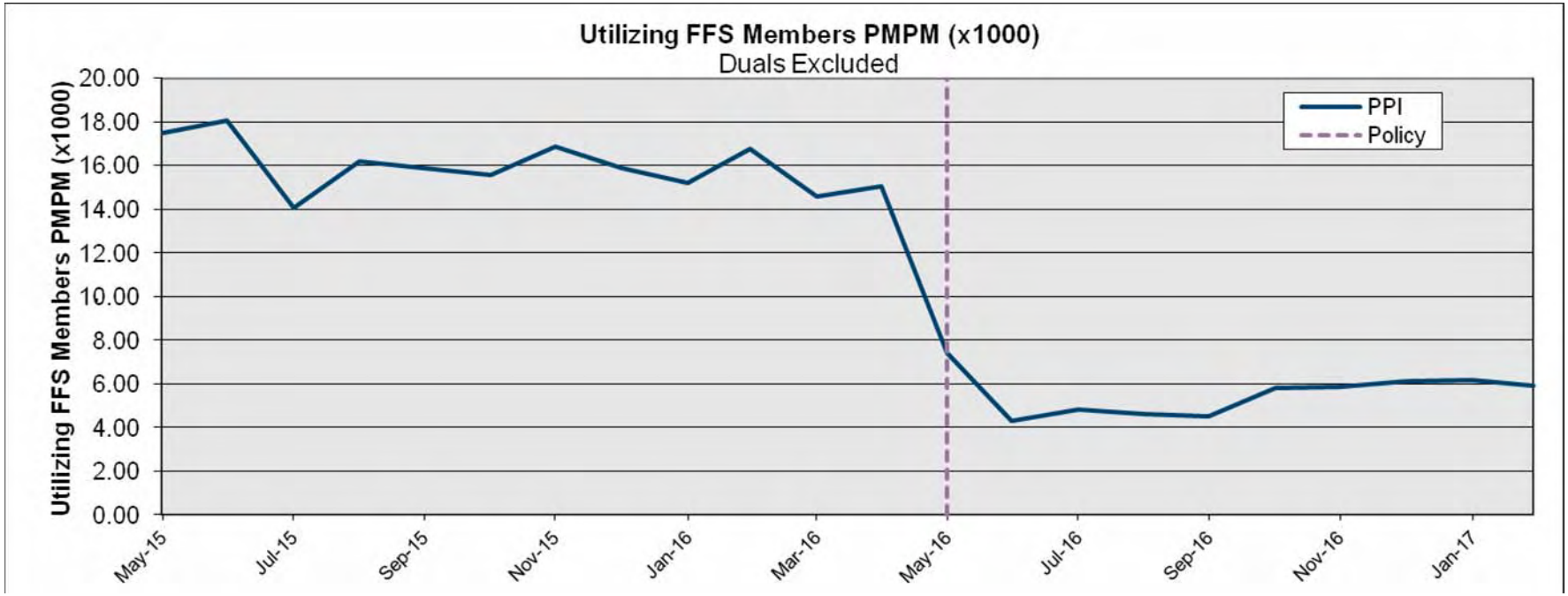
were included. Patients with less than 60 days of continuous therapy were excluded. This group was also flagged for any diagnosis in **Appendix 2** during the 12 months prior to the index claim.

Patients with a denied index claim, those who did not receive a PPI within 14 days, between 15 and 90 days, or who never received the drug were identified within FFS and CCO claims. Those who never received the drug with an ICD-9 or ICD-10 diagnosis for a severe condition listed in **Appendix 2**, were identified.

Results:

Figure 1 shows the utilization of PPIs by FFS per member per month (PMPM) from June 2015 to March 2017. A significant decrease in utilization occurred near June 2016 following the PA policy implementation (from 15 PMPM to 7.4 PMPM).

Figure 1: Utilization of PPIs: Unique patients per 10,000 members per month



Demographics of FFS members in the control and study groups are listed in Table 1. A total of 1,310 IEs were identified in the control group and 1,390 IEs were identified in the study group. The majority of FFS members in both the control and study groups (approximately 88% in both groups) had a mean age of 19-64 years. The percentage of patients < 19 years old and > 64 years old were similar in both groups. The amount of females in each group was similar as well (69.4% in the control group and 62.9% in the study group). There were significantly less paid claims for therapy > 8 weeks in the study group (12.1%) compared to the control group (30.4%). There were more claims for H2As or antacids in the 90 days after the IE in the study group (71 total claims) compared to the control group (43 total claims). Within the study group, there were more H2A claims if the PPI IE was a denied claim.

Table 1: Demographics

	Before PA (Control Group)						After PA (Study Group)					
	All Index Events		**Index Event Paid Claim**		**Index Event Denied Claim**		**All Index Events**		**Index Event Paid Claim**		**Index Event Denied Claim**	
N=	**1,310**		1,178	89.9%	132	10.1%	**1,387**		743	53.6%	644	46.4%
Mean age (range)	37.2	(0-87)	37.7	(3-87)	32.5	(0-64)	37.7	(0-73)	36.6	(2-73)	39.0	(0-66)
< 19 years	119	11.8%	119	9.1%	36	2.7%	164	11.8%	99	7.1%	65	4.7%
19-64 years	1,051	87.6%	1,051	80.2%	96	7.3%	1,216	87.7%	641	46.2%	575	41.7%
> 64 years	8	0.6%	8	0.6%	0	0.0%	7	0.5%	3	0.2%	4	0.3%
Female	909	69.4%	816	62.3%	93	7.1%	872	62.9%	461	33.2%	411	29.6%
White	498	38.0%	441	33.7%	57	4.4%	360	26.0%	182	13.1%	178	12.8%
Therapy > 8 Weeks	400	30.5%	398	30.4%	2	0.2%	178	12.8%	168	12.1%	10	0.7%
FFS or CCO H2A claim in 90 days after IE	35	2.7%	25	1.9%	10	0.8%	60	4.3%	18	1.3%	42	3.0%
FFS or CCO Antacid claim in 90 days after IE	8	0.6%	8	0.6%	0	0.0%	11	0.8%	8	0.6%	3	0.2%

Table 2 compares associated diagnoses in the control and study groups. Of the 1,310 IEs identified in the control group, the majority (89.9%) were paid claims. Of the 1,387 IEs identified in the study group, following PA implementation, there were 743 (53.6%) paid claims and 644 (46.4%) denied claims. Only 2 IEs in the study group were for severe funded conditions, both of which were paid claims. There were no claims for severe funded conditions in the control group. Four hundred thirty-six claims (33.3%) in the control group were for funded conditions compared to 278 claims (20%) in the study group. However, there was a larger number of IEs without diagnoses identified in the study group (77%), compared to the control group (57.3%). Of the 436 IEs for funded conditions, 283 of these were for esophageal reflux or esophagitis < 8 weeks duration, with less IEs for this indication in the study group (63 of 276; 4.5%). There were more IEs for PPIs for esophageal reflux or esophagitis > 8 weeks duration in the control group (7.9%) compared to the study group (0.4%). All of these were paid claims in both groups.

Table 2: Use of PPIs based on diagnoses

	Before PA (Control Group)						After PA (Study Group)					
	All Index Events		Index Event Paid Claim		Index Event Denied Claim		All Index Events		Index Event Paid Claim		Index Event Denied Claim	
N=	1,310		1,178	89.9%	132	10.1%	1,390		742	53.4%	648	46.6%
Funded (Severe conditions)	**0**	**0.0%**		**0.0%**		**0.0%**	**2**	**0.1%**	**2**	**0.1%**		**0.0%**
Malignant mast cell tumors	0	0.0%		0.0%		0.0%	1	0.1%	1	0.1%		0.0%
Neoplasm of uncertain behavior of other and unspecified endocrine glands	0	0.0%		0.0%		0.0%	1	0.1%	1	0.1%		0.0%
Multiple endocrine neoplasia (MEN) type I	0	0.0%		0.0%		0.0%	0	0.0%		0.0%		0.0%
Zollinger-Ellison	0	0.0%		0.0%		0.0%	0	0.0%		0.0%		0.0%
Funded	**436**	**33.3%**	**384**	**29.3%**	**52**	**4.0%**	**278**	**20.0%**	**142**	**10.2%**	**136**	**9.8%**
GI Ulcers; Gastritis; Duodenitis; GI hemorrhage	194	14.8%	182	13.9%	12	0.9%	216	15.6%	121	8.7%	95	6.8%
H. pylori infection	24	1.8%	21	1.6%	3	0.2%	19	1.4%	12	0.9%	7	0.5%
Perforation of esophagus	0	0.0%		0.0%		0.0%	0	0.0%		0.0%		0.0%
Stricture and stenosis of esophagus	6	0.5%	6	0.5%		0.0%	12	0.9%	3	0.2%	9	0.6%
Barrett's esophagus with dysplasia; Cancer of esophagus	13	1.0%	12	0.9%	1	0.1%	4	0.3%	1	0.1%	3	0.2%
Barrett's esophagus without dysplasia	0	0.0%		0.0%		0.0%	9	0.6%	3	0.2%	6	0.4%
Esophageal reflux; Esophagitis (< 8 weeks duration)	283	21.6%	241	18.4%	42	3.2%	63	4.5%	20	1.4%	43	3.1%
Unfunded	**123**	**9.4%**	**121**	**9.2%**	**2**	**0.2%**	**39**	**2.8%**	**24**	**1.7%**	**15**	**1.0%**
Esophageal reflux; Esophagitis (> 8 weeks duration)	103	7.9%	103	7.9%		0.0%	5	0.4%	5	0.4%		0.0%
Esophageal spasm; Diverticulum of esophagus	11	0.8%	11	0.8%		0.0%	22	1.6%	11	0.8%	11	0.8%
Dyspepsia	18	1.4%	16	1.2%	2	0.2%	12	0.9%	10	0.7%	2	0.1%
Dyskinesia of esophagus	2	0.2%	2	0.2%		0.0%	3	0.2%	1	0.1%	2	0.1%
None of the Above	**751**	**57.3%**	**673**	**51.4%**	**78**	**6.0%**	**1,068**	**77.0%**	**575**	**41.5%**	**493**	**35.5%**

Table 3 highlights the disposition of denied claims in both the control and study groups. Of the 132 denied claims in the control group, 38 (28.8%) received the drug (through FFS or CCOs) within 14 days and 10 (7.6%) received the drug within 15 to 90 days. Of the 644 denied claims in the study group, 132 (20.5%) received the drug within 14 days and 124 (19.3%) received the drug within 15 to 90 days. There were 84 IEs in the control group and 388 in the study group who never received the drug, however none of these in either group had a prior severe condition. Table 4 shows the majority of patients with a denied claim never followed through with a PA request in both the control group (n=107; 81.1%) and study group (n=468; 72.7%). This is similar to results from previous policy evaluations.

Table 3: Disposition of denied claims (both FFS and CCO)

Before PA (Control Group)

			Days to Claim	
Patients with Denied Pharmacy Claim	**132**	**%**	**Avg**	**(min-max)**
Receive drug within 14 days	38	28.8%	3.7	(0-14)
Receive drug between 15 and 90 days	10	7.6%	38	(17-81)
Never receive drug (or more than 90 days)	84	63.6%	n/a	n/a
- Never receive a drug - with prior severe condition	0			

After PA (Study Group)

			Days to Claim	
Patients with Denied Pharmacy Claim	**644**	**%**	**Avg**	**(min-max)**
Receive drug within 14 days	132	20.5%	5.0	(0-14)
Receive drug between 15 and 90 days	124	19.3%	42	(15-89)
Never receive drug (or more than 90 days)	388	60.2%	n/a	n/a
- Never receive a drug - with prior severe condition	0			

Table 4: PA Status for Patients with Denied Pharmacy Claim as Index Event

PA Requested within 14 days of Denied Claim

	Control Group		Study Group	
Patients with Denied Claim =	132		644	
PA Requested	25	18.9%	176	27.3%
Approved	25	18.9%	174	27.0%
Denied	0	0.0%	2	0.3%
No PA Request	107	81.1%	468	72.7%

Discussion:

A decrease in PPI utilization was observed following the PA criteria implementation in June 2016, which limits the use of PPIs for esophageal reflux and esophagitis to no more than 8 weeks. The PA criteria successfully limited the use of PPIs for this indication as illustrated by the decrease in IEs for esophageal reflux and esophagitis for > 8 weeks between the control and study groups (7.9% vs. 0.4%). There were significantly less paid claims for therapy > 8 weeks in the study group (12.8%) compared to the control group (30.5%). There was overall low utilization for severe conditions and the PA criteria did not result in a barrier to therapy for those with a severe funded condition. There were a large number of events in both groups without a correlating diagnosis (57.3% in the control group and 77% in the study group). This is somewhat expected for this class of medications, as they are often continued following hospital admissions or used for gastrointestinal ulcer prophylaxis with other agents, such as non-steroidal anti-inflammatory drugs. There were limited claims in FFS and CCO drug claims for H2As or antacids after IEs and there was no difference in claims between the control and study groups. Therefore, it does not appear that the PA criteria resulted in an increase in these other classes.

Similar to what has been seen in other policy evaluations, the impact of having a PA policy in place has a significant impact on utilization. The majority of denied claims were not followed through with a PA request. However, for those who never received the drug, there were no patients who had a severe condition.

Limitations:

The data that was collected and analyzed were claims data, which makes it difficult to connect a specific diagnosis with the medication prescribed. Assumptions are made as to whether the medication is being prescribed for a certain diagnosis. This evaluation only looked at the first claim, or IE. More inclusive data would also include recurring claims for the medications of interest.

Another limitation of this review is the majority of the medications included for review are also available over the counter, without a prescription. If a patient is purchasing a PPI, H2A, or antacid over the counter, that data will not be included in the claims data collected. The high percentage of patients who never received the drug following a denied claim (63.6% in the control group and 61.9% in the study group), may be increased due to the availability of PPIs over the counter.

Additionally, due to the time constraints of this evaluation, data regarding other potential consequences of the PA criteria, such as hospitalization due to GERD symptoms, could not be included. In further analyses, this may be a potential area to review in order to determine additional impact of the PA criteria.

References:

1. Katz PO, Gerson LB, Vela MF. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol*. 2013;108(3):308-328. doi:10.1038/ajg.2012.444.

2. Drug Result Page - MICROMEDEX®. http://www.micromedexsolutions.com/micromedex2/librarian/CS/954CFD/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/BF9146/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=pantoprazole&UserSearchTerm=pantoprazole&SearchFilter=filterNone&navitem=searchALL#. Accessed November 3, 2016.

3. Class Update: Proton Pump Inhibitors and Histamine-2 Receptor Antagonists. http://www.orpdl.org/durm/meetings/meetingdocs/2015_03_26/archives/2015_03_26_PPIandH2RAClassUpdate.pdf. Accessed January 26, 2017.

4. Reducing Adverse Effects of Proton Pump Inhibitors - American Family Physician. http://www.aafp.org/afp/2012/0701/p66.html. Accessed November 3, 2016.

5. Chen Y, Liu B, Glass K, Du W, Banks E, Kirk M. Use of Proton Pump Inhibitors and the Risk of Hospitalization for Infectious Gastroenteritis. *PLoS ONE*. 2016;11(12). doi:10.1371/journal.pone.0168618.

6. Popular heartburn medication may increase ischemic stroke risk | American Heart Association. http://newsroom.heart.org/news/Xpopular-heartburn-medication-may-increase-ischemic-stroke-risk. Accessed January 26, 2017.

7. Health Evidence Review Commission Searchable Prioritized List, Guideline Notes, Multisector Interventions and Services Recommended for Non-Coverage. http://www.oregon.gov/oha/herc/Pages/Searchable-List.aspx. Accessed April 19, 2017.

Appendix 1: Codes identifying PPI/H2A/Antacid in claims data

HSN	Generic
Drug Class: PPI	
004673	OMEPRAZOLE
011115	OMEPRAZOLE MAGNESIUM
033512	OMEPRAZOLE/SODIUM BICARBONATE
022008	PANTOPRAZOLE SODIUM
021607	ESOMEPRAZOLE MAGNESIUM
008993	LANSOPRAZOLE
036085	DEXLANSOPRAZOLE
018847	RABEPRAZOLE SODIUM
Drug Class: H2A	
004520	RANITIDINE HCL
004518	CIMETIDINE
009793	CIMETIDINE HCL
004521	FAMOTIDINE
021332	FAMOTIDINE/CA CARB/MAG HYDROX
004522	NIZATIDINE
Drug Class: Antacid	
001163	CALCIUM CARBONATE
001153	CALCIUM CARB/MAGNESIUM HYDROX
001162	CALCIUM CARBONATE/SIMETHICONE
001179	ALUMINUM HYDROXIDE
001172	MAG CARB/AL HYDROX/ALGINIC AC
001168	MAG HYDROX/AL HYDROX/SIMETH
001173	MAGNESIUM CARBONATE/AL HYDROX
001169	MAGNESIUM, ALUMINUM HYDROXIDE
001142	MG TRISILICATE/ALH/NAHCO3/AA
001152	CALCIUM CARB/MAG HYDROX/SIMETH
001185	DIHYDROXYALUMINUM SODIUM CARB
001170	MAGNESIUM HYDROXIDE

Appendix 2: PPI Diagnoses with correlating OHP funding line

Unfunded Diagnoses

Diagnosis	Diagnosis Code		OHP Funding Line
	ICD-9	ICD-10	
Esophageal reflux (> 8 weeks duration); Esophagitis (> 8 weeks duration)	530.10 – 530.19; 530.81	K20.8-K20.9; K21.0-K21.9	516
Esophageal spasm; Diverticulum of esophagus, acquired; Asymptomatic diaphragmatic hernia	530.20; 530.6x; 553.3x	K22.10; K22.5; K44.9	516
Dyspepsia	536.8x	K30	531
Dyskinesia of esophagus	530.5x	K22.4	664

Funded Diagnoses

Diagnosis	Diagnosis Code		OHP Funding Line
	ICD-9	ICD-10	
GI Ulcers; Gastritis; Duodenitis; GI hemorrhage; H. pylori infection (2 weeks duration) (Ulcer of esophagus; Gastro-esophageal laceration-hemorrhage syndrome; Esophageal hemorrhage; Esophageal leukoplakia; Unspecified disorder of esophagus; Gastric ulcer; Duodenal ulcer; Peptic ulcer, site unspecified; Gastrojejunal ulcer; Gastritis and duodenitis)	041.86x; 456.1x-456.20; 456.8x; 530.21; 530.7x; 530.82; 530.83; 530.89-535.71; 777.8	B96.81; I85.00-I85.11; I86.4; K22.11; K22.6; K22.8; K25.0 - K29.91; P78.82	60
Perforation of esophagus	530.4x	K22.3	231
Cancer of esophagus; Barrett's esophagus with dysplasia	150.0x-150.9x; 171.5x; 230.0x; 284.11; 530.85; V10.03	C15.3-C15.9; C49.A1; D00.0; D61.810; K22.710-K22.719; Z85.01	319
Achalasia and cardiospasm; Stricture and stenosis of esophagus	530.0x; 530.3x	K22.0; K22.2	383
Barrett's esophagus without dysplasia	530.85	K22.70	385
Esophageal reflux (8 weeks duration); Esophagitis (8 weeks duration)	530.10 – 530.19; 530.81	K20.8-K20.9; K21.0-K21.9	385
Severe Conditions			
Malignant mast cell tumors	202.6x	C96.2	162
Neoplasm of uncertain behavior of other and unspecified endocrine glands	237.4x	D44.0; D44.2	215, 229
Multiple endocrine neoplasia (MEN) type I	258.01	E31.21	260
Zollinger-Ellison	251.5x	E16.4	347

Appendix 3: Prior Authorization Criteria

Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions

Requires PA:

- Preferred PPIs beyond 60 days' duration
- Non-preferred PPIs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Individual components for treatment of *H. pylori* that are preferred products

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the request for a preferred PPI?	Yes: Go to 5	No: Go to 3
3. Is the treating diagnosis an OHP-funded condition (see **Table**)?	Yes: Go to 4	No: Pass to RPh; deny, not funded by OHP.
4. Will the prescriber consider changing to a preferred PPI product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives.	No: Go to 5
5. Has the patient already received 68 days of PPI therapy for either of the following diagnoses: • GERD [esophageal reflux (53081), esophagitis (53010 – 53019)] or • *H. pylori* infection (04186)?	Yes: Go to 6	No: Go to 7
6. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalizations?	Yes: Approve for 1 year	No: Pass to RPh; not funded by OHP. RPh may approve a quantity limit of 30 doses (not to exceed the GERD dose in the **Table**) over 90 days if time is needed to taper off PPI. Note: No specific PPI taper regimen has proven to be superior. H2RAs may be helpful during the taper. Preferred H2RAs are available without PA.

7. Does the patient have a history of gastrointestinal ulcer or bleed and have one or more of the following risk factors? • Age 65 years or older • Requires at least 3 months of continuous daily: i. Anticoagulant, ii. Aspirin or non-selective NSAID, or iii. Oral corticosteroid	Yes: Approve for 1 year	No: Go to 8
8. Are the indication, daily dose and duration of therapy consistent with criteria outlined in the **Table**? Message: OHP-funded conditions are listed in the **Table**.	Yes: Approve for recommended duration.	No: Pass to RPh. Deny; medical appropriateness or not funded by OHP Message: Patient may only receive 8 weeks of continuous PPI therapy.

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

Drug Class Update: Vascular Endothelial Growth Factors

Date of Review: March 2017 **Date of Last Review:** January 2015

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

Purpose for Class Update:
Evidence for the anti-vascular endothelial growth factor (anti-VEGF) agents was last reviewed by the Oregon Pharmacy and Therapeutics Committee (P&T) in January 2015. Recently two medications (ranibizumab and aflibercept) have received expanded FDA indications for treatment of diabetic retinopathy in patients with diabetic macular edema. Ranibizumab has also been recently approved for choroidal neovascularization secondary to myopia. This review examines new comparative efficacy and safety data of anti-VEGF therapy for ocular conditions. Treatment of cancer with bevacizumab is not discussed.

Research Questions:
1. Is there any new comparative evidence to assess efficacy of anti-VEGF agents in the treatment of age-related macular degeneration (AMD), macular edema following retinal vein occlusion, diabetic macular edema, or diabetic retinopathy in patients with macular edema?
2. Is there any new comparative evidence to assess incidence and severity of short- or long-term harms associated with anti-VEGF agents?
3. Are there subpopulations of adults (specifically based on age, disease severity, or prior treatment experience) for which there are differences among anti-VEGF agents in efficacy or adverse effects?

Conclusions:
- There is high quality evidence based on data from multiple systematic reviews that there is no difference in best corrected visual acuity between ranibizumab and bevacizumab for neovascular AMD.[1-4]
- There is moderate quality evidence based on systematic reviews of 2 randomized controlled trials (RCTs) of no difference in visual acuity between ranibizumab and aflibercept at 1 or 2 years in patients with neovascular AMD.[3,4]
- There is no difference in efficacy between aflibercept and bevacizumab for treatment of neovascular AMD (low quality evidence based on indirect evidence).[4] There is no direct comparative evidence for pegaptanib sodium for the treatment of AMD.
- There is no difference between ranibizumab and bevacizumab in visual acuity for the treatment of macular edema due to retinal vein occlusion (moderate quality evidence).[4] There is no direct comparative evidence for other agents for the treatment of retinal vein occlusion.
- There is moderate quality evidence of no clinical meaningful difference in efficacy (defined as a change of >15 ETDRS letters) between anti-VEGF agents in patients treated for diabetic macular edema.[4,5]

Author: Sarah Servid, PharmD

- Patients with diabetic macular edema and worse visual acuity at baseline (<69 letters on the Early Treatment Diabetic Retinopathy Study scale [ETDRS]) may have improved visual acuity with aflibercept compared to bevacizumab (low quality evidence based on 1 RCT). [4,6] There is insufficient evidence to evaluate differences in other subpopulations of adults.
- There is low quality evidence of no difference in visual acuity between ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularization.[4,7] There was insufficient evidence for other treatments.
- There is no difference in serious ocular events (including endophthalmitis, eye pain, macular hole, macular edema, retinal hemorrhage or reduced visual acuity) between ranibizumab, bevacizumab or aflibercept (low quality evidence).[3,4]
- Evidence regarding comparative risk of thrombotic events and serious adverse effects with anti-VEGF agents is mixed. Several observational studies demonstrated an increased risk of mortality and cardiovascular events including venous thromboembolism (VTE) and stroke with bevacizumab compared to ranibizumab.[4] However, higher quality observational studies and systematic reviews of RCTs failed to demonstrate any difference in cardiovascular events between bevacizumab and ranibizumab.[1,3,4,8] Overall, differences in rate of cardiovascular events or mortality between agents is likely small (moderate quality evidence).

Recommendations:

- Evaluate comparative costs in the executive session to determine PDL status.
- Recommend PA criteria for non-preferred drugs which will apply to pharmacy and physician administered claims (see **Appendix 4**).

Previous Conclusions:

- There is high quality evidence of no difference between bevacizumab and ranibizumab for the treatment of neovascular age-related macular degeneration (AMD) in gain in visual acuity at one year (RR 0.90; 95% CI 0.73 to 1.11) or loss of visual acuity (RR 1.00; 95% CI 0.98 to 1.02). Two studies have confirmed that there is no difference in efficacy at two years.
- There is moderate quality evidence of no difference serious ocular adverse events between bevacizumab and ranibizumab in the treatment of neovascular AMD.
- For the treatment of neovascular AMD, there was moderate quality evidence of no significant difference in risk of death between bevacizumab and ranibizumab (3.7% vs. 3.4%; RR 1.10; 95% CI 0.78 to 1.57); p=0.59).
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with diabetic macular edema (DME) relative to laser treatment and sham injection, with similar improvements across agents.
- There is conflicting evidence regarding the comparative risk of serious systemic adverse events between bevacizumab and ranibizumab. A recent Cochrane Collaboration systematic review found low quality evidence of no difference in serious systemic adverse events (RR 1.08; 95% CI 0.90 to 1.31; p=0.41); however, when removing unpublished trials there was a significant difference favoring ranibizumab. The current evidence remains imprecise and suggests that if a difference does exist, it is likely to be small. There is evidence of no difference in arterial thrombotic events (RR 1.02; 95% CI 0.65 to 1.60) between ranibizumab and bevacizumab.
- There is insufficient comparative evidence to make conclusions on the relative efficacy and safety of pegaptanib or aflibercept.

Previous Recommendations:

- Overall, there is no difference in efficacy between ranibizumab and bevacizumab with potentially slight differences in systemic adverse events and no differences in mortality. Evaluate comparative costs in executive session to determine appropriate PDL placement. Maintain pegaptanib and aflibercept as non-preferred due to lower strength evidence.

Background:

Anti-vascular endothelial growth factor (anti-VEGF) agents are indicated for the treatment of a variety of retinal conditions characterized by abnormal blood vessel growth. Choroid neovascularization and macular edema can be caused by a variety of ocular conditions and diseases. They are commonly present in age-related macular degeneration (AMD), diabetic retinopathy, retinal vein occlusion, and myopia. Though the mechanism of treatment for all these conditions is similar, the exact etiology and risk factors for choroidal neovascularization vary by disease state.

Ranibizumab and aflibercept are both approved for neovascular AMD, macular edema due to retinal vein occlusion, diabetic macular edema, and diabetic retinopathy associated with macular edema. Ranibizumab is the only agent FDA-approved for treatment of myopic choroidal neovascularization, and pegaptanib octasodium is only FDA-indicated for AMD. Bevacizumab is primarily indicated for treatment of cancer, but it is used off-label for retinal conditions. In these diseases, vascular damage can trigger inflammatory responses, expression of vascular endothelial growth factor (VEGF), and formation of new blood vessels in the choroid layer of the eye located between the retina and sclera.[9] Accompanying features of choroidal neovascularization include sub-retinal exudation and hemorrhage, lipid deposits, retinal pigment epithelium detachment, and fibrotic scarring which cause progressive vision impairment and blindness.[9] Use of anti-VEGF agents in these conditions can help inhibit angiogenesis and preserve vision in these populations. In many RCTs, the visual acuity is evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A change of 10-15 letters on the ETDRS chart (corresponding to approximately 2-3 lines) is considered clinically significant.[4] Definitions for mild, moderate, or significant visual impairment can vary, but stable vision is typically defined as a loss of 15 letters or less.[1] Moderate visual changes correspond to 15 letters or more and severe vision loss is typically defined as a loss of greater than 30 letters (or 6 lines on the ETDRS chart).[1]

Age-related macular degeneration is defined as a chronic, progressive retinal disease eventually leading to visual impairment. It is most common in adults greater than 50 years of age and affects approximately 2-6% of older adults in the United States.[9-12] The exact etiology of age-related macular degeneration is unknown, but it is thought to be caused by a combination of genetic and environmental factors.[12] Incidence increases with age and is more common in white patients compared to other ethnic races.[10] Other risk factors include previous cataract surgery, darker iris pigmentation, prolonged sunlight exposure, smoking history, significant family history, and nutritional factors.[9,12] Severe visual symptoms are often only associated with late disease and onset of neovascular changes. Visual symptoms can manifest as progressive or sudden visual distortion of objects, difficulties with light adaptation, perceived flashes of light, or central vision impairment.[9,12] Disease may also be classified as wet (referring to the presence of neovascular changes) or dry (characterized by primarily presence of acellular debris). If untreated, approximately 5% of patients with early disease will progress to late-stage disease within 5 years.[12] Guidelines from the American Academy of Ophthalmology recommend anti-VEGF agents as first-line therapy to manage AMD associated with neovascular changes to slow disease progression.[13]

Anti-VEGF agents are also used to treat diabetic macular edema. In patients with uncontrolled diabetes, chronic exposure to elevated glycemic levels can result in damage to the microvasculature of the eye causing macular edema and retinopathy. Retinopathy is often asymptomatic but can cause progressive visual changes and impairment if untreated. Retinopathy may be classified as proliferative or non-proliferative disease, and it can occur in conjunction with or separately from development of macular edema.[9] Proliferative diabetic retinopathy is more commonly associated with neovascularization and preretinal or

vitreous hemorrhage.[9] Risk factors for retinopathy include ethnicity (Hispanic, African American, and Asian patients), uncontrolled diabetes, longer disease duration, history of cataract surgery, and comorbid dyslipidemia or hypertension.[9] Guidelines from the American Diabetes Association and American Academy of Ophthalmology recommend laser photocoagulation as first-line therapy in patients with proliferative diabetic retinopathy.[14,15] Anti-VEGF agents are recommended in patients with diabetic macular edema.[14,15] Recently, the indications for both ranibizumab and aflibercept were expanded to include patients with diabetic retinopathy associated with diabetic macular edema. Approval of anti-VEGF agents in patients with retinopathy was based on secondary analyses of trials in patients with diabetic macular edema. The majority of patients included in these trials had moderate to severe nonproliferative diabetic retinopathy.[16,17] More patients treated with aflibercept and ranibizumab had an improvement greater than or equal to 2 steps on the diabetic retinopathy severity scale (DRSS) compared to patients given laser photocoagulation therapy or sham injections. The DRSS classifies retinopathy into 5 categories based on observable findings upon dilated ophthalmoscopy (i.e. presence of microaneurysms, intraretinal hemorrhages, venous beading, neovascularization or other vascular abnormalities).[18] Categories include no apparent retinopathy, mild non-proliferative diabetic retinopathy, moderate non-proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy.[18]

Macular edema may also occur as a result of retinal vein occlusion. Risk factors for retinal vein occlusion include older age, hypertension, arteriosclerosis and diabetes.[19] Obstruction of retinal veins leads to decreased circulation, retinal vascular leakage, macular edema, and an increase in intraocular pressure.[19] Depending on the severity and location of the occlusion, visual symptoms may resolve without treatment.[19] However, untreated persistent macular edema may cause progressive visual loss.[19] Guidelines from the American Academy of Ophthalmology recommend use of anti-VEGF agents in patients with macular edema due to retinal vein occlusion in order to reduce vision loss and prevent neovascular complications.[19] Other treatment options include intraocular corticosteroids and peripheral panretinal photocoagulation for patients with neovascularization of the iris and retina.[19]

Myopia, also known as nearsightedness or shortsightedness, is a common eye condition affecting approximately 2% of the United States population.[7] Patients with myopia are able to see close objects clearly, have difficulty seeing objects at a distance.[7] Patients with pathologic myopia have progressive elongation of the eyeball which eventually leads to thinning of the retinal epithelium and choroid.[7] In approximately 5-10% of patients with pathologic myopia, choroidal neovascularization is also present.[7] Approximately 90% of patients with myopic choroidal neovascularization will have progressive vision loss and macular atrophy eventually leading to blindness.[7] Current standard of care for myopic choroidal neovascularization includes verteporfin photodynamic therapy which has demonstrated stabilization of disease for up to 1 year.[7] However, treatment has shown little benefit beyond 1 year.[7] Other treatment options include laser photocoagulation and surgery, but the efficacy of these treatments is limited by high rates of disease recurrence.[7] Anti-VEGF agents have also been used off-label for the treatment of myopic choroidal neovascularization and have shown promising short-term results. In 2016, ranibizumab was the first anti-VEGF agent FDA-approved for the treatment of myopic choroidal neovascularization.[20] It was approved on the basis of results from one RCT demonstrating improvement in vision over the course of 1 year.[20]

In the Oregon fee-for-service Medicaid population, these medications are given as intravitreal injections and are billed as physician administered drugs. They are not currently billed through pharmacy claims and are not restricted by prior authorization. In the past year (October 2015 to September 2016), bevacizumab, the current preferred agent, accounted for 85% of claims. Of the patients using bevacizumab, approximately 33% had a diagnosis of cancer within the previous year. Twelve percent of claims were for aflibercept and 6% were for ranibizumab during this time.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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.

Systematic Reviews:
In 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) performed a systematic review of the anti-VEGF agents for treatment of ocular conditions.[4] The review included 30 RCTs evaluating bevacizumab, ranibizumab and aflibercept for neovascular AMD (13 studies), diabetic macular edema (5 studies), retinal vein occlusion (9 studies), or choroidal neovascularization secondary to pathologic myopia (3 studies).[4] The primary outcome in these trials was improvement in best corrected visual acuity, typically measured by a gain of 15 or more letters on the ETDRS scale.[4] In neovascular AMD, there was no difference in the number of patients who experienced a gain of greater than 15 ETDRS letters between ranibizumab and bevacizumab (OR 1.13, 95% CI 0.96 to 1.34) or ranibizumab and aflibercept (OR 1.01, 95% CI 0.75 to 1.37).[4] In addition, there were no differences between ranibizumab and bevacizumab when comparing the mean difference in best corrected visual acuity (OR 0.51, 95% CI –0.82 to 1.83), the proportion of patients who had a loss of greater than 15 ETDRS letters (OR 0.95, 95% CI 0.70 to 1.27), or the number of patients who progressed to legal blindness (OR 0.46, 95% CI 0.07 to 3.26).[4] Similarly, no difference in these visual outcomes was observed between ranibizumab and aflibercept.[4] No trials directly compared aflibercept and bevacizumab in AMD, though results from a network meta-analysis indicate that there is no statistically significant difference between anti-VEGF agents.[4] In patients with retinal vein occlusion, there was no difference between ranibizumab and bevacizumab in vision gain (OR 1.03, 95% CI, 0.55 to 1.94) or mean difference in best corrected visual acuity (standardized mean difference [SMD] 0.00, 95% CI –0.30 to 0.30).[4] Data were lacking for other comparisons in patients with retinal vein occlusion.[4] Direct comparative data for patients with choroidal neovascularization secondary to pathologic myopia was limited to 2 small RCTs (n=80) comparing ranibizumab and bevacizumab which observed no difference in best corrected visual acuity (SMD: –0.13, 95% CI –0.57 to 0.31).[4] No evidence was found for other anti-VEGF agents. In diabetic macular edema, direct evidence was limited to a single comparative study. Vision gain, measured as greater than 15 ETDRS letters at 1 year, was statistically less common with bevacizumab and ranibizumab compared to aflibercept (OR 0.60, 95% CI 0.40 to 0.80 and OR 0.70, 95% CI 0.44 to 0.98, respectively).[4] Comparisons between bevacizumab and ranibizumab were not statistically significant.[4] Mean difference from baseline in best corrected visual acuity was a 13.3 letter improvement with aflibercept compared to a mean 11.2 letter improvement with ranibizumab and 9.7 letter improvement with bevacizumab.[4] These differences were primarily driven by a subgroup of patients in the aflibercept group who had worse visual acuity at baseline (initial letter score <69). These patients exhibited a greater relative improvement in best corrected visual acuity when on aflibercept compared to bevacizumab (6.50 letters, 95% CI 2.90 to 10.10; p<0.001) or ranibizumab (4.70 letters, 95% CI 1.40 to 8.00; p=0.003). However, these differences did not achieve a clinically significant difference of 10 to 15 ETDRS letters. There was no significant difference in vision loss (> 15 ETDRS letters) between agents.[4] At 2 years, the difference in visual acuity between ranibizumab and aflibercept was no longer statistically significant.[6]

Harms examined in the CADTH report included adverse events (including increases in intraocular pressure), serious adverse events (particularly arterial thromboembolism, bacterial endophthalmitis and retinal detachment), withdrawals due to adverse events, and mortality.[4] In neovascular AMD, direct comparative data was not available for comparisons of aflibercept and bevacizumab. In addition, safety data in patients with retinal vein occlusion were limited to a few small RCTs in patients taking ranibizumab or bevacizumab. No comparative safety data were available in patients with choroidal neovascularization. Overall, no difference was observed between agents with regard to these adverse effects in patients with neovascular AMD, diabetic macular edema, or retinal vein occlusion.[4] However, harms were infrequently reported and studies were not powered adequately to determine differences in these rare adverse effects.[4] These results must be interpreted with caution. Authors do note that because bevacizumab is not marketed for intravitreal injection, improper handling or preparation may result in increased risk of microbial contamination.[4] To further evaluate safety of bevacizumab compared to other anti-VEGF agents, an additional 24 observational studies were included in the review.[4] Data included one large cohort study with more than 383,000 injections of bevacizumab or ranibizumab which demonstrated no difference in risk of endophthalmitis (adjusted OR 0.66, 95% CI 0.39 to 1.09; p=0.11).[4] Evidence regarding the cardiovascular safety of anti-VEGF agents was mixed. Several observational studies demonstrated an increased risk of mortality and cardiovascular events including VTE and stroke with bevacizumab compared to ranibizumab.[4] However, these studies also had significant confounding factors including lack of reported cardiovascular risk factors, selection biases, and unequal follow-up times which may bias results in favor or ranibizumab.[4] Higher quality observational studies failed to demonstrate any difference in cardiovascular events between bevacizumab and ranibizumab.[4] Therefore, the authors concluded that if properly prepared and stored, bevacizumab is not associated with greater risk of adverse effects compared to other anti-VEGF agents.[4] Overall, bevacizumab was recommended as the preferred first-line therapy because it demonstrated equivalent efficacy and safety to other anti-VEGF agents and was associated with lower costs.[4] Ranibizumab or aflibercept may be used in patients non-responsive to bevacizumab (defined as no improvement after 3 months or < 15 letters improvement after 6 months of therapy) or in patients at high risk for cardiovascular disease.[4] High risk for cardiovascular disease was defined as individuals with clinical evidence of atherosclerosis, have undergone coronary or arterial revascularization, or have prior history of myocardial infarction (MI), cerebrovascular accident (CVA), or peripheral arterial disease.[4]

A systematic review by the Cochrane Collaboration examined direct comparative evidence for efficacy and safety of ranibizumab or aflibercept for the treatment of neovascular AMD.[3] Evidence was derived from 2 high quality RCTs (n=2457 patients, 2457 eyes).[3] Patients included in these trials were on located in the United States, Canada, Europe, Latin America, Asia Pacific and the Middle East.[3] After 1 year of treatment, the best-corrected visual acuity (measured using the ETDRS scale) was similar between treatments (MD -0.15 letters, 95% CI -1.47 to 1.17; high quality evidence).[3] The number of patients who achieved significant improvements in the ETDRS scale (>15 letters) was 32% for both groups (RR 0.97, 95% CI 0.85 to 1.11; high quality evidence), and there was no difference in the proportion of patients who lost 15 or more letters (RR 0.89, 95% CI 0.61 to 1.30; high quality evidence).[3] In addition, there was no difference in quality of life measures at 1 year (MD -0.39, 95% CI -1.71 to 0.93; high quality evidence).[3] Similarly, after 2 years, there was no difference between aflibercept and ranibizumab in the mean change in best corrected visual acuity from baseline (7.2 vs. 7.9 ETDRS letters) or the proportion of patients with greater than 15 letter improvement (RR 0.98, 95% CI 0.85 to 1.12; high quality evidence).[3] Overall safety of ranibizumab and aflibercept was comparable.[3] The rate of serious adverse events was similar in patients treated with aflibercept or ranibizumab at 1 year (RR 0.99, 95% CI 0.79 to 1.25, moderate quality evidence).[3] There was no difference between groups in the rate of arterial thrombotic events, vascular death, non-fatal MI and non-fatal stroke.[3] Serious ocular events occurred rarely and results failed to achieve statistical differences (RR 0.62, 95% CI 0.36 to 1.07, moderate quality evidence due to imprecision), though events were less common in the aflibercept group.[3] There is moderate quality evidence of no difference in risk for specific adverse events between groups at 1 year, including risk of congestive heart failure events (RR 0.77, 95% CI 0.20 to 2.97), retinal hemorrhage (RR 0.65, 95 % CI 0.16 to 2.60), and non-ocular hemorrhagic events (RR 2.30, 95% CI 0.42 to 12.70).[3] These events were rare, imprecise, and failed to achieve statistical significance, leading to uncertainty in the true estimate of effect.[3] In addition, differences in these all events at 2 years failed to achieve statistical significance.[3] Another systematic review reported similar outcomes, with no clinical difference in efficacy or safety between ranibizumab and aflibercept.[8]

A systematic review conducted in 2015 compared bevacizumab to ranibizumab for the treatment of neovascular AMD.[2] Six high quality RCTs were included in the meta-analysis (n=2612 patients).[2] The majority of patients included in these trials were on average 76 to 79 years of age.[2] Overall, there was no difference between bevacizumab and ranibizumab in the mean change in best-corrected visual acuity after follow-up of 1 year (MD -0.40, 95% CI -1.48 to 0.69, p=0.47) or 2 years (weighted MD -1.16, 95% CI -2.82 to 0.51, p=0.17).[2] Serious adverse events were slightly more common with bevacizumab than ranibizumab at 1 year (18.6% vs 14.9%; RR 1.24, 95% CI 1.04 to 1.48; p=0.02; NNH=27) and 2 years (35.6% vs 29.7%; RR 1.20, 95% CI 1.05 to 1.37; p=0.008; NNH=17).[2] Though there was no difference in individual risk of death, MI, stroke, or VTE, increased risk of serious adverse events appeared to be primarily driven by a higher rate of VTE in patients treated with bevacizumab.[2] Other high quality systematic reviews reported similar outcomes, with no difference in clinical efficacy or safety between bevacizumab or ranibizumab treatment for neovascular AMD.[8,21]

In 2016, a systematic review evaluated safety and efficacy of anti-VEGF agents for the treatment of neovascular AMD.[1] Outcomes examined included visual acuity (measured by the change in ETDRS letters), quality of life and adverse events (especially thrombotic events, infection, bleeding, and death) at 1 and 2 years.[1] Five publications from 4 studies evaluated efficacy of bevacizumab versus ranibizumab.[1] Data from these trials were not pooled in a meta-analysis, but overall, there was no difference between groups in the proportion of patients with clinically significant vision changes (> 15 letters on the ETDRS chart) or mean change in best-corrected visual acuity score (low quality evidence).[1] Similarly, in trials which reported adverse effects, there was no difference in risk of death, arterial thrombotic events (including MI or stroke), endophthalmitis or infection.[1] Adverse events that were more common with bevacizumab than ranibizumab included serious systemic adverse events (40% vs 32%, RR 1.30, 95% CI 1.07 to 1.57; p=0.009; NNH=12, 1 RCT for 2 years), and serious ocular events at 12 to 18 months (3 vs 1%, RR 2.77, 95% CI 1.18 to 6.54; p=NR; NNH=50, 3 RCTs).[1] Serious systemic adverse events included hypertension, arteriothrombotic events, systemic hemorrhage, congestive heart failure, VTE, or vascular death.[22] Specific ocular events included endophthalmitis, uveitis, retinal/choroidal detachment, retinal tear, ocular vessel embolism or occlusion and vitreous hemorrhage.[1] Evidence from 7 RCTs evaluated different dosing regimens of ranibizumab. Regimens included doses of 0.3 mg, 0.5 mg, and 2 mg administered monthly, quarterly, or on an as needed basis over the course of 1 to 2 years.[1] Overall, there was insufficient evidence to assess changes in vision or serious adverse effects with different dosing regimens due to lack of reported comparative outcomes.[1] Low quality evidence from 1 RCT (n=353) indicates that fixed monthly regimens of 0.3 mg may be more effective than quarterly injections of 0.3 mg (MD -3.9 letters, 95% CI -7.7 to -0.9) or 0.5 mg (MD -5.2 letters, 95% CI -8.6 to -1.7) ranibizumab.[1] The proportion of patients who had an improvement of greater than 15 ETDRS letters was 14% in patients given quarterly injections compared to 29% with monthly injections.[1] Similarly, 8% of patients given 0.3 mg quarterly compared to 3% receiving 0.3 mg monthly injections progressed to legal blindness (20/200) in 12 months.[1] Statistical significance for these outcomes was not reported.[1] Evidence from 2 RCTs compared aflibercept to ranibizumab.[1] Overall, aflibercept and ranibizumab demonstrated similar efficacy in the mean change in best-corrected visual acuity and proportion of patients with a gain of 15 or more ETDRS letters (moderate quality evidence).[1] Adverse events were similar between groups though events were infrequent and studies were not powered to evaluate these outcomes.[1] There was insufficient evidence evaluating differences in dosing regimens of aflibercept (given monthly or every 2 months).[1] Evidence comparing different regimens of bevacizumab (either monthly or as needed dosing) was limited to 2 RCTs.[1] Overall, changes in visual acuity were similar between groups, though statistical significance was not assessed for the majority of outcomes (low quality evidence).[1] There was no comparative data on adverse effects between patients taking bevacizumab monthly or as needed.[1] Authors do note that bevacizumab is not formulated for intravitreal injections and requires compounding which may increase risk of infections due to potential contamination.[1]

Two systematic reviews have examined comparative efficacy and safety of different dosing regimens of ranibizumab in neovascular AMD.[8,23] Patients in these reviews were treated with injections of 0.5 mg ranibizumab on a scheduled basis or with a 1-3 months of scheduled doses followed by as needed treatment for patients with progressive disease.[8] The efficacy of ranibizumab when given alone or in conjunction with photodynamic therapy was also examined.[8] Evidence examining difference in ranibizumab regimens included data from 6 RCTs.[8] Patients were on average 73 to 80 years of age and were followed for 1 to 2 years.[8]

The authors found a slight statistical benefit when ranibizumab was administered as needed compared to a scheduled regimen (2 RCTs, weighted MD 1.97 letters, 95% CI 0.14 to 3.794, p=0.04, I^2=0%) and combination treatment of ranibizumab plus photodynamic therapy versus ranibizumab alone (4 RCTs, weighted MD 2.74, 95% CI 0.26 to 5.21, p=0.03, I^2=0%), though differences were not clinically significant.[8] Another systematic review which examined differences in dosing regimens of ranibizumab (either scheduled monthly doses or therapy given as needed depending on diseases progression) reached similar conclusions.[23] The meta-analysis included similar studies (3 RCTs, n=1844) and found no clinical difference in best corrected visual acuity between groups after 2 years (weighted MD 1.9, 95% CI 0.5 to 3.3, p=0.008, I^2=0%).[23] At 2 years, the total number of intravitreal injections was significantly less in patients treated on an as needed basis compared to patients receiving scheduled monthly therapy (MD 8.4, 95% CI 7.9 to 8.9, p<0.00001, I^2=95%).[23] Heterogeneity between these trials was significant, but results all demonstrated consistently fewer injections when therapy was given as needed.

A Cochrane review in 2016 examined the efficacy of anti-VEGF agents for the treatment of choroidal neovascularization due to pathological myopia.[7] The review included 6 RCTs or quasi-RCTs (n=594) which compared anti-VEGF agents to photodynamic therapy, placebo, or other anti-VEGF agents.[7] Direct comparative evidence between anti-VEGF agents was limited to 2 trials which evaluated bevacizumab and ranibizumab.[7] Treatment was primarily given as 1 injection followed by as needed treatment depending on disease activity upon optical imaging.[7] Compared to photodynamic therapy, the current standard of care, anti-VEGF agents improved mean visual acuity by approximately 7 and 13 ETDRS letters at 1 and 2 years, respectively.[7] The proportion of patients achieving a clinically significant improvement in visual acuity (corresponding to >3 ETDRS lines) was also greater in patients given anti-VEGF agents after 1 year (RR 1.86, 95% CI 1.27 to 2.73, 226 people, moderate quality evidence) and 2 years of treatment (RR 3.43, 95% CI 1.37 to 8.56, 92 people, low quality evidence) compared to those receiving photodynamic therapy.[7] In 1 of these trials, patients in the control groups were allowed to receive anti-VEGF treatment after 3 months, which may lead to a more conservative estimate of efficacy.[7] Similar improvements were seen with bevacizumab compared to laser photocoagulation therapy with mean improvements of approximately 11 and 14 ETDRS letters after 1 and 2 years (low quality evidence).[7] In 2 RCTs directly comparing bevacizumab and ranibizumab, there was no difference in change in visual acuity after 1 year (RR 0.79, 95% CI 0.50 to 1.27, P=0.33, moderate quality evidence).[7] Adverse events were rarely reported, and no serious adverse events occurred in patients randomized to control groups.[7] Differences in adverse events failed to achieve statistical significance, though adverse events were more common in patients treated with anti-VEGF therapy (RR 1.82, 95% CI 0.23 to 14.71, p=0.14). Serious systemic adverse events occurred in 15 patients (4.2%) taking anti-VEGF agents, and ocular adverse events occurred in 5 patients (1.4%).[7]

Similar results were documented in another systematic review of anti-VEGF agents for the treatment of choroidal neovascularization in conditions unrelated to AMD.[24] This review included both RCTs and comparative non-randomized trials. Of the 16 included studies, 13 (n=1017) were in patients with myopic choroidal neovascularization.[24] The majority of patients included in these trials were female and 35 to 67 years of age.[24] Mean baseline best corrected visual acuity was between 81 and 99 letters.[24] Three study regimens required 3 monthly loading doses and continued treatment in all studies was based on clinical assessment at follow-up visits.[24] Patients received an average of 1.6 to 4.72 injections over the course of these studies.[24] Due to significant heterogeneity between studies, results were not pooled in a meta-analysis. However, in myopic choroidal neovascularization, the proportion of patients with a clinical improvement of greater than 15 letters ranged from 27% to 70% in patients taking anti-VEGF therapy compared to 14% to 20% in patients given photodynamic therapy.[24] Evidence was limited by quality of the included trials, limited population size, and significant methodological heterogeneity between studies.[24] Differences in baseline visual acuity and treatment regimens may have contributed to the wide difference in treatment outcomes. In trials directly comparing bevacizumab and ranibizumab, no statistical difference in best corrected visual acuity was reported between groups.[24]

A systematic review examined safety of anti-VEGF agents in patients with diabetic macular edema and consistent exposure to anti-VEGF agents (i.e. receiving monthly injections for at least 2 years).[25] Four RCTs (n=1078) of aflibercept and ranibizumab versus sham treatment were included in the review.[25] Outcomes examined included risk of MI, CVA, VTE, and mortality.[25] The mean age of patients enrolled in trials was 61 to 64 years.[25] Baseline cardiovascular risk

factors were not evaluated, though patients with recent stroke or MI (within 3 to 6 months) were excluded from these trials.[25] Compared to sham-laser treatment, patients treated with anti-VEGF therapy had a higher risk of all-cause mortality (OR 2.57, 95% CI 1.31 to 5.05, p=0.006), CVA (OR 2.33, 95% CI 1.04 to 5.22), and vascular-related death (OR 2.23, 95% CI 1.01 to 4.89, p=0.05).[25] Risk for VTE and MI failed to achieve statistical significance.[25] All outcomes were graded as moderate quality evidence.[25] In addition, similar outcomes were observed in subgroup analyses of ranibizumab 0.5 mg and 0.3 mg doses, and no difference was observed between patients receiving either ranibizumab or aflibercept.[25]

A systematic review published in 2016 examined the comparative efficacy and safety of anti-VEGF agents in patients with diabetic macular edema. The review included updated evidence from 8 systematic reviews and 4 RCTs.[5] Overall, due to quality of included trials and lack of direct comparative data, evidence for improvements in visual acuity was graded as low quality.[5] Overall, authors concluded that in patients with good baseline visual acuity (>69 ETDRS letters), ranibizumab, aflibercept, and bevacizumab were equally effective at improving visual acuity at 6 to 12 months.[5] Results from 1 RCT indicate that in patients with worse baseline visual acuity (<69 ETDRS letters), aflibercept may have improved visual acuity at 1 year compared to ranibizumab or bevacizumab (MD 4.7 and 6.5 letters, respectively).[5] The clinical significance of these differences remains unclear. Regarding adverse effects, there were no significant differences between agents.[5] However, studies were not powered to examine these rare events and many studies excluded patients at high risk for thrombotic events.[5] Authors note that all intravitreal injections have an increased risk of endophthalmitis with reported rates of 0.05 to 1.6%, but direct comparative evidence between agents is lacking.[5]

New Guidelines:
Guidance from the National Institute for Health and Care Excellence (NICE) for the use of aflibercept in patients with diabetic macular edema was published in 2015.[26] Recommendations were based on evidence from 2 RCTs evaluating change in best corrected visual acuity at 1 year.[26] The clinical and cost effectiveness was evaluated in the total population and in subgroups of patients with prior cataract surgery and baseline central retinal thickness less than 400 micrometers.[26] Clinically, aflibercept demonstrated a significant improvement in the best corrected visual acuity compared to laser photocoagulation when given every 4 or 8 weeks.[26] Subgroup analyses demonstrated that in patients with a central retinal thickness of less than 400 micrometers, differences failed to achieve statistical significance.[26] The analysis was limited due to the small population of patients with central retinal thickness less than 400 micrometers (n=78) and lack of balanced baseline characteristics in this subgroup.[26] Based on cost-effectiveness results, NICE guidance recommends initiation of aflibercept only in patients with a central retinal thickness greater than 400 micrometers.[26]

In the past few years, the American Academy of Ophthalmology has updated guidelines on the use of anti-VEGF agents in retinal vein occlusion, neovascular AMD and diabetic retinopathy. Guidelines recommend anti-VEGF agents as a first-line therapy for the treatment of macular edema associated with branched or central retinal vein occlusion (strong recommendation based on good quality evidence).[19] No specific recommendations are made for any particular agent. Intraocular steroids have also demonstrated benefit in treatment of macular edema due to retinal vein occlusion and are recommended as a second-line treatment due to their associated with increased risk of cataracts and glaucoma (strong recommendation based on good quality evidence).[19] Similar recommendations are made in guidelines for the treatment of neovascular AMD.[13] Anti-VEGF agents are recommended as first-line therapy in patients with neovascular AMD (strong recommendation based on good quality evidence), but no recommendations are made for any particular agent or treatment regimen.[13] Guidelines for diabetic retinopathy state anti-VEGF agents may be used for the treatment of retinopathy associated with clinically significant macular edema regardless of retinopathy severity (strong recommendation based on good quality evidence).[15] Anti-VEGF agents are first-line therapy in patients with central macular edema.[15] They may be used as monotherapy or in combination with focal laser treatment or panretinal photocoagulation.[15] Anti-VEGF agents are not recommended for treatment of mild or moderate severity retinopathy alone (strong recommendation based on good quality evidence).[15] Though

evidence is limited, treatment may be considered in patients with high-risk proliferative diabetic retinopathy with or without macular edema (strong recommendation based on observational studies).[15] Guidelines note that treatment decision should be based on the individual risks and benefits of the patient.[15]

New Formulations or Indications:
In 2016, bevacizumab labeling was updated to include a new indication for treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer either in combination with carboplatin and paclitaxel, in combination with carboplatin and gemcitabine, and as monotherapy following combination therapy.[27]

Since 2015, aflibercept and ranibizumab were FDA-approved for treatment of diabetic retinopathy in patients with diabetic macular edema, and ranibizumab achieved approval for the treatment of myopic choroidal neovascularization.[20,28]

A new formulation for pre-filled 0.5 mg syringes of ranibizumab was also approved in 2015.[20]

New FDA Safety Alerts:
In 2016, labeling for aflibercept was updated to include contraindications for hypersensitivity reactions including rash, pruritus, urticarial, or severe anaphylactic/anaphylactoid reactions.[27]

Randomized Controlled Trials:
A total of 324 citations were manually reviewed from the initial literature search. After further review, 314 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). If multiple publications presented results from the same trial, the publication with the most recent results and longest follow-up was included. Data supporting the use of aflibercept and ranibizumab for recently FDA-approved indications of diabetic retinopathy in patients with diabetic macular edema and for ranibizumab in patients with treatment of myopic choroidal neovascularization are also included. The remaining 10 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Berg K, et al. 2016.[29] DB, MC, NI, RCT Duration: 2 years N=441	1. Ranibizumab 0.5 mg 2. Bevacizumab 1.25 mg T&E protocol: Intravitreal injections given monthly until achievement of inactive disease then injections were extended by 2 weeks at a time up to 12 weeks. Treatment periods were shortened in 2 week periods with disease recurrence.	Treatment naïve adults >50 years of age with neovascular AMD and BCVA between 20/25 and 20/320.	Mean change in BCVA at 2 years (measured by ETDRS chart)	Ranibizumab: 6.6 letters (SD 15.2) Bevacizumab: 7.4 letters (SD 16.0) MD 0.8 letters (95% CI -4.1 to 2.5; p=0.634)

Chakravarthy U, et al. 2015.[30] MC, NI, RCT Duration: 2 years N=628	1. Ranibizumab 0.5 mg continuous monthly intravitreal injections 2. Ranibizumab 0.5 mg intravitreal injections for 3 months followed by retreatment with active disease 3. Bevacizumab 1.25 mg continuous monthly intravitreal injections 4. Bevacizumab 1.25 mg intravitreal injections for 3 months followed by retreatment with active disease	Treatment naïve adults ≥50 years of age with neovascular AMD and BCVA ≥25 letters	BCVA at 2 years	Ranibizumab (Groups 1 and 2): 67.8 letters (SD 17.0) Bevacizumab (Groups 3 and 4): 66.1 letters (SD 18.4) MD –1.37 letters (95% CI –3.75 to 1.01; p=0.26) Continuous treatment (Groups 1 and 3): 66.6 (SD 17.9) Retreatment upon disease recurrence (Groups 2 and 4): 37.3 (SD 17.5) MD –1.63 letters (95% CI –4.01 to 0.75; p=0.18)
Wiley HE, et al. 2016.[31] DB, 3-month crossover, RCT Duration: 9 months N=56	1. Ranibizumab 0.3 mg monthly 2. Bevacizumab 1.25 mg monthly	Adults with type 1 or 2 diabetes and DME	Mean change in BCVA (ETDRS chart) at 3 months	Ranibizumab: 6.6 letters (95% CI 4.5 to 8.7) Bevacizumab: 5.3 letters (95% CI 3.2 to 7.4) MD 1.3 letters (95% CI 0.07 to 2.5; P=0.039)
Wells JA, et al. 2016.[6] MC, NI, RCT Duration: 2 years N=660	1. Aflibercept 2.0 mg 2. Bevacizumab 1.25 mg 3. Ranibizumab 0.3 mg Treatment was given monthly for 12 months then every 1-4 months thereafter depending on disease stability. Addition of focal grid laser photocoagulation could be added at 6 months with persistent disease activity.	Adults with DME and BCVA of 20/32 to 20/320 on the Snellen chart	Mean change in visual acuity at 2 years (post-hoc exploratory analysis)	1. Aflibercept 12.8 letters (SD 12.4) 2. Bevacizumab 10.0 letters (SD 11.8) 3. Ranibizumab 12.3 letters (SD 10.5) Aflibercept vs. bevacizumab: MD 2.7 (95% CI 0.3 to 5.2; P=0.02) Aflibercept vs. ranibizumab: MD 0.7 (95% CI -1.3 to 2.8; P=0.47) Ranibizumab vs. bevacizumab: MD 2.0 (95% CI -0.4 to 4.4; P=0.11)
Bressler SB, et al. 2016.[32] DB, MC, RCT Duration: 5 years N=450	1. Laser photocoagulation + very deferred ranibizumab (1.5 to 3 years later) 2. Ranibizumab + prompt laser photocoagulation 3. Laser photocoagulation + triamcinolone + very deferred ranibizumab (1.5 to 3 years later) 4. Ranibizumab + deferred laser photocoagulation (≥6 months later)	Adults with DME and BCVA of 20/32 to 20/320 on the Snellen chart	Mean change in BCVA at 5 years (post-hoc exploratory analysis)	1. 5 letters (SD 14) 2. 8 letters (SD 13) 3. 7 letters (SD 14) 4. 10 letters (SD 13) Compared to ranibizumab + deferred laser 1. MD 4.4 (95% CI 1.2 to 7.6; p=0.001) 2. MD 2.0 (95% CI -1.6 to 5.7; p=0.186)

				3. MD 2.8 (95% CI -0.9 to 6.5; p=0.067)
Pece A, et al. 2015.[33] RCT Mean duration: 19 months N=80	1. Bevacizumab 0.5 mg 2. Ranibizumab 1.25 mg Treatment was once then as needed upon presence of active lesions, progressive disease, or worsening of BCVA >1 line (5 letters)	Adults with myopic CNV and BCVA >20/400 on the Snellen chart	Mean change in BCVA	Bevacizumab: 55 letters (SD 26) Ranibizumab: 58 letters (SD 21) OR 2.46 (95% CI 0.88 to 6.83; p=0.138)
Brown DM, et al. 2015.[34] DB, MC, RCT Duration: 2 years N=466	1. Aflibercept 2 mg every 4 weeks 2. Aflibercept 2 mg every 8 weeks after 5 monthly doses 3. Macular laser photocoagulation at baseline and upon follow-up if clinically significant macular edema was present	Adults with retinopathy, DME and BCVA of 73-24 letters (20/40 to 20/320)	Proportion of patients with ≥ 2 step improvement in the DRSS score (pre-specified exploratory outcome)	1. 37.0% (95% CI NR); p<0.0001 vs. laser 2. 37.1% (95% CI NR); p<0.0001 vs. laser 3. 15.6% (95% CI NR) Aflibercept vs. laser photocoagulation ARR 22%, NNT=5
Brown DM, et al. 2015.[34] DB, MC, RCT Duration: 2 years N=406	1. Aflibercept 2 mg every 4 weeks 2. Aflibercept 2 mg every 8 weeks after 5 monthly doses 3. Macular laser photocoagulation at baseline and upon follow-up if clinically significant macular edema was present	Adults with retinopathy, DME and BCVA of 73-24 letters (20/40 to 20/320)	Proportion of patients with ≥ 2 step improvement in the DRSS score (pre-specified exploratory outcome)	1. 29.3% (95% CI NR); p=0.0004 vs. laser; ARR 21.1%, NNT=5 2. 32.6%(95% CI NR); p<0.0001 vs. laser; ARR 24.4%, NNT=4 3. 8.2%
Ip MS, et al. 2015.[16] DB, MC, RCT Duration: 3 years N=759	1. Ranibizumab 0.3 mg monthly 2. Ranibizumab 0.5 mg monthly 3. Sham injections monthly Patients randomized to sham injections could receive ranibizumab 0.5 mg monthly after 25 months	Adults with retinopathy, DME and BCVA of 20/40 to 20/320	Proportion of patients with ≥ 2 or ≥3 step improvement in the DRSS score (post-hoc exploratory outcome)	1. 38.9% (95% CI NR); p<0.0001 vs. sham injections 2. 39.3% (95% CI NR); p<0.0001 vs. sham injections 3. 23.8% (95% CI NR) Ranibizumab vs: sham injections ARR 15%, NNT=7
Wolf S, et al. 2014.[35]	1. Ranibizumab 0.5 mg on day 1 and at 1 month with further treatment based on change in VA	Adults with myopic CNV and BCVA of	Mean change in BCVA at 1-3 months (ETDRS letters)	1. 10.5 letters (SD 8.2), p<0.00001 vs. verteporfin photodynamic therapy 2. 10.6 letters (SD 7.3), p<0.00001 vs. verteporfin photodynamic therapy

Phase 3, Superiority and NI, DB, MC, RCT Duration: 1 year N=244	2. Ranibizumab 0.5 mg on Day 1 with further treatment based on presence of active disease upon exam 3. Verteporfin photodynamic therapy on Day 1 with further treatment based on active disease upon exam. Cross-over treatment with ranibizumab was permitted after 3 months.	24-78 ETDRS letters		3. 2.2 letters (SD 9.5) Noninferiority between ranibizumab groups achieved

Abbreviations: AMD = age-related macular degeneration; ARR = absolute risk reduction; BCVA = best corrected visual acuity; CNV= choroidal neovascularization; DB = double blind; DME = diabetic macular edema; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; MC = multicenter; MD = mean difference; NI = noninferiority; NNT = number needed to treat; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation

References:

1. Arnold J. Age-related macular degeneration: anti-vascular endothelial growth factor treatment. Systematic review 701. BMJ Clinical Evidence. 2016; http://clinicalevidence.bmj.com/x/systematic-review/0701/overview.html. Accessed December 29, 2016.
2. Chen G, Li W, Tzekov R, Jiang F, Mao S, Tong Y. Bevacizumab versus ranibizumab for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials. *Retina.* 2015;35(2):187-193.
3. Sarwar S, Clearfield E, Soliman MK, et al. Aflibercept for neovascular age-related macular degeneration. *Cochrane Database Syst Rev.* 2016;2:Cd011346.
4. Anti-Vascular Endothelial Growth Factor Drugs for Retinal Conditions: A Therapeutic Review. CADTH Therapeutic Reviews. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2015; https://www.ncbi.nlm.nih.gov/pubmed/27170968. Accessed December 29, 2016.
5. Mohamed QA FE, Buckle M. Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema. Systematic review 702. BMJ Clinical Evidence. 2016; http://clinicalevidence.bmj.com/x/systematic-review/0702/overview.html. Accessed December 29, 2016.
6. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology.* 2016;123(6):1351-1359.
7. Zhu Y, Zhang T, Xu G, Peng L. Anti-vascular endothelial growth factor for choroidal neovascularisation in people with pathological myopia. *Cochrane Database Syst Rev.* 2016;12:Cd011160.
8. Ba J, Peng RS, Xu D, et al. Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis. *Drug Des Devel Ther.* 2015;9:5397-5405.
9. DynaMed [internet database]. Ipswich, MA: EBSCO Publishing. Updated December 20, 2016. Accessed December 28, 2016.
10. Klein R, Klein BE. The prevalence of age-related eye diseases and visual impairment in aging: current estimates. *Invest Ophthalmol Vis Sci.* 2013;54(14):Orsf5-orsf13.
11. Bailey RN, Indian RW, Zhang X, Geiss LS, Duenas MR, Saaddine JB. Visual impairment and eye care among older adults - five States, 2005. *MMWR Morb Mortal Wkly Rep.* 2006;55(49):1321-1325.
12. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet.* 2012;379(9827):1728-1738.

13. American Academy of Ophthalmology and Preferred Practice Pattern Committee. Age-related macular degeneration. American Academy of Ophthalmology. 2015; https://www.aao.org/. Accessed January 30, 2017.
14. American Diabetes Association. Microvascular Complications and Foot Care. *Diabetes Care.* 2017;40(Supplement 1):S88-S98.
15. American Academy of Ophthalmology and Preferred Practice Pattern Committee. Diabetic Retinopathy. American Academy of Ophthalmology. 2016; https://www.aao.org/. Accessed January 30, 2017.
16. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. *Ophthalmology.* 2015;122(2):367-374.
17. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;121(11):2247-2254.
18. Fong DS, Aiello LP, Ferris FL, Klein R. Diabetic Retinopathy. *Diabetes Care.* 2004;27(10):2540-2553.
19. American Academy of Ophthalmology and Preferred Practice Pattern Committee. Retinal Vein Occlusions. American Academy of Ophthalmology. 2015; https://www.aao.org/. Accessed January 30, 2017.
20. Lucentis (ranibizumab injection) [package insert]. San Francisco, CA: Genentech, Inc; 2017.
21. Solomon SD, Lindsley KB, Krzystolik MG, Vedula SS, Hawkins BS. Intravitreal Bevacizumab Versus Ranibizumab for Treatment of Neovascular Age-Related Macular Degeneration: Findings from a Cochrane Systematic Review. *Ophthalmology.* 2016;123(1):70-77.e71.
22. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology.* 2012;119(7):1388-1398.
23. Schmucker CM, Rucker G, Sommer H, et al. Treatment as Required versus Regular Monthly Treatment in the Management of Neovascular Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis. *PLoS ONE [Electronic Resource].* 2015;10(9):e0137866.
24. Stuart A, Ford JA, Duckworth S, Jones C, Pereira A. Anti-VEGF therapies in the treatment of choroidal neovascularisation secondary to non-age-related macular degeneration: a systematic review. *BMJ Open.* 2015;5(4):e007746.
25. Avery RL, Gordon GM. Systemic Safety of Prolonged Monthly Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema: A Systematic Review and Meta-analysis. *JAMA Ophthalmol.* 2016;134(1):21-29.
26. National Institute for Health and Care Excellence. Aflibercept for treating diabetic macular oedema. Technology appraisal guidance [TA346]. 2015; nice.org.uk/guidance/ta346. Accessed December 29, 2016.
27. Food and Drug Administration. Medical Product Safety Information. http://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/ Accessed December 27, 2016.
28. Eylea (aflibercept injection) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2016.
29. Berg K, Hadzalic E, Gjertsen I, et al. Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol: Two-Year Results. *Ophthalmology.* 2016;123(1):51-59.
30. Chakravarthy U, Harding SP, Rogers CA, et al. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). *Health Technology Assessment (Winchester, England).* 2015;19(78):1-298.
31. Wiley HE, Thompson DJ, Bailey C, et al. A Crossover Design for Comparative Efficacy: A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema. *Ophthalmology.* 2016;123(4):841-849.
32. Bressler SB, Glassman AR, Almukhtar T, et al. Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema. *Am J Ophthalmol.* 2016;164:57-68.
33. Pece A, Milani P, Monteleone C, et al. A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV. *Graefes Arch Clin Exp Ophthalmol.* 2015;253(11):1867-1872.

34. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. *Ophthalmology.* 2015;122(10):2044-2052.
35. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology.* 2014;121(3):682-692.e682.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAVEN	VIAL	AVASTIN	BEVACIZUMAB	Y
INTRAOCULR	SYRINGE	MACUGEN	PEGAPTANIB SODIUM	N
INTRAOCULR	VIAL	EYLEA	AFLIBERCEPT	N
INTRAOCULR	SYRINGE	BEVACIZUMAB	BEVACIZUMAB	N
INTRAOCULR	VIAL	LUCENTIS	RANIBIZUMAB	N
INTRAOCULR	VIAL	LUCENTIS	RANIBIZUMAB	N

Appendix 2: Abstracts of Comparative Clinical Trials

Berg K, et al. 2016.[29]
Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol: Two-Year Results

Purpose: To compare the efficacy and safety of bevacizumab (Avastin; F. Hoffmann-La Roche Ltd, Basel,
Switzerland) versus ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) for neovascular age-related macular degeneration (nAMD) after 2 years when using a treat-and-extend protocol. Design: Multicenter, randomized, noninferiority trial with a noninferiority limit of 5 letters. Participants: Patients 50 years of age or older with previously untreated nAMD in 1 eye and best-corrected visual acuity 20/25 to 20/320. Methods: Patients were assigned randomly to receive intravitreal injections with either ranibizumab 0.5 mg or bevacizumab 1.25 mg. Injections were given every 4 weeks until inactive disease was achieved. The treatment interval then was extended by 2 weeks at a time up to a maximum of 12 weeks. In the event of a recurrence, the treatment interval was shortened by 2 weeks at a time. Main Outcome Measure: Mean change in visual acuity at 2 years. Results: Of a total of 441 randomized patients, 339 patients (79%) completed the 2-year visit. According to perprotocol analysis at 2 years, bevacizumabwasequivalent to ranibizumab, with 7.4 and 6.6 letters gained, respectively (95%confidence interval [CI] of mean difference, 4.1 to 2.5; P=0.634). Intention-to-treat analysis was concordant, with a gain of 7.8 letters for bevacizumab and 7.5 letters for ranibizumab (95%CI of mean difference, 3.2 to 2.7; P=0.873). The 2-year results did not show any significant difference in mean central retinal thickness, with a decrease of113 mmfor bevacizumab and122 mm for ranibizumab (95%CI of mean difference, 32 to 15; P=0.476). There was a statistically significant difference between the drugs regarding the number of treatments given, with 18.2 injections for bevacizumab and 16.0 injections for ranibizumab (95%CI of mean difference, 3.4 to1.0; P<0.001). The number of serious adverse events was similar between the groups over the course of the study. Conclusions: At 2 years, bevacizumab and ranibizumab had an equivalent effect on visual acuity and reduction of central retinal thickness when administered according to a treat-and-extend protocol for nAMD. There was no significant difference in the number of serious adverse events between the treatment groups.

Chakravarthy U, et al. 2015.[30]
A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)

Background: Bevacizumab (Avastin®, Roche), which is used in cancer therapy, is the 'parent' molecule from which ranibizumab (Lucentis®, Novartis) was derived for the treatment of neovascular age-related macular degeneration (nAMD). There were reports in the literature on the effectiveness of bevacizumab in treating nAMD, but no trials. The cost per dose of bevacizumab is about 5–10% that of ranibizumab. This trial was a head-to-head comparison of these two drugs.
Objective: To compare the clinical effectiveness and cost-effectiveness of ranibizumab and bevacizumab, and two treatment regimens, for nAMD.
Design: Multicentre, factorial randomised controlled trial with within-trial cost–utility and cost-minimisation analyses from the perspective of the UK NHS. Participants, health professionals and researchers were masked to allocation of drug but not regimen. Computer-generated random allocations to combinations of ranibizumab or bevacizumab, and continuous or discontinuous regimen, were stratified by centre, blocked and concealed.
Setting: Twenty-three ophthalmology departments in NHS hospitals
Participants: Patients ≥ 50 years old with active nAMD in the study eye with best corrected distance visual acuity (BCVA) ≥ 25 letters measured on a Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Previous treatment for nAMD, long-standing disease, lesion diameter > 6000 µm, thick blood at the fovea and any other confounding ocular disease were exclusion criteria. One eye per participant was studied; the fellow eye was treated according to usual care, if required.

Interventions: Ranibizumab and bevacizumab were procured commercially. Doses were ranibizumab 0.5 mg or bevacizumab 1.25 mg. The repackaged bevacizumab was quality assured. All participants were treated at visits 0, 1 and 2. Participants randomised to the continuous regimen were treated monthly thereafter. Participants randomised to the discontinuous regimen were not retreated after visit 2 unless pre-specified criteria for active disease were met. If retreatment was needed, monthly injections over 3 months were mandated.
Main outcome measures: The primary outcome was BCVA. The non-inferiority margin was 3.5 letters. Secondary outcomes were contrast sensitivity; near visual acuity; reading index; neovascular lesion morphology; generic and disease-specific patient-reported outcomes, including macular disease-specific quality of life; survival free from treatment failure; resource use; quality-adjusted life-years (QALYs); and development of new geographic atrophy (GA) (outcome added during the trial). Results are reported for the study eye, except for patient-reported outcomes.
Results: Between 27 March 2008 and 15 October 2010, 610 participants were allocated and treated (314 ranibizumab, 296 bevacizumab; at 3 months, 305 continuous, 300 discontinuous). After 2 years, bevacizumab was neither non-inferior nor inferior to ranibizumab [–1.37 letters, 95% confidence interval (CI) –3.75 to +1.01 letters] and discontinuous treatment was neither non-inferior nor inferior to continuous treatment (–1.63 letters, 95% CI –4.01 to +0.75 letters). Lesion thickness at the fovea was similar by drug [geometric mean ratio (GMR) 0.96, 95% CI 0.90 to 1.03; p = 0.24] but 9% less with continuous treatment (GMR 0.91, 95% CI 0.85 to 0.97; p = 0.004). Odds of developing new GA during the trial were similar by drug [odds ratio (OR) 0.87, 95% CI 0.61 to 1.25; p = 0.46] but significantly higher with continuous treatment (OR 1.47, 95% CI 1.03 to 2.11; p = 0.033). Safety outcomes did not differ by drug but mortality was lower with continuous treatment (OR 0.47, 95% CI 0.22 to 1.03; p = 0.05). Continuous ranibizumab cost £3.5M per QALY compared with continuous bevacizumab; continuous bevacizumab cost £30,220 per QALY compared with discontinuous bevacizumab. These results were robust in sensitivity analyses.
Conclusions: Ranibizumab and bevacizumab have similar efficacy. Discontinuing treatment and restarting when required results in slightly worse efficacy. Safety was worse with discontinuous treatment, although new GA developed more often with continuous treatment. Ranibizumab is not cost-effective, although it remains uncertain whether or not continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at £20,000 per QALY threshold. Future studies should focus on the ocular safety of the two drugs, further optimisation of treatment regimens and criteria for stopping treatment.

Wiley HE, et al. 2016.[31]
A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema

Purpose: To investigate the comparative efficacy of bevacizumab (Avastin) and ranibizumab (Lucentis; both Genentech, Inc, South San Francisco, CA) for diabetic macular edema (DME) using a crossover study design. Design: Randomized, double-masked, 36-week, 3-period crossover clinical trial. Participants: Fifty-six subjects with DME involving the center of the macula in one or both eyes. Methods: Monthly intravitreous injections of bevacizumab (1.25 mg) or ranibizumab (0.3 mg). Main Outcome Measures: Comparison of mean changes in visual acuity and central retinal thickness, tested using a linear mixed-effects model. Results: Based on the linear mixed-effects model, the 3-month estimated mean improvement in visual acuity was 5.3 letters for bevacizumab and 6.6 letters for ranibizumab (difference, 1.3 letters; P ¼ 0.039). Estimated change in optical coherence tomography (OCT) central subfield mean thickness (CSMT) was 89 mm for bevacizumab and 137 mm for ranibizumab (difference, 48 mm; P < 0.001). Incorporating cumulative treatment benefit, the model yielded a predicted 36-week (9-month) average improvement in visual acuity of 7.1 letters (95% confidence interval [CI], 5.0e9.2) for bevacizumab and 8.4 letters (95% CI, 6.3e10.5) for ranibizumab, and a change in OCT CSMT of 128 mm (95% CI, 155 to 100) for bevacizumab and 176 mm (95% CI, 202 to 149) for ranibizumab. There was no significant treatment-by-period interaction (i.e., treatment difference was constant in all 3 periods), nor was there a significant differential carryover effect from one period to the next. Conclusions: This trial demonstrated a statistically significant but small relative clinical benefit of ranibizumab compared with bevacizumab for treatment of DME, using a markedly reduced sample size relative to a full comparative efficacy study. The effects on visual acuity and central retinal thickness for the 2 drugs are consistent with those reported at 1 year for the concurrent parallel-group trial by the Diabetic Retinopathy Clinical Research

Network testing bevacizumab, ranibizumab, and aflibercept for DME. The 3-period crossover design allowed for meaningful and efficient comparison, suggesting that this approach may be useful for future comparative efficacy studies of antievascular endothelial growth factor drugs for DME.

Wells JA, et al. 2016.[6]
Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial

Purpose: To provide 2-year results comparing anti-vascular endothelial growth factor (VEGF) agents for center-involved diabetic macular edema (DME) using a standardized follow-up and retreatment regimen. Design: Randomized clinical trial. Participants: Six hundred sixty participants with visual acuity (VA) impairment from DME. Methods: Randomization to 2.0-mg aflibercept, 1.25-mg repackaged (compounded) bevacizumab, or 0.3mg ranibizumab intravitreous injections performed up to monthly using a protocol-specific follow-up and retreatment regimen. Focal/grid laser photocoagulation was added after 6 months if DME persisted. Visits occurred every 4 weeks during year 1 and were extended up to every 4 months thereafter when VA and macular thickness were stable. Main Outcome Measures: Change in VA, adverse events, and retreatment frequency. Results: Median numbers of injections were 5, 6, and 6 in year 2 and 15, 16, and 15 over 2 years in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global P ¼ 0.08). Focal/grid laser photocoagulation was administered in 41%, 64%, and 52%, respectively (aflibercept vs. bevacizumab, P < 0.001; aflibercept vs. ranibizumab, P ¼ 0.04; bevacizumab vs. ranibizumab, P ¼ 0.01). At 2 years, mean VA improved by 12.8, 10.0, and 12.3 letters, respectively. Treatment group differences varied by baseline VA (P ¼ 0.02 for interaction). With worse baseline VA (20/50 to 20/320), mean improvement was 18.1, 13.3, and 16.1 letters, respectively (aflibercept vs. bevacizumab, P ¼ 0.02; aflibercept vs. ranibizumab, P ¼ 0.18; ranibizumab vs. bevacizumab, P ¼ 0.18). With better baseline VA (20/32 to 20/40), mean improvement was 7.8, 6.8, and 8.6 letters, respectively (P > 0.10, for pairwise comparisons). Anti-Platelet Trialists' Collaboration (APTC) events occurred in 5% with aflibercept, 8% with bevacizumab, and 12% with ranibizumab (global P ¼ 0.047; aflibercept vs. bevacizumab, P ¼ 0.34; aflibercept vs. ranibizumab, P ¼ 0.047; ranibizumab vs. bevacizumab, P ¼ 0.20; global P ¼ 0.09 adjusted for potential confounders). Conclusions: All 3 anti-VEGF groups showed VA improvement from baseline to 2 years with a decreased number of injections in year 2. Visual acuity outcomes were similar for eyes with better baseline VA. Among eyes with worse baseline VA, aflibercept had superior 2-year VA outcomes compared with bevacizumab, but superiority of aflibercept over ranibizumab, noted at 1 year, was no longer identified. Higher APTC event rates with ranibizumab over 2 years warrants continued evaluation in future trials.

Bressler SB, et al. 2016.[32]
Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema

PURPOSE: To compare long-term vision and anatomic effects of ranibizumab with prompt or deferred laser vs laser or triamcinolone D laser with very deferred ranibizumab in diabetic macular edema (DME). DESIGN: Randomized clinical trial. METHODS: Eight hundred and twenty-eight study eyes (558 [67%] completed the 5-year visit), at 52 sites, with visual acuity 20/32 to 20/320 and DME involving the central macula were randomly assigned to intravitreous ranibizumab (0.5 mg) with either (1) prompt or (2) deferred laser; (3) sham injection D prompt laser; or (4) intravitreous triamcinolone (4 mg) D prompt laser. The latter 2 groups could initiate ranibizumab as early as 74 weeks from baseline, for persistent DME with vision impairment. The main outcome measures were visual acuity, optical coherence central subfield thickness, and number of injections through5years. RESULTS: At 5 years mean (± standard deviation) change in Early Treatment Diabetic Retinopathy Study visual acuity letter scores from baseline in the ranibizumab D deferred laser (N=111), ranibizumab D prompt laser (N= 124), laser/very deferred ranibizumab (N=198), and triamcinolone D laser/very deferred ranibizumab (N=125) groups were 10 ± 13, 8 ± 13, 5 ± 14, and 7 ± 14, respectively. The difference (95% confidence interval) in mean change between ranibizumab D deferred laser and laser/very deferred ranibizumab and triamcinolone D laser/very deferred ranibizumab was 4.4 (1.2–7.6, P <0.001) and 2.8 (L0.9 to 6.5, P=0.067), respectively, at 5 years. CONCLUSIONS: Recognizing

limitations of follow-up available at 5 years, eyes receiving initial ranibizumab therapy for center-involving DME likely have better long-term vision improvements than eyes managed with laser or triamcinolone D laser followed by very deferred ranibizumab for persistent thickening and vision impairment.

Pece A, et al. 2015.[33]
A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV

Aims: The aim was to compare the efficacy of intravitreal therapy with bevacizumab and ranibizumab for choroidal neovascularization (CNV) in pathologic myopia (PM). Methods: This was a prospective multicenter randomized non-blinded trial. Results: In seven centers, 78 eyes were randomized 1:1 to treatment with bevacizumab (group B, 40 eyes) or ranibizumab (group R, 38 eyes) given with an "on demand" regimen (PRN). The mean follow-up was 19 months (SD 2, range 12–24). The mean BCVA at baseline was 0.60 logMAR (20/80 Snellen equivalent, Seq) and 50 letter score (ls). Mean final BCVA was 0.51 LogMAR (20/63 Seq) and 57 ls (p= 0.0009 and p=0.0002, respectively). In group B, mean basal BCVA was 0.52 logMAR (20/63 Seq) and 54 ls, and final BCVA was 0.51 logMar (20/63 Seq) and 57 ls. In group R, mean basal BCVA was 0.62 logMAR (20/80 Seq) and 45 ls, and the final values were 0.50 logMAR (20/63 Seq) and 58 ls. Statistical comparison of the two groups showed no significant difference (logMAR p=0.90 and letters p=0.78). Multivariate analysis showed no influence of age or previous photodynamic treatment (PDT) on final visual changes. The mean number of treatments in the first year was 2.7 in group B and 2.3 in group R (p=0.09). Conclusion: Myopic CNV equally benefits from on-demand intravitreal injection of either bevacizumab or ranibizumab; the therapeutic effect is independent of previous PDT and age.

Brown 2015[34]
Intravitreal Aflibercept for Diabetic Macular Edema 100-Week Results From the VISTA and VIVID Studies

Purpose: To compare efficacy and safety of 2 dosing regimens of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME). Design: Two similarly designed, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}. Participants: Patients (eyes; n=872) with type 1 or 2 diabetes mellitus who had DME with central involvement. Methods: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control. Main Outcome Measures: The primary end point was mean change from baseline in best-corrected visual acuity (BCVA) at week 52. This report presents the 100-week results including mean change from baseline in BCVA, proportion of eyes that gained ≥15 letters, and proportion of eyes with a ≥2-step improvement in the Diabetic Retinopathy Severity Scale (DRSS) score. Results: Mean BCVA gain from baseline to week 100 with IAI 2q4, IAI 2q8, and laser control was 11.5, 11.1, and 0.9 letters (P < 0.0001) in VISTA and 11.4, 9.4, and 0.7 letters (P < 0.0001) in VIVID, respectively. The proportion of eyes that gained ≥15 letters from baseline at week 100 was 38.3%, 33.1%, and 13.0% (P < 0.0001) in VISTA and 38.2%, 31.1%, and 12.1% (P≤0.0001) in VIVID. The proportion of eyes that lost ≥15 letters at week 100 was 3.2%, 0.7%, and 9.7% (P≤0.0220) in VISTA and 2.2%, 1.5%, and 12.9% (P≤0.0008) in VIVID. Significantly more eyes in the IAI 2q4 and 2q8 groups versus those in the laser control group had a ≥2 step improvement in the DRSS score in both VISTA (37.0% and 37.1% vs. 15.6%; P < 0.0001) and VIVID (29.3% and 32.6% vs. 8.2%; P≤0.0004). In an integrated safety analysis, the most frequent serious ocular adverse event was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control). Conclusions: In both VISTA and VIVID, the 52-week visual and anatomic superiority of IAI over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups. Safety in these studies was consistent with the known safety profile of IAI**.**

Ip MS, et al. 2015.[16]
Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy
Purpose: To assess the effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity when administered for up to 3 years, evaluate the effect of delayed initiation of ranibizumab therapy on DR severity, and identify baseline patient characteristics associated with the development of proliferative DR (PDR).

Design: Exploratory analyses of phase III, randomized, double-masked, sham-controlled multicenter clinical trials.
Participants: Adults with diabetic macular edema (DME) (N = 759), baseline best-corrected visual acuity 20/40 to 20/320 Snellen equivalent, and central foveal thickness ≥275 mm.
Methods: Patients were randomized to monthly 0.3 or 0.5 mg ranibizumab or sham injections. Sham participants could switch to 0.5 mg ranibizumab during the third year (sham/0.5 mg crossover). Baseline risk factors were evaluated to explore potential associations with development of PDR. Time to first development of PDR was analyzed by Kaplan-Meier methods to calculate cumulative probabilities by group.
Main Outcome Measures: Study eye change on the Early Treatment Diabetic Retinopathy Study severity scale and a composite clinical outcome evaluating progression to PDR based on photographic changes plus clinically important events defining PDR.
Results: At month 36, a greater proportion of ranibizumab-treated eyes had ≥2- or ≥3-step DR improvement compared with sham/0.5 mg crossover. A ≥3-step improvement was achieved at 36 months by 3.3%, 15.0%, and 13.2% of sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab-treated eyes, respectively (P < 0.0001). Through 36 months, 39.1% of eyes in the sham/0.5 mg group developed PDR, as measured by composite outcome, compared with 18.3% and 17.1% of eyes treated with 0.3 or 0.5 mg ranibizumab, respectively. The presence of macular capillary nonperfusion at baseline seems to be associated with progression to PDR in ranibizumab treated eyes but did not meaningfully influence visual acuity improvement in eyes with DME after ranibizumab therapy.
Conclusions: Ranibizumab, as administered to patients with DME for 12 to 36 months in these studies, can both improve DR severity and prevent worsening. Prolonged delays in initiation of ranibizumab therapy may limit this therapeutic effect. Although uncommon, the development of PDR still occurs in a small percentage of eyes undergoing anti-vascular endothelial growth factor therapy and may be related to the presence of macular nonperfusion.

Wolf S, et al. 2014.[35]
RADIANCE: A Randomized Controlled Study of Ranibizumab in Patients with Choroidal Neovascularization Secondary to Pathologic Myopia

Objective: To compare the efficacy and safety of ranibizumab 0.5 mg, guided by visual acuity (VA) stabilization or disease activity criteria, versus verteporfin photodynamic therapy (vPDT) in patients with visual impairment due to myopic choroidal neovascularization (CNV). Design: Phase III, 12-month, randomized, double-masked, multicenter, active-controlled study. Participants: Patients (N ¼ 277) with visual impairment due to myopic CNV. Methods: Patients were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed guided by VA stabilization criteria (group I, n ¼ 106); ranibizumab on day 1 and thereafter as needed guided by disease activity criteria (group II, n ¼ 116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n ¼ 55). Main Outcome Measures: Mean average best-corrected visual acuity (BCVA) change from baseline to month 1 through months 3 (primary) and 6, mean BCVA change and safety over 12 months. Results: Ranibizumab treatment in groups I and II was superior to vPDT based on mean average BCVA change from baseline to month 1 through month 3 (group I: þ10.5, group II: þ10.6 vs. group III: þ2.2 Early Treatment Diabetic Retinopathy Study [ETDRS] letters; both P<0.0001). Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment based on mean average BCVA change from baseline to month 1 through month 6 (group II: þ11.7 vs. group I: þ11.9 ETDRS letters; P<0.00001). Mean BCVA change from baseline to month 12 was þ13.8 (group I), þ14.4 (group II), and þ9.3 ETDRS letters (group III). At month 12, 63.8% to 65.7% of patients showed resolution of myopic CNV leakage. Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months. No deaths or cases of endophthalmitis and myocardial infarction occurred. Conclusions: Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3. Ranibizumab treatment guided by disease activity criteria was noninferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1, 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 29, 2016

1	exp Bevacizumab/	8913
2	aflibercept.mp.	1014
3	pegaptanib.mp.	594
4	exp Ranibizumab/	2302
5	exp Vascular Endothelial Growth Factors/	43787
6	1 or 2 or 3 or 4 or 5	50503
7	exp Retinal Diseases/	66915
8	exp Macular Degeneration/	16476
9	7 or 8	66915
10	6 and 9	5982
11	limit 10 to yr="2015 -Current"	1075
12	limit 11 to (english language and humans)	946
13	limit 12 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	324

Ocular Vascular Endothelial Growth Factors

Goal(s):

- Promote use of preferred drugs and ensure that non-preferred drugs are used appropriately for OHP-funded conditions.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes**: Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve for 12 months, or for length of the prescription, whichever is less
4. RPh only: All other indications need to be evaluated as to whether they are funded or contribute to a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve for 12 months, or for length of the prescription, whichever is less. • If not funded: Deny; not funded by the OHP.		

P&T / DUR Review: *3/17 (SS)*
Implementation: *TBD*

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

Class Update: Tetracyclines

Date of Review: May 2017 **Date of Last Review:** May 2015

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

Purpose for Class Update:
Current Oregon Health Plan (OHP) fee-for-service (FFS) drug policy for tetracyclines limit the use of these antibiotics to one 14-day supply every 6 months to prevent use for non-funded conditions like acne or rosacea. However, this drug policy may cause unnecessary delay therapy in patients with skin and soft tissue infections (e.g., MRSA infections), osteomyelitis, or other conditions like chronic suppression for non-removable infected prostheses or other foreign body. A class update will be performed with the purpose of identifying if there is a need to change the current drug policy.

Research Questions:
1. Is there evidence to support extended therapy of tetracyclines beyond 14 days? For which clinical indications does the evidence support extended use?
2. Are there any safety concerns when using extended therapy of tetracyclines for chronic suppression or other indications?
3. Is there any new evidence for differences in efficacy or effectiveness or safety between the tetracycline agents?

Conclusions:
- There is no new comparative evidence for differences in efficacy/effectiveness or safety between tetracycline antibiotic formulations.
- There is insufficient evidence to support extended use of tetracycline antibiotics beyond 14 days outside of acne and rosacea. However, some exceptions may include bacillary angiomatosis, glanders, and bone and joint infections (e.g., osteomyelitis) for those not candidates for surgical intervention.
- There is insufficient evidence to support differences in safety or efficacy of Doryx® (doxycycline hyclate delayed-release tablets) and other oral delayed-release doxycycline formulations.
- There is insufficient evidence to address the safety of extended therapy with tetracycline antibiotics. Tetracyclines should generally be avoided in pregnant women or children under the age of 8 years.
- Doxycycline is the most commonly used tetracycline and is recommended as first- or second-line options for multiple indications or as part of combination therapy based on low quality evidence.
- From 7/1/2016 to 9/30/2016, there were 45 denied claims that did not result in a PA request and treatment was not received. Of the 27 denied claims for preferred products, 44% (n=12) of claims were associated with an unfunded condition (acne, rosacea, Hidradenitis suppurativa) and were prescribed for more than 14 days. The remaining claims were associated with funded conditions, including skin and soft tissue infections and upper respiratory tract infections.

Recommendations:

- Evaluate comparative costs in executive session.
- Change quantity limit to allow two 14 day supplies in a 3 month timeframe.

Previous Conclusions:

- Doxycycline is the most commonly recommended tetracycline and is recommended for multiple indications as first line, second line, or as part of combination therapy based on limited, low quality evidence.
- Tetracycline is recommended for select indications based on expert opinion and low quality evidence.
- Minocycline is a potential agent for methicillin-susceptible *S. aureus* (MSSA) and MRSA in non-pregnant adults and children over 7 years based on limited, low quality evidence.
- The majority of members (69.2%) received a single prescription with an average of a 13-day supply. A minority of members (17.8%) received more than two tetracycline prescriptions.
- Most tetracycline claims were for short-term therapy (57%), followed by medium-term duration (28%) and long-term duration (15%).
- Members with claims data indicating treatment of tetracyclines for only unfunded conditions comprised 27.9% of the total study population and represented 43.3% of the total prescription drug expenditures ($28,439).
- When a funded condition for a tetracycline was identified, 86% of members received only short-term treatment.

Previous Recommendations:

- Restrict use of all (preferred and non-preferred) tetracycline antibiotics to a 14-day supply every 6 months.
- Make tetracycline antibiotic therapy exceeding 14 days every 6 months subject to prior authorization to verify the presence of an OHP funded condition.

Background:

Tetracycline antibiotics work by entering the bacterial cell wall, binding reversibly to the 30s ribosomal subunit to inhibit protein synthesis.[1] They are indicated for a variety of infections caused by many aerobic gram-positive and gram-negative bacteria, including sexually transmitted diseases, respiratory tract infections, urinary tract infections (UTI), skin and soft tissue infections (SSTI), acne vulgaris, rosacea, as well as a variety of less common infections (e.g., anthrax). For most indications, duration of treatment does not exceed 14 days. Extended therapy is indicated most commonly for acne and rosacea.[2] Rosacea and most mild forms of acne fall below the current Oregon Health Plan (OHP) funded line on the Prioritized List of Health Services.[3] The only funded form of acne is acne conglobata in the presence of recurrent abscesses or communicating sinuses. [3] In the tetracycline class, doxycycline is one of the most active agents and used most often clinically. Doxycycline can be administered twice daily, has both intravenous and oral formulations, can be given with food, and is less likely to cause photosensitivity. However, the spectrum of activity is similar between the agents in the class. Tetracyclines should generally be avoided in pregnant women or children under the age of 8 years.[1] Recent changes in generic manufacturing of tetracyclines has resulted in significant price increases for both oral tetracycline and oral doxcycline products.[4]

Demeclocycline is a tetracycline that antagonizes the actions of vasopressin at the collecting duct in the nephron, producing diuresis by inhibiting ADH-induced water reabsorption in the distal portion of the convoluted tubules.[5] The use of demeclocycline is limited to treatment of Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

In 2015, a drug use evaluation of OHP FFS patients showed that the majority of members (69.2%) received a single prescription per year with an average 13-day supply dispensed.[6] Approximately 28% of prescriptions were associated with unfunded diagnoses and a small number (15%) of members received chronic therapy. As a result of this, a policy was implemented to restrict use of all tetracyclines to a 14-day supply every 6 months to limit extended therapy for unfunded conditions. Claims that exceed this limit require prior authorization to confirm treatment for an OHP-funded condition. [6]

Tetracyclines are one of the few classes with oral agents available to cover community-acquired methicillin resistant *staphylococcus aureus* (MRSA).[7] Current Infectious Disease Society of America (IDSA) guidelines recommend doxycycline as a preferred empiric treatment option for purulent moderate skin and soft tissue infections (SSTI) when MRSA is suspected or confirmed.[8] Other oral options include clindamycin and sulfamethoxazole-trimethoprim. However, resistance rates are higher for clindamycin than the other agents. Treatment duration of tetracyclines for common conditions is usually 5-10 days. According to the guidelines, a duration of longer than 14 days is only recommended for the treatment of bacillary angiomatosis and glanders, in which treatment can extend up to 6 months. For recurrent skin abscesses, an additional 5- to 10-day course of an active antibiotic is recommended. Additionally, due to the excellent bioavailability of doxycycline, IDSA guidelines recommend it as an oral treatment option for vertebral osteomyelitis.[9] Duration of therapy for osteomyelitis can extend to 3 months. For those with osteomyelitis not suitable for surgery, long-term suppressive therapy may be used after initial parenteral therapy. For bone and joint infections caused by *staphylococcus aureus* in patients who not candidates for surgical intervention, up to 6-12 weeks of combination therapy with doxycycline can be considered.[7,10] Uncomplicated cystitis or pyelonephritis due to MRSA is uncommon and extended therapy of tetracyclines is not routinely recommended for the treatment of complicated or uncomplicated urinary tract infections.[11]

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), Cochrane Collection, 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:

A systematic review from the Cochrane Collaboration was completed in 2015 to assess the efficacy and safety of treatments for rosacea.[12] Overall, oral tetracycline and low dose doxycycline (40 mg) were associated with improvements in populopustular rosacea compared with placebo and isotretinoin was associated with improvement compared to doxycycline. There is high quality evidence from 2 studies that oral doxycycline (40 mg) compared to placebo was associated with 2 grades of improvement among 90 of 269 participants (33% vs. 21%; RR 1.63; 95% CI 1.22-2.18) over 16 weeks. [12] There was no statistically significant difference in effectiveness between 100 mg and 40 mg doxycycline, but there were fewer adverse effects with the lower dose (RR 0.25; 95% CI 0.11 to 0.54) Evidence only supports doxyxcline for papulopustular rosacea (subtype 2). [12] Currently rosacea falls below the funding line on the Oregon Health Plan's prioritized list.

Guidelines:
None identified.

New Safety Alerts:
None identified.

New Formulations or Indications:
In May, 2016 the FDA approved Doryx® MPC (doxycycline hyclate) delayed-release (DR) tablets for the treatment of rickettsial infections, sexually transmitted infections, respiratory tract infections, other bacterial infections, ophthalmic infections, anthrax, severe acne and prophylaxis of malaria.[13] It is available as 60 mg and 120 mg DR tablets. This new formulation was approved around the same time doxycycline hyclate DR tablets became available as a generic tablet. Doryx® MPC incorporates a modified polymer coat designed to further delay the release of doxycycline. Doryx® MPC 120 mg is equivalent to doxycycline DR 100 mg and 60 mg MPC is equivalent to 50 mg due to a reduced bioavailability. There is no evidence of clinical superiority of Doryx MPC compared to doxycycline delayed release. Approval was based on pharmacokinetic data from phase 1 clinical trials.[14]

Randomized Controlled Trials:
A total of 30 citations were manually reviewed from the literature search. After manual review, 30 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Drug Use Evaluation:

Methods:
FFS paid and denied claims were evaluated from 7/1/2016 and 9/30/2016 to determine the disposition of the PA and potential effects from the quantity limit (Table 1). Categories are mutually exclusive but members requesting different medications during the reporting period may be counted on more than one row. Claims that resulted in no drugs within the class paid for within 90 days of the index event (first request) were further evaluated for a follow up PA or reason for no paid claim (Table 2). Members with Medicare plans were excluded. Patient profiles for denied claims with no PA requested were further reviewed for diagnosis and duration.

Results:
Table 1 includes data on requests for tetracycline antibiotics including paid claims or paid claims for an alternative in the class. The majority of claims were for doxycycline, a preferred product. Approximately 60% of claims resulted in paid drug claim for the requested product or an alternative in the class within 90 days. However, the other 40% (n=260) resulted in no paid claim within 90 days after the index event, with a little over half of those from non-preferred agents (doxycycline tablet and minocycline). Of those claims that did not result in drug treatment, 75% of those can be explained by another source of payment (Table 2). A PA was never requested after a total of 45 claims (17%), which could be a result of the quantity limit in place. Only 8 of the PA requests were denied.

For preferred products only, there were 27 denied claims that did not result in a PA request. Of these claims, 12 of them (44%) were associated with an unfunded condition (acne, rosacea, and Hidradenitis suppurativa). All of these claims were for extended therapy (>29 days). However, the remaining denied

claims (56%) were associated with a funded condition, including sinusitis, skin or soft tissue infection, bite wound, prostatitis, pneumonia). Only 2 of these claims were for treatment beyond 14 days.

Table 1: Outcome of Paid and Denied Claims from 7/1/2016 to 9/30/2016

	Initially Paid		Paid Within 30 days		Paid Within 31-90 Days		Another Drug in PDL Class Paid Within 30 days		Another Drug in PDL Class Paid Within 31-90 days		No Drugs Within PDL Class Paid Within 90 Days		Total #	Total %
Row Labels	#	%	#	%	#	%	#	%	#	%	#	%		
Tetracyclines, Oral	300	47%	35	6%	0	0%	37	6%	1	0%	260	41%	637	100%
Y	286	66%	19	4%	0	0%	9	2%	1	0%	121	28%	436	100%
DOXYCYCLINE HYCLATE	160	68%	8	3%	0	0%	6	3%	1	0%	61	26%	236	100%
DOXYCYCLINE MONOHYDRATE	122	65%	10	5%	0	0%	3	2%	0	0%	53	28%	188	100%
TETRACYCLINE HCL	4	33%	1	8%	0	0%	0	0%	0	0%	7	58%	12	100%
N	14	7%	20	10%	0	0%	28	14%	0	0%	139	69%	201	100%
DEMECLOCYCLINE HCL	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%
DOXYCYCLINE HYCLATE	0	0%	0	0%	0	0%	2	40%	0	0%	3	60%	5	100%
DOXYCYCLINE IR-DR	0	0%	1	33%	0	0%	0	0%	0	0%	2	67%	3	100%
DOXYCYCLINE MONOHYDRATE	6	5%	11	10%	0	0%	25	23%	0	0%	69	62%	111	100%
MINOCYCLINE HCL	8	10%	8	10%	0	0%	1	1%	0	0%	62	78%	79	100%
ORACEA	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%
SOLODYN	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%	1	100%

Table 2: Denied Claims from 7/1/2016 to 9/30/2016

Row Labels	Enrolled in CCO		Lost Eligibility		Has Other Insurance		Indian Health Service Coverage		PA Approved		PA Denied		PA Not Requested		Total #	Total %
	#	%	#	%	#	%	#	%	#	%	#	%	#	%		
Tetracyclines, Oral	42	35%	13	11%	28	23%	7	6%	0	0%	4	3%	27	22%	121	100%
Y	42	35%	13	11%	28	23%	7	6%	0	0%	4	3%	27	22%	121	100%
DOXYCYCLINE HYCLATE	20	33%	5	8%	19	31%	0	0%	0	0%	0	0%	17	28%	61	100%
DOXYCYCLINE MONOHYDRATE	18	34%	8	15%	9	17%	7	13%	0	0%	2	4%	9	17%	53	100%
TETRACYCLINE HCL	4	57%	0	0%	0	0%	0	0%	0	0%	2	29%	1	14%	7	100%
N	40	29%	19	14%	54	39%	4	3%	0	0%	4	3%	18	13%	139	100%
DEMECLOCYCLINE HCL	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	1	100%
DOXYCYCLINE HYCLATE	0	0%	1	33%	0	0%	0	0%	0	0%	0	0%	2	67%	3	100%
DOXYCYCLINE IR-DR	1	50%	0	0%	1	50%	0	0%	0	0%	0	0%	0	0%	2	100%
DOXYCYCLINE MONOHYDRATE	16	23%	11	16%	26	38%	4	6%	0	0%	1	1%	11	16%	69	100%
MINOCYCLINE HCL	23	37%	7	11%	24	39%	0	0%	0	0%	3	5%	5	8%	62	100%

References:

1. Chopra I, Roberts M. Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology, and Epidemiology of Bacterial Resistance. *Microbiol Mol Biol Rev*. 2001;65(2):232-260. doi:10.1128/MMBR.65.2.232-260.2001.

2. van Zuuren EJ, Fedorowicz Z. Interventions for Rosacea. *JAMA*. 2015;314(22):2403-2404. doi:10.1001/jama.2015.15287.

3. Oregon Health Policy and Research. Current Prioritized List of Health Servic. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed January 19, 2017.

4. Barlas S. Generic Prices Take Flight. *P T*. 2014;39(12):833-845.

5. Lederle Pharmaceuticals. Declomycin® (demeclocycline hydrochloride) for oral use prescribing information. Pearl River, NY. 2002 Mar 14.

6. Williams T. Drug Use Evaluation: Tetracycline Antibiotics. OSU College of Pharmacy g Use Research & Management Program. September 2015. Available at: http://www.orpdl.org/durm/meetings/meetingdocs/2015_09_24/archives/2015_09_24_TetracyclinesDUEARCHIVED.pdf.

7. Liu C, Bayer A, Cosgrove SE, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children. *Clin Infect Dis*. 2011;52(3):e18-e55. doi:10.1093/cid/ciq146.

8. Stevens DL, Bisno AL, Chambers HF, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10-e52. doi:10.1093/cid/ciu296.

9. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. *Clin Infect Dis*. 2015;61(6):e26-e46. doi:10.1093/cid/civ482.

10. Tone A, Nguyen S, Devemy F, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care*. 2015;38(2):302-307. doi:10.2337/dc14-1514.

11. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103-e120. doi:10.1093/cid/ciq257.

12. van Zuuren EJ, Fedorowicz Z, Carter B, van der Linden MMD, Charland L. Interventions for rosacea. *Cochrane Database Syst Rev*. 2015;(4):CD003262. doi:10.1002/14651858.CD003262.pub5.

13. Doryx MPC. (dosycycline hyclate delayed-release tablets). Prescribing Information. 5/2016. Mylan pharmaceuticals.

14. Hopkins AM, Wojciechowski J, Abuhelwa AY, Mudge S, Upton RN, Foster DJR. Population Pharmacokinetic Model of Doxycycline Plasma Concentrations – Pooled Study Data. *Antimicrob Agents Chemother*. January 2017:AAC.02401-16. doi:10.1128/AAC.02401-16.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	CAPSULE	MORGIDOX	DOXYCYCLINE HYCLATE	Y
ORAL	CAPSULE	VIBRAMYCIN	DOXYCYCLINE HYCLATE	Y
ORAL	TABLET	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	TABLET	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	Y
ORAL	SUSP RECON	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	Y
ORAL	SUSP RECON	VIBRAMYCIN	DOXYCYCLINE MONOHYDRATE	Y
ORAL	CAPSULE	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	Y
ORAL	CAPSULE	TETRACYCLINE HCL	TETRACYCLINE HCL	Y
ORAL	SYRUP	VIBRAMYCIN	DOXYCYCLINE CALCIUM	N
ORAL	TABLET DR	DORYX	DOXYCYCLINE HYCLATE	N
ORAL	TABLET DR	DOXYCYCLINE HYCLATE	DOXYCYCLINE HYCLATE	N
ORAL	CAP IR DR	DOXYCYCLINE IR-DR	DOXYCYCLINE MONOHYDRATE	N
ORAL	CAP IR DR	ORACEA	DOXYCYCLINE MONOHYDRATE	N
ORAL	CAPSULE	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	N
ORAL	TABLET	DOXYCYCLINE MONOHYDRATE	DOXYCYCLINE MONOHYDRATE	N
ORAL	TABLET	DEMECLOCYCLINE HCL	DEMECLOCYCLINE HCL	N
ORAL	CAPSULE	MINOCYCLINE HCL	MINOCYCLINE HCL	N
ORAL	TAB ER 24H	MINOCYCLINE HCL ER	MINOCYCLINE HCL	N
ORAL	TAB ER 24H	SOLODYN	MINOCYCLINE HCL	N
ORAL	TABLET	MINOCYCLINE HCL	MINOCYCLINE HCL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

# ▲	Searches	Results
1	tetracyclines.mp. or Tetracyclines/	3142
2	doxycycline.mp. or Doxycycline/	9726
3	minocycline.mp. or Minocycline/	5175
4	limit 3 to (english language and humans and yr="2015 -Current" and (controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	30
5	from 4 keep 19, 24-25	3

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 Literature Scan: ACE Inhibitors, ARBs, Direct Renin Inhibitors and Sacubitril/Valsartan

Date of Review: May 2017

Date of Last Review: January and September 2015
Literature Search: 01/01/2015—03/01/2017

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

Conclusions:

- Since the last review additional evidence has become available with the publication of 4 new guidelines,[1–4] 4 new systematic reviews and meta-analyses,[5–8] 1 randomized controlled trial,[9] 2 new formulations,[10,11] and 1 Food and Drug Administration (FDA) safety alert.[12]
- There is moderate quality evidence of no difference between angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) for total mortality, cardiovascular (CV) events, or CV mortality in patients with hypertension. Incidence of adverse effects was slightly lower for ARBs compared with ACEIs primarily due to a higher incidence of dry cough with ACEIs.[5]
- In patients with hypertension, moderate quality evidence demonstrates that compared with calcium channel blockers (CCBs), renin-angiotensin system (RAS) inhibitors reduce death or hospitalizations for heart failure (HF) (absolute risk reduction (ARR) 1.2%), increase fatal and non-fatal stroke (absolute risk increase (ARI) 0.7%) and are similar for all-cause death, total CV events and end stage renal failure (ESRF) events.[6]
- Moderate quality evidence reveals that compared with thiazides, RAS inhibitors increase hospitalizations for heart failure (ARI 1%) and increase fatal and non-fatal stroke (ARI 0.6%). RAS inhibitors are similar to thiazides for all-cause death, total CV events, fatal and non-fatal myocardial infarction (MI) and ESRF events.[6]
- Low quality evidence shows that compared with beta-blockers, RAS inhibitors reduce total CV events (ARR 1.7%) and fatal and non-fatal stroke (ARR 1.7%) and are similar for all-cause death, HF, and total MI.[6]
- Low to moderate quality evidence shows when ARBs were compared to placebo they did not produce statistically significant reductions in the risk of MI, heart failure (HF), hospitalization, or mortality.[7]
- Moderate quality evidence concluded the direct renin inhibitor (DRI), aliskiren, shows no benefit for the outcomes of major CV events, total mortality, cardiac death, MI, or stroke.[8]
- The FDA issued a warnings and precautions update regarding the possibility of sprue-like enteropathy associated with olmesartan use.[12]
- Guidelines recommend sacubitril/valsartan as an option for patients with the following characteristics:[2,3]
  - with New York Heart Association (NYHA) class II to IV HF symptoms and
  - with a left ventricular ejection fraction of 35% or less and
  - who are already taking a stable dose of ACEI or ARB

Recommendations:

- For ACEIs, ARBs and DRIs, no further review or research is needed at this time. Evaluate comparative drug costs in the executive session.
- No changes to Entresto (sacubitril/valsartan) prior authorization (PA) criteria are recommended based on evidence review.

Previous Conclusions:

- There is moderate quality evidence of no difference between ACEI and ARBs in regards to reduction in mortality, CV mortality, hospitalizations or stroke, or progression to chronic kidney disease in patients with primary hypertension. There is insufficient evidence at this time to suggest DRIs offer any benefit in these clinically relevant outcomes.
- There is moderate quality evidence that risk of dry cough and angioedema associated with ACEIs is higher than with ARBs or DRIs. Incidence of angioedema is also more common in heart failure patients than other populations. However, angioedema remains a very rare adverse effect of ACEIs.
- There is moderate quality evidence that dual blockade of the RAS does not provide additional benefit in clinically relevant outcomes compared with monotherapy and increases risk of harm, specifically the risk of hyperkalemia, hypotension, renal failure and withdrawal due to adverse events.
- There is insufficient evidence that fixed combination drug formulations containing an ACEI, AIIRA or DRI offer additional benefit in clinically relevant outcomes compared to the respective free drug combination.
- Evidence for use of sacubitril/valsartan is limited to one 27-month clinical trial (n=8,399) with low and moderate risk of selection and performance bias, respectively. The study was composed of patients with stable, mildly symptomatic HFrEF (New York Heart Association [NYHA] Classes II and III) with a mean ejection fraction (EF) of 29%. Patients in the study remained on standard HF therapy (i.e., beta-blocker, diuretic(s), and aldosterone antagonist).
- There is low to moderate quality evidence that sacubitril/valsartan 97/103 mg twice daily (BID) can reduce risk of death from CV causes or hospitalization for HF by an absolute difference of 4.7% compared to enalapril 10 mg BID (21.8% vs. 26.5%, respectively; Hazard Ratio [HR]=0.80 (95% Confidence Interval [CI] 0.73-0.87; p<0.001; number needed-to-treat [NNT] 22).
- There is low quality evidence, based on a secondary endpoint, that sacubitril/valsartan may reduce all-cause mortality, driven almost entirely by reduction in CV mortality, by an absolute difference of 2.8% compared to enalapril (17.0% vs. 19.8%, respectively; HR=0.84 (95% CI, 0.76-0.93; p<0.001; NNT 36).
- There is low quality evidence that sacubitril/valsartan may not reduce perceived quality of life and health status versus enalapril when assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The difference in KCCQ scores were statistically significant when assessed at 8 months (a difference of 1.61 points on a 100-point scale), but a much larger difference is needed to be clinically meaningful.
- There is insufficient evidence to determine if the results seen were driven by the maximum daily dose of valsartan (320 mg) or by the addition of the neprilysin inhibitor sacubitril to maximally dosed valsartan. Additional studies will help guide place in therapy for sacubitril/valsartan in the management of HFrEF, including whether a neprilysin inhibitor with an ARB will replace an ACE-I or ARB in most HFrEF patients.
- Safety data are limited to the one trial. There is low quality evidence that sacubitril/valsartan may be tolerated similarly as enalapril, but sacubitril/valsartan was associated with more episodes of symptomatic hypotension than enalapril (14.0% vs. 9.2%, respectively). Enalapril was associated higher incidence of cough than sacubitril/valsartan (14.3% vs. 11.3%, respectively) and higher incidence of hyperkalemia >6.0 mEq/L (5.6% vs. 4.3%, respectively).
- Based on study methodology, there is insufficient evidence of a dose-response for sacubitril/valsartan, and a daily dose of 400 mg is needed to expect the mortality and morbidity benefits demonstrated in the trial.
- Based on the population studied, there is insufficient evidence for the use of sacubitril/valsartan in the following populations: NYHA class I or IV, HF patients with preserved EF, pediatric populations, very elderly populations, patients with refractory hypertension or marginally low blood pressure, or ACEI-naïve patients. Blacks were also underrepresented in this trial despite the high prevalence of HF and higher incidence of angioedema in this population.

Previous Recommendations:

- For ACEIs, ARBs and DRIs, no further review or research is needed at this time. After review of costs in the executive session, no changes to the PDL recommended.
- Restrict use of sacubitril/valsartan to populations where it has demonstrated efficacy.

Methods:

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

ACEIs versus angiotensin receptor blockers ARBs for primary hypertension

A 2014 Cochrane review compared the effects of ACEIs and ARBs on total mortality and CV events, and the rates of withdrawals due to adverse effects in patients with primary hypertension.[5] Studies included in this systematic review were randomized controlled trials (RCTs) comparing ACEI versus ARB lasting greater than one year in patients with uncontrolled or controlled primary hypertension. Hypertension was defined as systolic blood pressure (SBP) > 140 mm Hg or a diastolic blood pressure (DBP) > 90 mm Hg or both at baseline. The ACEIs included in the analysis were: enalapril, ramipril, fosinopril, quinapril and lisinopril. Telmisartan, losartan, candesartan, irbesartan, and valsartan were the ARBs that were studied in the RCTs. Nine trials with 11,007 subjects met inclusion criteria. Five trials reported on total mortality, 3 reported on total CV events, and 4 reported on CV mortality. Eight trials had data on adverse effects and safety. Studies were of good to moderate quality with minimal risk of bias. There was no evidence of a difference between ACEIs and ARBs for total mortality (risk ratio (RR) 0.98; 95% confidence interval (CI) 0.88 to 1.10), total CV events (RR 1.07; 95% CI 0.96 to 1.1 9), or CV mortality (RR 0.98; 95% CI 0.85 to 1.13).[5] Incidence of adverse effects was slightly lower for ARBs compared with ACEIs (RR 0.83; 95% CI 0.74 to 0.93; ARR 1.8%, NNTB 55 over 4.1 years), primarily due to a higher incidence of dry cough with ACEIs.[5] Forty three percent of adverse events in the ACEI patients were due to cough compared to 4% in the ARB arms.[5] Other adverse effects associated with ACEIs included atrial flutter, edema, rash, and rise in creatinine.[5] Adverse effects prompting withdrawal of ARB therapy included dizziness, hypotension, palpitations, dyspnea, headache, nausea, edema, urticaria and macroalbuminuria.[5]

First-line drugs inhibiting renin-aldosterone system (RAS) versus other first-line antihypertensive drug classes for hypertension

The purpose of a 2015 Cochrane review was to evaluate efficacy of RAS inhibitors compared to other first line antihypertensive agents.[6] The population of interest was patients with primary hypertension (≥ 130/85 mm Hg). A blood pressure less than the standard 140/90 mm Hg was selected to include more patients including diabetics, who have a lower target threshold for blood pressure control. RCTs had to have at least 6 months of follow-up data for inclusion in the review. RAS inhibitors included ACEIs, ARBs, and renin inhibitors. ACEI available in the United States (U.S.) that were evaluated in the trials included

benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. The ARBs marketed in the U.S. included candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. The two renin inhibitors were aliskiren and remikiren. Only aliskiren is available in the U.S. Comparators included thiazide diuretics, beta blockers, and CCBs. Primary outcomes were all-cause mortality, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction (MI), fatal and non-fatal HF requiring hospitalization, total CV events and ESRF.[6] Forty two studies met inclusion criteria involving 65,733 subjects with a mean age of 66 years. The CCB and thiazide studies were rated as moderate to high quality by the reviewers. The beta blocker studies were evaluated as low quality due to insufficient details regarding methods of blinding, allocation of concealment and randomization, or incomplete reporting of outcome data.[6] Over half of all the studies included in this review were completed in Europe.

Comparator CCBs included amlodipine, nifedipine, diltiazem, felodipine, and verapamil. Compared with CCBs moderate quality evidence showed that RAS inhibitors decreased HF (RR 0.83, 95% CI 0.77 to 0.90), but they increased stroke (RR 1.19, 95% CI 1.08 to 1.32).[6] CCBs and RAS inhibitors had similar effects on all-cause death (RR 1.03, 95% CI 0.98 to 1.09), total CV events, (RR 0.98, 95% CI 0.93 to 1.02), total MI (RR 1.01, 95% CI 0.93 to 1.09), and ESRF (RR 0.88, 95% CI 0.74 to 1.05).[6]

Thiazides included in the studies were chlorthalidone and hydrochlorothiazide. Compared with thiazides, moderate quality evidence revealed that RAS inhibitors increased HF (RR 1.19, 95% CI 1.07 to 1.31), and increased stroke (RR 1.14, 95% CI 1.02 to 1.28).[6] They had similar effects on all-cause death (RR 1.00, 95% CI 0.94 to 1.07), total CV events (RR 1.05, 95% CI 1.00 to 1.11), total MI (RR 0.93, 95% CI 0.86 to 1.01), and ESRF (RR 1.10, 95% CI 0.88 to 1.37).[6]

Beta blockers included atenolol, carvedilol, metoprolol, bisoprolol, and acebutolol. Compared with beta-blockers, low quality evidence demonstrated that RAS inhibitors decreased total CV events (RR 0.88, 95% CI 0.80 to 0.98), and decreased stroke (RR 0.75, 95% CI 0.63 to 0.88).[6] No significant differences were noted between RAS inhibitors and beta-blockers for all-cause death (RR 0.89, 95% CI 0.78 to 1.01), HF (RR 0.95, 95% CI 0.76 to 1.18), and total MI (RR 1.05, 95% CI 0.86 to 1.27)[6] The effect on ESRD could not be assessed due to insufficient data.

In summary, compared with CCBs, RAS inhibitors reduce death or hospitalizations for HF (absolute risk reduction (ARR) 1.2%), increase fatal and non-fatal stroke (absolute risk increase (ARI) 0.7%) and are similar for all-cause death, total CV events and ESRF events. Compared with thiazides, RAS inhibitors increase hospitalizations for HF (ARI 1%) and increase fatal and non-fatal stroke (ARI 0.6%). RAS inhibitors are similar to thiazides for all-cause death, total CV events fatal and non-fatal MI and ESRF events. Compared with beta-blockers, RAS inhibitors reduce total CV events (ARR 1.7%) and fatal and non-fatal stroke (ARR 1.7%) and are similar for all-cause death, HF, and total MI.

Cardiovascular and cerebrovascular outcomes of long-term angiotensin receptor blockade in essential hypertension

The purpose of this systematic review and meta-analysis was to assess the long-term effects of ARBs on blood pressure (BP) control, MI, hospitalization for HF, cerebrovascular events, CV mortality, and all-cause mortality.[7] Hypertension trials were included if they reported on ARB efficacy in either BP control (relative to placebo for periods ≥6 months) or cardiovascular/cerebrovascular outcomes (relative to non-ARB antihypertensive therapies for periods ≥24 months).[7] A total of 7 articles were included in the analysis with a total of 16,864 subjects. Studies were rated as low to moderate quality due to insufficient reporting of study methodology or selective outcome reporting.[7] Six ARB agents were studied: candesartan, eprosartan, irbesartan, olmesartan, losartan and telmisartan. ARB therapy significantly reduced mean systolic BP (weighted mean difference (WMD) −4.86; 95% CI: −6.19 to −3.53 mm Hg) and diastolic BP (WMD: −2.75; 95% CI: −3.65 to −1.86 mm Hg] compared to placebo.[7] The risk of stroke was reduced by 21% in the ARB group compared with alternative antihypertensives (RR: 0.79; 95% CI: 0.66 to 0.96).[7] ARBs did not produce statistically significant reductions in the risk of MI, HF hospitalization, or mortality. The findings from this review

suggest that ARBs are more effective than placebo therapy in long-term BP lowering in patients with essential hypertension. Long-term ARB treatment may also confer enhanced protection against stroke but no other cardiovascular outcomes relative to placebo.[7]

Effect of aliskiren on cardiovascular outcomes

The aim of this meta-analysis was to evaluate the effects of aliskiren monotherapy on major cardiovascular outcomes.[8] All eligible studies were RCTs assessing the effect of aliskiren therapy compared with patients not taking aliskiren therapy. Six trials reporting data on 12,465 patients were included in the review. Follow-up periods ranged from 8 weeks to 32 months. The trials were rated as moderate to high quality evidence. The studies reported 1,886 occurrences of major cardiovascular events, 1,074 events of total mortality, 739 events of cardiac death, 366 events of myocardial infarction, and 319 events of stroke.[8] Aliskiren therapy had no effect on major CV events (RR, 0.93; 95% CI: 0.77 to 1.13; P=0.47), total mortality (RR, 1.00; 95% CI: 0.77 to 1.29; P=1.00), cardiac death (RR, 1.01; 95% CI: 0.79 to .29; P=0.95), MI (RR, 0.71; 95% CI: 0.36 to 1.38; P=0.31), or stroke (RR, 0.87; 95% CI: 0.48 to 1.58; P=0.64).[8] The authors concluded aliskiren monotherapy does not have an effect on the incidence of major cardiovascular events, total mortality, cardiac death, myocardial infarction, or stroke.

New Guidelines:

Department of Veterans Affairs (VA), Department of Defense (DoD)

In 2014, the VA/DoD updated clinical practice guidelines focused on the management of hypertension originally published in 2004.[1] Recommended first line antihypertensive therapy for the general population including patients with coronary disease, MI or diabetes are thiazide diuretics. Second line therapy for the general patient population includes ACEIs, ARBs, or long acting dihydropyridine CCBs (amlodipine, felodipine or nifedipine SR). Additional drug classes may be added to reach blood pressure goals. Strong evidence recommends to avoid using ACEI, ARBs, and DRIs in combination with each other.

Recommendations for specific patient populations are as follows:

1. For patients with chronic kidney disease (CKD) ACEIs or ARBs are recommended as first line therapy.
2. ACEIs or ARBs are not recommended as monotherapy for African Americans.
3. For African Americans with CKD, combination therapy with thiazide diuretic and ACEI or ARB is recommended.

American Heart Association (AHA)/American College of Cardiology (ACC)/American Society of Hypertension (ASH)

Members of AHA, ACC and ASH collaborated to develop a scientific statement of treatment of hypertension in patients with coronary artery disease. This 2015 publication updated a 2007 AHA statement on treatment of hypertension in ischemic heart disease.[4] A summary of the main recommendations for pharmacologic treatment of hypertension in patients with ischemic heart disease is presented in **Table 1.**

Table 1. Pharmacologic Recommendations for treatment of hypertension in ischemic heart disease[4]

	ACEI or ARB	Diuretic	B-Blocker	Non-DHP CCB	DHP CCB	Nitrates	Aldosterone Antagonist	Hydralazine/Isosorbide
Stable Angina	Drug of Choice	Drug of Choice*	Drug of Choice	Add on or alternative drug – *do not use if HF or LVD is present. Caution should be exercised if combining non-DHP CCB with BB*	Add on or alternative drug	Drug of Choice	Add on or alternative drug	
ACS	Drug of Choice – *especially if prior MI, LVD,*	Drug of Choice*	Drug of Choice – *esmolol (IV), metoprolol or bisoprolol*	Add on or alternative drug- *do not use if HF or LVD is present. Caution should be exercised if combining non-DHP CCB with BB*	Add on or alternative drug	Add on or alternative drug	Add on or alternative drug –	

	DM or CKD is present						*spironolactone or epelrenone if LVD, HF, or DM is present*	
HF	Drug of Choice	Drug of Choice*	Drug of Choice – *carvedilol, metoprolol succinate, or bisoprolol*			Add on or alternative drug	Add on or alternative drug- *spironolactone or epelrenone if LVD, HF, or DM is present*	Add on or alternative drug

Abbreviations: ACS = acute coronary syndrome, BB = beta blocker, CCB = calcium channel blocker, CKD = chronic kidney disease, DHP = dihydropyridine, DM = Diabetes Mellitus, HF = heart failure, LVD = Left ventricular dysfunction, MI = myocardial infarction

** Chlorthalidone is preferred. Loop diuretic should be used in the presence of HF (New York Heart Association class III or IV) or CKD with glomerular filtration rate <30 mL/.min. Caution should be exercised in HF with preserved ejection fraction.*

National Institute for Health and Care Excellence (NICE) Guidance

NICE guidance regarding the utilization of sacubitril/valsartan for treating symptomatic chronic heart failure with reduced ejection fraction was published in 2016.[2] The recommendation is that sacubitril/valsartan is an option for patients with the following characteristics:

- with New York Heart Association (NYHA) class II to IV HF symptoms and
- with a left ventricular ejection fraction of 35% or less and
- who are already taking a stable dose of ACEI or ARB

This recommendation was primarily based on evidence from the PARADIGM-HF trial which compared sacubitril/valsartan 200 mg twice daily with enalapril 10 mg twice daily.[13] The primary end point from this trial was a composite of death from cardiovascular causes or a first hospitalization for worsening heart failure, assessed at every study visit (0, 2, 4 and 8 weeks, 4 months, and then every 4 months).[13] The composite primary end point significantly favored sacubitril/valsartan compared with enalapril (hazard ratio [HR] 0.80; 95% CI 0.73 to 0.87, p<0.001).[13] During the 27 month duration of this trial, the overall safety of sacubitril/valsartan was comparable to enalapril; although the sacubitril/valsartan cohort experienced more hypotension and the enalapril patients experienced more cough, the differences were not significant.[13] The NICE reviewers noted that PARADIGM-HF subjects were relatively younger, had a higher proportion of men, were less likely to be using cardiac devices, and had a higher tolerability to the dose of valsartan used in the trial (equivalent to 160 mg) which made the generalizability of the trial to the UK population more difficult. There are no head to head trials comparing sacubitril/valsartan with ARBs and long term safety data is lacking. More evidence evaluating the long term safety and comparative efficacy of sacubitril/valsartan will assist in identifying the role of this drug in HF management.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA): Update on New Pharmacological Therapy for Heart Failure

The 2016 ACC/AHA/HFSA publication focused on updating the 2013 ACCF/AHA guideline for the management of heart failure with sacubitril/valsartan and ivabradine.[3] In this document, sacubitril/valsartan is referred to as angiotensin receptor-neprilysin inhibitor (ANRI). Recommendations were classified according to estimated magnitude and certainty of benefit in the following categories: Class 1 (strong); Class IIa (moderate); Class IIb (weak); Class III: No Benefit; or Class III: Harm. Level of evidence was graded by the panel after reviewing the quality of data from clinical trials and meta-analyses. Level A evidence was categorized as high quality from RCTs or meta-analyses, level B-R was based on moderate quality evidence from RCT's or meta-analyses, level B-NR was moderate quality evidence from nonrandomized or observational data, level C-LD was based on data with methodological limitations, and Level C-EO was a consensus of expert

opinion based on clinical experience. The committee arrived at the recommendations for pharmacologic treatment of heart failure with reduced ejection fraction (HF*r*EF) as presented in **Table 2**.

Table 2. Treatment of Heart Failure: Recommendations for Renin-Angiotensin System Inhibition with ACE-I, ARB, or ARNI[3]

Recommendation	Class of Recommendation	Quality of Evidence
The clinical strategy of inhibition of the renin-aldosterone system with ACE inhibitors or ARBs or ARNI in conjunction with evidence based beta blockers and aldosterone antagonists in selected patients is recommended for patients with HF*r*EF.	Class I – Strong Benefit >>> Risk	ACE-I : A (High) ARB : A (High) ANRI: B-R (Moderate)
The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HF*r*EF to reduce morbidity and mortality.	Class I – Strong Benefit >>> Risk	A (High)
The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HF*r*EF who are intolerant to ACE inhibitors because of cough or angioedema.	Class I –Strong Benefit >>> Risk	A (High)
In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.	Class I- Strong Benefit >>> Risk	B-R (Moderate)
ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.	Class III- Harm Risk > Benefit	B-R (Moderate)
ARNI should be administered to patients with a history of angioedema.	Class III- Harm Risk > Benefit	C-EO (Expert Opinion)

New Formulations:

Qbrelis™

A new formulation of lisinopril, Qbrelis™ is a 1mg/ml oral solution FDA approved July 2016 for:

- treatment of hypertension in adults and pediatric patients ≥ 6 years
- adjunct therapy for heart failure
- treatment of acute myocardial infarction

This new oral liquid formulation of lisinopril provides more options for pediatric patients who require weight based dosing or older patients who have difficulty swallowing tablets. The FDA approval was based on two bioequivalence studies which were single dose crossover studies of lisinopril 10mg in fasting and fed states.[14] The application relied upon previously submitted safety and efficacy date for Zestril® (lisinopril) tablets.[14] Pediatric dosing of lisinopril was based on a 2003 dose- response RCT.[15]

Byvalson™

Byvalson™ is a new fixed dose combination therapy of a beta blocker and an ARB containing nebivolol 5 mg with valsartan 80 mg. It was FDA approved June 2016 for treatment of hypertension.[11] This is the first product to combine a beta blocker with an ARB and the only combination antihypertensive that contains

nebivolol. FDA approval was based on evidence supporting the utilization of combination therapy at lower doses to reduce dose-related adverse effects and provide additive treatment effects on blood pressure reduction.[16] Clinical trial data supporting the efficacy of the combination therapy was based on an 8 -week randomized, double -blind, placebo-controlled, parallel -group, multiple -dose study of nebivolol and valsartan given either as a fixed dose combination or as monotherapy in patients with Stage 1 or Stage 2 hypertension.[17] The trial included 4161 patients who were randomly assigned to receive double-blind treatment with nebivolol (5 mg/day or 20 mg/day) or valsartan (80 mg/day or 160 mg/day) monotherapies, fixed-dose combinations (FDC) of nebivolol and valsartan (5 and 80 mg/day, 5 and 160 mg/day, or 10 and 160 mg/day), or placebo. Nebivolol 5 mg in a fixed dose combination with valsartan 80 mg produced statistically and clinically significantly greater reductions in SBP/DBP at week 4 compared to the individual agents (least square mean (LSM) difference of 2.7/3.7 mm Hg for FDC 5/80mg vs nebivolol 5mg and LSM difference of 3.3/2.9 mm Hg FDC 5/80 mg vs valsartan 80mg).[17] The rate of treatment-emergent adverse effects was similar across all study groups. There is no current evidence that evaluates the long term safety and efficacy of this fixed dose combination of beta blocker and ARB therapy.

New Safety Alerts:

Olmesartan-associated sprue-like enteropathy

An association between olmesartan and severe sprue-like enteropathy was first described as a case series in 2012.[18] The clinical presentation was chronic diarrhea and median weight loss of 18 kg (range 2.5-57 kg) which required hospitalization in 14 out of 22 patients included in the initial report.[18] Duodenal biopsies of these patients revealed villous atrophy and inflammation. Withdrawal of olmesartan led to clinical and histological improvement.

An observational cohort study published in 2016 assessed the risk of hospitalization for intestinal malabsorption associated with olmesartan compared to other ACEIs and ARBs using the French National Insurance claim database.[19] Approximately 4,500,000 patients were included in the analysis and 218 events were observed. Eighty seven patients in the ACEI group, 48 patients in the olmesartan group, and 83 in the other ARB group were identified. Compared with ACEIs, the adjusted rate ratio of hospitalization with a discharge diagnosis of intestinal malabsorption was 2.49 (95% CI 1.73 to 3.57, $p<0.0001$) in olmesartan users.[19] Median length of hospital stay for intestinal malabsorption was longer in the olmesartan group than in the other ARB group (9 days vs 2 days; $p=0.02$).[19] The risks of intestinal disease increased with duration of exposure up to 10-fold beyond 2 years of exposure.[19] This data lead to the conclusion that olmesartan is associated with an increased risk of hospitalization for intestinal malabsorption. This risk has not been associated with treatment with other ARBs. The FDA issued a warnings and precautions update regarding the possibility of sprue-like enteropathy associated with olmesartan use in July, 2103.[12] If a patient develops these symptoms during treatment with olmesartan, providers are encouraged to exclude other etiologies and consider discontinuation of olmesartan in cases where no other etiology is identified.

ACE/ARB/DRI Utilization in Fee for Service Population

During the fourth quarter of 2016 (10/1/16 through 12/31/16) most claims for a preferred ACEI were for lisinopril (73%). The preferred ARB with the highest utilization was losartan with 21% of claims overall. Sixty four claims were received for nonpreferred agents in this class of antihypertensives. For the nonpreferred agents 71% (n=25) of claims were processed through the member's CCO insurance and most of the requests were for irbesartan. The remaining unfilled claims were due to loss of eligibility (n=5), coverage through Indian Health Service (n=1) or because a prior authorization was never requested (n = 4). Most of the FFS clients were able to receive ACEI or ARB therapy when it was prescribed by their provider. There was one paid claim for sacubitril/valsartan in all 4 quarters of 2016. There was one request for the direct renin inhibitor, aliskiren, but it was switched to another drug in the ACEI/ARB class.

References:

1. VA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. | National Guideline Clearinghouse. https://www.guideline.gov/summaries/summary/48858/vadod-clinical-practice-guideline-for-the-diagnosis-and-management-of-hypertension-in-the-primary-care-setting?q=treatment+of+hypertension. Accessed March 9, 2017.

2. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction | 1-Recommendations | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/TA388/chapter/1-Recommendations. Accessed March 9, 2017.

3. Writing committee members, ACC/AHA task force members. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail*. 2016;22(9):659-669. doi:10.1016/j.cardfail.2016.07.001.

4. Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: A scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *J Am Soc Hypertens*. 2015;9(6):453-498. doi:10.1016/j.jash.2015.03.002.

5. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2014. doi:10.1002/14651858.CD009096.pub2.

6. Xue H, Lu Z, Tang WL, et al. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. *Cochrane Database Syst Rev*. 2015;1:CD008170. doi:10.1002/14651858.CD008170.pub2.

7. Akioyamen L, Levine M, Sherifali D, et al. Cardiovascular and cerebrovascular outcomes of long-term angiotensin receptor blockade: meta-analyses of trials in essential hypertension. *Journal of the American Society of Hypertension*. 2016;10(1):55-69. doi:10.1016/j.jash.2015.11.005.

8. Zhang J-T, Chen K-P, Guan T, Zhang S. Effect of aliskiren on cardiovascular outcomes in patients with prehypertension: a meta-analysis of randomized controlled trials. [Review]. *Drug design, development & therapy*. 2015:1963-1971. doi:10.2147/DDDT.S75111.

9. McMurray JJV, Krum H, Abraham WT, et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. *Journal of Medicine*. 2016;374(16):1521-1532. doi:10.1056/NEJMoa1514859.

10. CDER Application review of Byvlason™. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206302Orig1s000SumR.pdf. Accessed March 13, 2017.

11. Byvalson (valsartan/nebivolol) Prescribing Information. Irvine, CA. Allergan USA, Inc. June, 2016. https://www.allergan.com/assets/pdf/byvalson_pi. Accessed March 30, 2017.

12. Safety Information > Benicar (olmesartan medoxomil) Tablets. https://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258781.htm. Accessed March 14, 2017.

13. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077.

14. CDER Evalution of Qbrelis™. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208401Orig1s000SumR.pdf. Accessed March 13, 2017.

15. Soffer B, Zhang Z, Miller K, Vogt BA, Shahinfar S. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of lisinopril for children with hypertension. *Am J Hypertens*. 2003;16(10):795-800.

16. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SAE, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. *Hypertension*. 2009;53(4):646-653. doi:10.1161/HYPERTENSIONAHA.108.123455.

17. Giles TD, Weber MA, Basile J, et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomised, multicentre study. *Lancet*. 2014;383(9932):1889-1898. doi:10.1016/S0140-6736(14)60614-0.

18. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738. doi:10.1016/j.mayocp.2012.06.003.

19. Basson M, Mezzarobba M, Weill A, et al. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. *Gut*. 2016;65(10):1664-1669. doi:10.1136/gutjnl-2015-309690.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	ALTACE	RAMIPRIL	Y
ORAL	CAPSULE	RAMIPRIL	RAMIPRIL	Y
ORAL	TABLET	BENAZEPRIL HCL	BENAZEPRIL HCL	Y
ORAL	TABLET	BENICAR	OLMESARTAN MEDOXOMIL	Y
ORAL	TABLET	COZAAR	LOSARTAN POTASSIUM	Y
ORAL	TABLET	ENALAPRIL MALEATE	ENALAPRIL MALEATE	Y
ORAL	TABLET	LISINOPRIL	LISINOPRIL	Y
ORAL	TABLET	LOSARTAN POTASSIUM	LOSARTAN POTASSIUM	Y
ORAL	TABLET	LOTENSIN	BENAZEPRIL HCL	Y
ORAL	TABLET	MICARDIS	TELMISARTAN	Y
ORAL	TABLET	PRINIVIL	LISINOPRIL	Y
ORAL	TABLET	TELMISARTAN	TELMISARTAN	Y
ORAL	TABLET	VASOTEC	ENALAPRIL MALEATE	Y
ORAL	TABLET	ZESTRIL	LISINOPRIL	Y
ORAL	SOLN RECON	EPANED	ENALAPRIL MALEATE	N
ORAL	SOLUTION	QBRELIS	LISINOPRIL	N
ORAL	TABLET	ACCUPRIL	QUINAPRIL HCL	N
ORAL	TABLET	ATACAND	CANDESARTAN CILEXETIL	N
ORAL	TABLET	AVAPRO	IRBESARTAN	N
ORAL	TABLET	CANDESARTAN CILEXETIL	CANDESARTAN CILEXETIL	N
ORAL	TABLET	CAPTOPRIL	CAPTOPRIL	N
ORAL	TABLET	DIOVAN	VALSARTAN	N
ORAL	TABLET	EDARBI	AZILSARTAN MEDOXOMIL	N
ORAL	TABLET	EPROSARTAN MESYLATE	EPROSARTAN MESYLATE	N
ORAL	TABLET	FOSINOPRIL SODIUM	FOSINOPRIL SODIUM	N
ORAL	TABLET	IRBESARTAN	IRBESARTAN	N
ORAL	TABLET	MAVIK	TRANDOLAPRIL	N
ORAL	TABLET	MOEXIPRIL HCL	MOEXIPRIL HCL	N
ORAL	TABLET	PERINDOPRIL ERBUMINE	PERINDOPRIL ERBUMINE	N
ORAL	TABLET	QUINAPRIL HCL	QUINAPRIL HCL	N
ORAL	TABLET	TEKTURNA	ALISKIREN HEMIFUMARATE	N
ORAL	TABLET	TRANDOLAPRIL	TRANDOLAPRIL	N
ORAL	TABLET	VALSARTAN	VALSARTAN	N
ORAL	TABLET	ENTRESTO	SACUBITRIL/VALSARTAN	

Current Status of PDL Class:

Preferred Drugs	Non-Preferred Drugs
Angiotensin Converting Enzyme Inhibitors	
Benazepril (*Lotensin*) Benazepril (*generic)* Enalapril (*Vasotec*) Enalapril *(generic)* Lisinopril (*Prinivil*; *Zestril*) Lisinopril *(generic*) Ramipril (*Altace*) Ramipril *(generic)*	Captopril (*generic*) Enalapril oral susp (*Epaned*) Lisinopril oral susp *(Qbrelis)* Fosinopril (*generic*) Moexipril (*Univasc*) Moexipril *(generic)* Perindopril (*Aceon*) Perindopril *(generic)* Quinapril (*Accupril*) Quinapril *(generic*) Trandolapril (*Mavik*) Trandolapril *(generic)*
Angiotensin II Receptor Antagonists	
Losartan (*Cozaar*) Losartan (*generic)* Olmesartan (*Benicar*) Olmesartan *(generic*) Telmisartan (*Micardis*) Telmisartan (*generic)*	Azilsartan (*Edarbi*) Candesartan (*Atacand*) Candesartan *(generic)* Eprosartan (*Teveten*) Eprosartan *(generic*) Irbesartan (*Avapro*) Irbesartan (*generic)* Valsartan (*Diovan*) Valsartan *(generic)*
Direct Renin Inhibitors	
	Aliskiren (*Tekturna*)
Other Cardiovascular Combination	
	Sacubitril/Valsartan *(Entresto)*

Appendix 2: New Comparative Clinical Trials

A total of 327 citations were manually reviewed from the initial literature search. After further review, 326 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 1 trial is summarized in the table below. Full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>McMurray JV, etal[9]

DB, RCT, DD, MC</td>
<td>Enalapril 5 mg BID (low dose)
OR 10mg mg BID (high dose)
N = 2336

Vs

Aliskiren 300mg once daily
N = 2340

Vs

Aliskiren + Enalapril
N = 2340</td>
<td>HF with reduced ejection fraction defined as NYHA Class II to IV and EF ≤ 35% with BNP ≥ 150 pg/ml

Total N = 8835 patients</td>
<td>Primary composite outcome: death from CV causes or hospitalization for heart failure</td>
<td>
Table 1. Comparison of treatments for primary composite outcome: death from CV causes or first hospitalization for worsening HF
<table>
<tr><th>Treatment</th><th>Outcome (n)</th><th>Percent</th><th>Hazard Ratio for Primary Composite (95% CI)</th></tr>
<tr><td>Combination Therapy (Enalapril + Aliskiren)</td><td>Primary Composite (770)
Death from CV (512)
Hospitalization for HF (430)</td><td>32.9
21.9
18.4</td><td>Combo vs enalapril
0.93 (0.85 to 1.03) p = 0.17*</td></tr>
<tr><td>Enalapril</td><td>Primary Composite (808)
Death from CV (547)
Hospitalization for HF (452)</td><td>34.6
23.4
19.3</td><td></td></tr>
<tr><td>Aliskiren</td><td>Primary Composite (791)
Death from CV (562)
Hospitalization for HF (442)</td><td>33.8
24.0
18.9</td><td>Aliskiren vs enalapril
0.99 (0.9 to 1.1) p = 0.91*</td></tr>
<tr><td colspan="4">*Prespecified test for inferiority was not met</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations: BNP B-type natriuretic peptide = BNP, CI = confidence interval, CV = cardiovascular, DB = double blind, DD = double dummy, EF = ejection fraction, HF = heart failure, MC = multi center, NYHA = New York Heart Association, RCT = randomized clinical trial

Appendix 3: Abstract of Comparative Clinical Trials

Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure[13]

John J.V. McMurray, M.D., Henry Krum, M.B., B.S., Ph.D., William T. Abraham, M.D., Kenneth Dickstein, M.D., Ph.D., Lars V. Køber, M.D., D.M.Sc., Akshay S. Desai, M.D., M.P.H., Scott D. Solomon, M.D., Nicola Greenlaw, M.Sc., M. Atif Ali, B.A., Yanntong Chiang, Ph.D., Qing Shao, Ph.D., Georgia Tarnesby, M.B., B.Chir., and Barry M. Massie, M.D., for the ATMOSPHERE Committees Investigators†

N Engl J Med 2016; 374(16): 1521-1532

Background

Among patients with chronic heart failure, angiotensin-converting–enzyme (ACE) inhibitors reduce mortality and hospitalization, but the role of a renin inhibitor in such patients is unknown. We compared the ACE inhibitor enalapril with the renin inhibitor aliskiren (to test superiority or at least noninferiority) and with the combination of the two treatments (to test superiority) in patients with heart failure and a reduced ejection fraction.

Methods

After a single-blind run-in period, we assigned patients, in a double-blind fashion, to one of three groups: 2336 patients were assigned to receive enalapril at a dose of 5 or 10 mg twice daily, 2340 to receive aliskiren at a dose of 300 mg once daily, and 2340 to receive both treatments (combination therapy). The primary composite outcome was death from cardiovascular causes or hospitalization for heart failure.

Results

After a median follow-up of 36.6 months, the primary outcome occurred in 770 patients (32.9%) in the combination-therapy group and in 808 (34.6%) in the enalapril group (hazard ratio, 0.93; 95% confidence interval [CI], 0.85 to 1.03). The primary outcome occurred in 791 patients (33.8%) in the aliskiren group (hazard ratio vs. enalapril, 0.99; 95% CI, 0.90 to 1.10); the prespecified test for noninferiority was not met. There was a higher risk of hypotensive symptoms in the combination-therapy group than in the enalapril group (13.8% vs. 11.0%, P=0.005), as well as higher risks of an elevated serum creatinine level (4.1% vs. 2.7%, P=0.009) and an elevated potassium level (17.1% vs. 12.5%, P<0.001).

Conclusions

In patients with chronic heart failure, the addition of aliskiren to enalapril led to more adverse events without an increase in benefit. Noninferiority was not shown for aliskiren as compared with enalapril.

Appendix 4: Medline Search Strategy

[Example]

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2017

1. *Angiotensin-Converting Enzyme Inhibitors/ 23015*
2. *Angiotensin Receptor Antagonists/ or Angiotensin II Type 1 Receptor Blockers/ 13666*
3. *ramipril.mp. or Ramipril/ 1942*
4. *benazepril.mp. 556*
5. *Olmesartan Medoxomil/ or olmesartan.mp. 1208*
6. *Losartan/ 5379*
7. *Enalapril/ 2969*
8. *Lisinopril/ 1344*
9. *telmisartan.mp. 1761*
10. *quniapril.mp. 1*
11. *candesartan.mp. 2634*
12. *Captopril/ 3254*
13. *Valsartan/ 1913*
14. *azilsartan.mp. 109*
15. *eposartan.mp. 1*
16. *Fosinopril/ 310*
17. *irbesartan.mp. 1484*
18. *trandolapril.mp. 560*
19. *moexipril.mp. 75*
20. *Perindopril/ 1244*
21. *quinapril.mp. 541*
22. *aliskiren.mp. 990*
23. *sacubitril.mp. or Valsartan/ 1947*
24. *1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or "24".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 21907*
25. *limit 24 to (humans and yr="2015-current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 327*

Sacubitril/Valsartan (Entresto™)

Goal(s):
- Restrict use of sacubitril/valsartan in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:
- 60 days to 12 months

Requires PA:
- Sacubitril/valsartan (Entresto™)

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 continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Does the patient have stable New York Heart Association Class II or III heart failure with reduced ejection fraction less than 40% (LVEF <40%)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tolerated a minimum daily dose an ACE-inhibitor or ARB listed in Table 1 for at least 30 days?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by national and international heart failure guidelines.[1, 2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Approve for up to 60 days	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the patient currently taking sacubitril/valsartan at the target dose of 97/103 mg 2-times daily?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #2
2. What is the clinical reason the drug has not been titrated to the target dose of 97/103 mg 2-times daily?	Document rationale and approve for up to 60 days. Prior authorization required every 60 days until target dose achieved.	

Table 1. Minimum Daily Doses of ACE-inhibitors or ARBs Required.[1, 2]

ACE-inhibitor		Angiotensin-2 Receptor Blocker (ARB)	
Captopril	50 mg TID	Candesartan	32 mg QDay
Enalapril	10 mg BID	Losartan	150 mg QDay
Lisinopril	20 mg QDay	Valsartan	160 mg BID
Ramipril	5 mg BID		
Trandolapril	4 mg QDay		

Abbreviations: BID = twice daily; QDay = once daily; mg = milligrams; TID = three times daily.

Notes:
- Patients must achieve a minimum daily dose of one of the drugs listed for at least 30 days in order to improve chances of tolerability to the target maintenance dose of sacubitril/valsartan 97/103 mg 2-times daily.[3]
- Valsartan formulated in the target maintenance dose of sacubitril valsartan 97/103 mg 2-times daily is bioequivalent to valsartan 160 mg 2-times daily.[4]

- ACE-inhibitors and ARBs listed have demonstrated efficacy in heart failure with or without myocardial infarction.[1,2]
- Target daily doses of other ACE-inhibitors and ARBs for heart failure have not been established.[1,2]
- It is advised that patients previously on an ACE-inhibitor have a 36-hour washout period before initiation of sacubitril/valsartan to reduce risk of angioedema.[3,4]

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.
3. McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Eng J Med*. 2014;371:993-1004. doi:10.1056/NEJMoa1409077.
4. ENTRESTO (sacubitril and valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, July 2015.

P&T / DUR Review: *05/17(DM); 09/15*
Implementation: *10/1/15*

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 Literature Scan: Anaphylaxis Rescue Agents

Date of Review: May 2017

Date of Last Review: November 2014
Literature Search: 2/8/17-2/14/17

Current Status of PDL Class: All epinephrine auto-injectors (EAI) are on the PDL
See **Appendix 1**.

Conclusions:

- Three new guidelines on anaphylaxis management from the American Heart Association (AHA) and the Red Cross (RC), the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Pediatrics (AAP) have been published since the last review.[1–3] Guidelines recommend first aid responders administer an intramuscular (IM) dose of epinephrine, or assist a patient with their own device, if there is an anaphylactic reaction. The dose of epinephrine when using the auto-injectors should be 0.3 mg IM for adults and children greater than 30 kg and 0.15 mg IM for children 15-30 kg.
- There is insufficient comparative evidence between EAI products. There is insufficient evidence in subgroups populations.

Recommendations:

- No changes are recommended to the OHP PDL based on the review of current evidence. Review comparative drug costs in the executive session.

Previous Conclusions:

- There is insufficient evidence from randomized, double-blind, placebo-controlled clinical trials to define the benefits from administering epinephrine for anaphylaxis due to ethical concerns.
- There is moderate evidence from one systematic review that intramuscular injection is superior to subcutaneous route.
- There is insufficient evidence comparing the effectiveness of administering epinephrine via auto-injector versus other injectable formulations.
- Epinephrine is recommended as first-line initial therapy for anaphylaxis in both children and adults. In addition, the auto-injector is recommended as the preferred injectable formulation in the community.

Previous Recommendations:

- The Committee recommended adding “anaphylaxis rescue” as a drug class to the PMPDP under the Allergy/Cold section and to include epinephrine auto-injector products as preferred.
- After comparative costs in executive session, the Committee recommended making all auto-injector products preferred on the PMPDP.

Author: Sentena

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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:
No systematic reviews were identified.

New Guidelines:

American Heart Association and Red Cross First Aid Guidelines
The AHA and RC formed an International Liaison Committee on Resuscitation (ILCOR) First Aid Task Force to evaluate the literature related to first aid preparation and management. The Committee used Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate the evidence. Evidence related to first aid management is limited due to the difficulty of obtaining high quality data in emergency situations. The AHA/RC anaphylaxis recommendations are as follows:

- A first aid responder should administer epinephrine or assist a person with anaphylaxis with their own epinephrine if they are having a reaction.
- The recommended dose is epinephrine 0.3 mg IM for adults and children greater than 30 kg, 0.15 mg IM for children 15-30 kg or the dose prescribed by a physician.
- Providers of first aid should call 9-1-1 immediately when assisting a person with a severe allergic reaction or anaphylaxis.
- A second epinephrine dose should be given if there is not an adequate response to the first dose.

Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology
The EAACI provided guidance on the diagnosis and management of anaphylaxis in 2014.[2] Recommendations were based on 2 systematic reviews on the epidemiology and treatment of anaphylaxis as well as complementary anaphylaxis guidelines. The Appraisal of Guidelines for Research and Evaluation (AGREE II) tool was used for guideline development and recommendations were assigned a level and grade of evidence. IM adrenaline is recommended as first-line and there are no absolute contraindications to its use (based on descriptive studies or extrapolation from primary evidence). An IM injection in the thigh should be given at a dose of 0.01 ml/kg to a max dose of 0.5 ml. Patients weighing 7.5 –25 kg and using an auto-injector should receive 0.15 mg dose and patients weighing 25-30 kg should move up to the 0.3 mg dose.[2] Patients weighing 25 kg or more should also receive the 0.3 mg dose. Repeat doses can be given every 5 minutes if needed. An adrenaline infusion may be appropriate for patients not responding to IM adrenaline. Second-line interventions include removal of the trigger, administration of high-flow oxygen, intravenous (IV) fluid for cardiovascular instability and inhaled short-acting beta-2 agonists for patients with

bronchoconstriction. H1- and H2-antihistamines are considered third-line and have only demonstrated relief of cutaneous symptoms during anaphylaxis. Oral and IV glucocorticoids are an additional third-line treatment as a mechanism to prevent protracted anaphylaxis symptoms. Glucagon may be useful in patients, especially in those taking beta-blockers, with anaphylaxis who fail to respond to adrenaline.

American Pediatric Society: Clinical Guidance on First-Aid Management

The APS released a clinical report on the guidance for first-aid management of anaphylaxis.[3] Recommendations for the identification of pediatrics at risk of anaphylaxis and the appropriate use of EAI is discussed. Methodology of guideline development was based on clinical expertise but due to the paucity of evidence on anaphylaxis management the recommendations will be included. Epinephrine is recommended as the treatment of choice for anaphylaxis. Intramuscular administration given in the outer thigh at a dose of 0.01 mg/kg, up to 0.3 mg in pre-pubertal children and 0.5 mg in teenagers. EAI can be used to deliver the recommended dose of 0.15 mg for patients weighing 15 to 30 kg and 0.3 mg for patients over 30 kg. Repeated epinephrine doses can be given up to two additional times at intervals of 5 to 15 minutes if symptoms of anaphylaxis persist. Adverse events seen with epinephrine include transient pallor, tremor, anxiety and palpitations, similar to endogenous epinephrine.

New Formulations:

No new formulations were identified.

New FDA Safety Alerts:

In May of 2016 the FDA issued safety labeling changes for all EAI.[4–7] Reports of serious infections at in the injection site due to necrotizing fasciitis and myonecrosis caused by Clostridia have been identified. To minimize this risk, it is recommended that EAIs are not injected into the buttock. Reports of injection-related complications have also been reported in small children who are uncooperative during injections given in the thigh. Movement should be minimized when injecting to prevent lacerations, bent needles and embedded needles.

Safety labeling changes were updated for Adrenaline® 30 mL multi-dose vial, advising against ophthalmic use due to potential ophthalmic injury.[4] The multi-dose vial contains chlorobutanol which may be harmful to the cornea.

References:

1. Singletary EM, Charlton NP, Epstein JL, et al. Part 15: First Aid: 2015 American Heart Association and American Red Cross Guidelines Update for First Aid. *Circulation*. 2015;132(18 Suppl 2):S574-589. doi:10.1161/CIR.0000000000000269.

2. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69(8):1026-1045. doi:10.1111/all.12437.

3. Sicherer S, Simons E. Epinephrine for First-aid Management of Anaphylaxis. Pediatrics. 2017;139(3):e20164006. doi:10.1542/peds.2016-4006.

4. The Food and Drug Administration. Safety Information - Adrenalin (epinephrine injection, USP). Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505854.htm. Accessed February 9, 2017.

5. The Food and Drug Administration. Safety Information - Twinject, Adrenaclick & Epinehrine Injection USP Auto-Injector. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505917.htm. Accessed February 9, 2017.

6. The Food and Drug Administration. Safety Information - EpiPen and EpiPen Jr. (epinephrine injection) Auto-Injector. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505913.htm. Accessed February 9, 2017.

7. The Food and Drug Administration. Safety Information - AUVI-Q Autoinjector (epinephrine injection, USP). Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505855.htm. Accessed February 9, 2017.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
IM	AUTO INJCT	ADRENACLICK	EPINEPHRINE	Y
IM	AUTO INJCT	EPIPEN JR	EPINEPHRINE	Y
IM	AUTO INJCT	EPIPEN	EPINEPHRINE	Y
IM	AUTO INJCT	EPINEPHRINE	EPINEPHRINE	Y

Appendix 2: New Comparative Clinical Trials

A total of 48 citations were manually reviewed from the initial literature search. After further review, none of the citations were included because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to January Week 4 2017

Search Strategy:

#	Searches	Results
1	Epinephrine/	11993
2	Anaphylaxis/	7491
3	1 and 2	929
4	limit 3 to (english language and humans and yr="2014 -Current")	187
5	limit 4 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "review" or systematic reviews)	48

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 Literature Scan: Antianginals

Date of Review: May 2017

Date of Last Review: November 2014
Literature Search: 01/01/2014 – 04/2017

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

Conclusions:
- This class scan identified 2 systematic reviews from the Cochrane Collaboration[1,2], 1 new randomized controlled trial[3] and 1 new formulation.[4]
- There is no pivotal new evidence since the last review that does not support current first line treatment of angina with beta blockers or calcium channel blockers. Ranolazine and long-acting nitrates should be reserved for add-on therapy when a combination of 2 first line drugs cannot be used or as monotherapy when neither of the first-line drugs can be used. Short acting nitroglycerin should remain available for the immediate relief of angina in patients with stable ischemic heart disease.
- There is insufficient to very low quality evidence that perioperative prophylactic administration of nitrates does not significantly decrease the incidence of perioperative cardiac events or reduce all-cause mortality up to 30 days post operation. However, data remains limited and were not able to be combined for meta-analysis.
- There is low quality evidence that ranolazine as monotherapy compared to placebo does not reduce cardiovascular mortality (21/1317 vs. 20/1287; RR 1.03; 95% CI 0.56 to 1.88).
- There is moderate quality evidence from 3 trials, that add-on ranolazine reduced the frequency of angina episodes from 4.1 episodes per week to 0.66 lower per week (MD -0.66; 95% CI -0.97 to -0.35) compared to placebo, but also moderate quality evidence of an increase in the risk of non-serious adverse events (29% vs. 24%; RR 1.22; 95% CI 1.06 to 1.40; NNH 20).
- There is insufficient evidence that the sublingual powder formulation of nitroglycerin provides any clinical benefit over other formulations currently available.

Recommendations:
- Make sublingual powder nitroglycerin (GONITRO™) non-preferred on the PDL.
- No other review or research needed.
- Evaluate comparative costs in executive session.

Previous Conclusions:
- There is high quality evidence sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with stable ischemic heart disease.

Author: Megan Herink, PharmD, BCPS

- There is high quality evidence long-acting nitrates are recommended for relief of symptoms when first-line therapy (i.e., beta-blockers or calcium channel blockers) is contraindicated or causes unacceptable side effects. Long-acting nitrates may also be used in combination with beta-blockers for symptom relief when initial treatment with beta-blockers is unsuccessful.
- There is low quality evidence that ranolazine reduces weekly angina frequency compared to placebo (mean difference -0.687 episodes per week; 95% CI, -0.973 to -0.402).
- There is insufficient evidence comparing ranolazine to nitrates at reducing angina frequency.
- Available formulations for nitrate products differ in both onset and duration of action. There is insufficient evidence demonstrating clinical differences between formulations.
- Headache, dizziness and hypotension are common side effects associated with nitrate use. Nitrate tolerance is a limitation of continuous, around-the-clock use.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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:
Nitrates:
A Cochrane Systematic review was published in 2016 that assessed the effects of nitrates compared with other interventions or placebo in reducing cardiac risk in patients undergoing non-cardiac surgery.[5] A literature search through January 2016 identified 27 RCTs (n=8244) that were included in the analysis. The primary outcome was all-cause mortality up to 30 days post operation and secondary outcomes included perioperative incidence of cardiac morbidity (acute myocardial infarction, heart failure, arrhythmia, etc.) There were 12 different comparisons of 3 different nitrates, including nitroglycerin, isosorbide dinitrate and nicorandil. Nicorandil is not available in the U.S. and will not be discussed further. Studies included surgical procedures mostly that were low to moderate risk for perioperative cardiac complications and almost all of the participants were in the hospital for elective non-cardiac surgery with a wide range of baseline cardiovascular risk. [5] Due to a variety of morbidity outcomes and differences in reporting, there were limited results available for meta-analysis. The overall methodological quality of the studies was fair to low.

Only one study (n=60) evaluated differences in all-cause mortality up to 30 days post operation and found very low quality evidence of no difference between nitroglycerin and no treatment (0 vs. 1; RR 0.33; 95% CI 0.01 to 7.87). [5] There was also very low quality evidence of no difference between nitroglycerin in

placebo in all-cause mortality (1 vs. 0; RR 2.81; 95% CI 0.12 to 63.83; 2 studies; n=89). [5] There were no comparisons that resulted in a significant difference in secondary outcomes, including angina, acute myocardial infarction, acute heart failure, cardiac arrhythmia or cardia arrest. Overall, data did not suggest that nitroglycerin or isosorbide dinitrate is associated with improvements in mortality or cardiac complications in patients undergoing non-cardiac surgery. However, data is insufficient to draw strong conclusions or see differences between nitrates and placebo.[5]

Ranolazine

A second Cochrane Systematic Review evaluated ranolazine for stable angina pectoris.[2] RCTs comparing ranolazine monotherapy or ranolazine add-on therapy versus placebo or other anti-anginals in people with stable angina were included from a literature search through February 2016. Seventeen RCTs (n=9975) were included. Most studies were either fully or partly funded by drug companies and most were performed in North America, Europe and Australia. Two studies provided data for 62% of participants and were from 2007 and 2016. [2] Seven studies evaluated ranolazine as add-on therapy to either beta blockers, calcium channel blockers or both. Overall, risk of bias was assessed as unclear and there were limited data to inform most planned comparisons on outcomes of interest. There were insufficient evidence to compare ranolazine to other anti-anginals. [2]

There were no studies evaluating add-on ranolazine compared to placebo on cardiovascular or non-cardiovascular mortality (the primary outcomes). There was only one study that reported data on cardiovascular mortality for ranolazine as monotherapy compared to placebo. The authors concluded an uncertain effect from low quality evidence (21/1317 vs. 20/1287; RR 1.03; 95% CI 0.56 to 1.88). [2] There was moderate quality evidence from 3 trials, that add-on ranolazine 1000 mg twice daily reduced the frequency of angina episodes from 4.1 episodes per week to 0.66 lower per week (MD -0.66; 95% CI -0.97 to -0.35) compared to placebo, but also moderate quality evidence of an increase in the risk of non-serious adverse events (29% vs. 24%; RR 1.22; 95% CI 1.06 to 1.40). [2] There was low quality evidence of no difference in all-cause mortality (RR 0.83; 95% CI 0.26 to 2.71), moderate quality evidence of no difference in quality of life and low quality evidence of similar risk of non-fatal acute myocardial infarction (RR 0.40; 95% CI 0.08 to 2.07) [2]. Quality of evidence was downgraded due to insufficient number of events. For comparisons of ranolazine as monotherapy versus placebo, there was an very low to low quality evidence of no difference in cardiovascular mortality (16 per 1000 in both groups), all-cause mortality (49 per 1000 in both groups), quality of life (mean quality of life in ranolazine group was 0.28 points higher on a scale from 0-100), non-fatal acute myocardial infarction (7.5% vs. 85%; RR 0.88; 95% CI 0.69 to 1.12), and frequency of angina episodes (mean angina episode frequency of 0.08 higher per week in ranolazine group from baseline of 2.08 episodes per week). There was very low quality evidence from 3 studies of an increased risk for non-serious adverse events (RR 1.50; 95% CI 1.12 to 2.00). [2] There was insufficient data on serious adverse events. The authors concluded that there was evidence of clinical benefit from the use of ranolazine as add-on therapy only by reducing the frequency of angina episodes; however, there was also evidence of clinical harm for the use of ranolazine as either monotherapy or add-on therapy by increasing the risk of non-serious adverse events. Additionally, studies varied in the dosage and type of formulation used, the presence of comorbidities, and duration of follow-up (1 week to more than 2 years). [2]

New Guidelines:

A 2014 focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease was published from the American College of Cardiology and American Heart Association (ACC/AHA).[6] The intent of the focused update is to include pivotal new evidence that may effect changes in current recommendation. However, new recommendations based on this new evidence were made only for diagnostic testing, chelation therapy, and revascularization. Since no new data or recommendations were considered for treatment with anti-anginals, this updated guideline will not be presented further.

New Formulations:
In June, 2016 the FDA approved a sublingual powder formulation of nitroglycerin (GONITRO™) for prevention or acute relief of an attack of angina pectoris.[4] It is the first powder formulation available in the US. Currently, sublingual and spray formulations are available. Approval was based on a comparative bioavailability study comparing nitroglycerin powder to the nitrolingual pump spray product.[7] The recommended dosage is one or two 400 mcg packets at the onset of an attack to be placed under the tongue. [4]

In one unpublished, randomized, double-blind, crossover trial in 51 patients with exertional angina pectoris, doses of nitroglycerin powder from 200-1600 mcg were shown to cause a dose-related increase in exercise tolerance, time to onset of angina, and time to ST-segment depression, compared to placebo. [4] Information could only be found from the package insert. There are no clinical studies available comparing this product to other available formulations and no evidence it improves clinical outcomes. Adverse reactions that occurred at a frequency greater than 2% or more than placebo included headache, dizziness and paresthesia. [4]

New FDA Safety Alerts:
None

Fourth Quarter 2016 Utilization:
Utilization of antianginals in the Oregon Medicaid fee for service (FFS) population from 10/1/16 through 12/31/16 consisted primarily for preferred products (98%) with only 31 paid claims for a non-preferred agent. There was only 1 paid claim for ranolazine in this quarter. Most of the unpaid claims were for patients enrolled in a CCO. Of the non-preferred medications, most of the claims were for isosorbide mononitrate ER.

References:

1. Zhao N, Xu J, Singh B, Yu X, Wu T, Huang Y. Nitrates for the prevention of cardiac morbidity and mortality in patients undergoing non-cardiac surgery. *Cochrane Database Syst Rev.* 2016(8).
2. Salazar CA, Basilio Flores JE, Veramendi Espinoza LE, Mejia Dolores JW, Rey Rodriguez DE, Loza Munarriz C. Ranolazine for stable angina pectoris. *Cochrane Database Syst Rev.* 2017;2:Cd011747.
3. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2015;373(24):2314-2324.
4. GONITRO (nitroglycerin) sublingual powder Prescribing Information. 06/2016. Espero pharmaceuticals.
5. Zhao N, Xu J, Singh B, Yu X, Wu T, Huang Y. Nitrates for the prevention of cardiac morbidity and mortality in patients undergoing non-cardiac surgery. *Cochrane Database Syst Rev.* 2016(8):CD010726.
6. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology.* 2014;64(18):1929-1949.
7. Ferreiro-Iglesias R, Barreiro-de Acosta M, Otero Santiago M, et al. Fecal Calprotectin as Predictor of Relapse in Patients With Inflammatory Bowel Disease Under Maintenance Infliximab Therapy. *J Clin Gastroenterol.* 2016;50(2):147-151.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE ER	DILATRATE-SR	ISOSORBIDE DINITRATE	Y
ORAL	CAPSULE ER	NITROGLYCERIN	NITROGLYCERIN	Y
ORAL	TABLET	ISORDIL	ISOSORBIDE DINITRATE	Y
ORAL	TABLET	ISORDIL TITRADOSE	ISOSORBIDE DINITRATE	Y
ORAL	TABLET	ISOSORBIDE DINITRATE	ISOSORBIDE DINITRATE	Y
ORAL	TABLET	ISOSORBIDE MONONITRATE	ISOSORBIDE MONONITRATE	Y
SUBLINGUAL	TAB SUBL	NITROSTAT	NITROGLYCERIN	Y
TRANSDERM	PATCH TD24	MINITRAN	NITROGLYCERIN	Y
TRANSDERM	PATCH TD24	NITRO-DUR	NITROGLYCERIN	Y
TRANSDERM	PATCH TD24	NITROGLYCERIN PATCH	NITROGLYCERIN	Y
ORAL	TAB ER 12H	RANEXA	RANOLAZINE	N
ORAL	TAB ER 24H	ISOSORBIDE MONONITRATE ER	ISOSORBIDE MONONITRATE	N
ORAL	TABLET	BIDIL	ISOSORB DINIT/HYDRALAZINE HCL	N
ORAL	TABLET ER	ISOSORBIDE DINITRATE	ISOSORBIDE DINITRATE	N
SUBLINGUAL	TAB SUBL	ISOSORBIDE DINITRATE	ISOSORBIDE DINITRATE	N
TRANSDERM	OINT. (G)	NITRO-BID	NITROGLYCERIN	N
TRANSLING	SPRAY	NITROGLYCERIN	NITROGLYCERIN	N
TRANSLING	SPRAY	NITROLINGUAL	NITROGLYCERIN	N
TRANSLING	SPRAY	NITROMIST	NITROGLYCERIN	N

Appendix 2: New Comparative Clinical Trials

A total of 65 citations were manually reviewed from the initial literature search. After further review, 64 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Redfield, et al.[3] RCT, DB, PC	Isosorbide Mononitrate 120 mg vs. placebo	Heart Failure with Preserved Ejection Fraction (n=110)	Daily activity level measured by the average daily accelerometer units	<u>Daily activity level:</u> Isosorbide: 8922 units Placebo: 9303 units Treatment difference -381 (-780 to 17); p=0.06 There was also no significant difference in the six-minute walk test or quality of life.

Abbreviations: DB = double-blind; PC = placebo-controlled; RCT = randomized clinical trial

1. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2015 Dec 10;373(24):2314-24. doi: 10.1056/NEJMoa1510774. Epub 2015 Nov 8.

BACKGROUND:

Nitrates are commonly prescribed to enhance activity tolerance in patients with heart failure and a preserved ejection fraction. We compared the effect of isosorbide mononitrate or placebo on daily activity in such patients.

METHODS:

In this multicenter, double-blind, crossover study, 110 patients with heart failure and a preserved ejection fraction were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate (from 30 mg to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. The primary end point was the daily activity level, quantified as the average daily accelerometer units during the 120-mg phase, as assessed by patient-worn accelerometers. Secondary end points included hours of activity per day during the 120-mg phase, daily accelerometer units during all three dose regimens, quality-of-life scores, 6-minute walk distance, and levels of N-terminal pro-brain natriuretic peptide (NT-proBNP).

RESULTS:

In the group receiving the 120-mg dose of isosorbide mononitrate, as compared with the placebo group, there was a nonsignificant trend toward lower daily activity (-381 accelerometer units; 95% confidence interval [CI], -780 to 17; P=0.06) and a significant decrease in hours of activity per day (-0.30 hours; 95% CI, -0.55 to -0.05; P=0.02). During all dose regimens, activity in the isosorbide mononitrate group was lower than that in the placebo group (-439 accelerometer units; 95% CI, -792 to -86; P=0.02). Activity levels decreased progressively and significantly with increased doses of isosorbide mononitrate (but not placebo). There were no significant between-group differences in the 6-minute walk distance, quality-of-life scores, or NT-proBNP levels.

CONCLUSIONS:

Patients with heart failure and a preserved ejection fraction who received isosorbide mononitrate were less active and did not have better quality of life or submaximal exercise capacity than did patients who received placebo. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT02053493.).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 1 2017
1 exp isosorbide dinitrate.mp. or Isosorbide Dinitrate/ 1532
2 nitroglycerin.mp. or Nitroglycerin/ 5983
3 isosorbide mononitrate.mp. 230
4 ranolazine.mp. or Ranolazine/ 681
5 1 or 2 or 3 or 4 7990
6 limit 5 to (English language and humans and yr="2015-Current" and 9clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or systematic reviews)) 65

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 Literature Scan: Otic Antibiotics

Date of Review: May 2016

Date of Last Review: May 2015
Literature Search: February 24, 2017

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

Conclusions:

- Since the last review, one systematic review and 2 randomized controlled trials (RCTs) have been published which provide updated evidence for the treatment of otitis media in children with tympanostomy tubes.[1,2] Two new formulations (ciprofloxacin intratympanic injection and ototopical ciprofloxacin/fluocinolone) have also been recently FDA approved for the treatment of otitis media in patients with tympanostomy tubes. One systematic review provides updated evidence on the use of otic antibiotics for otitis externa.[3]
- There is insufficient evidence to determine differences in safety or efficacy of ototopical antibiotics or antibiotic/corticosteroid combinations for the treatment of acute otitis externa.
- There is no new comparative evidence evaluating safety or efficacy between ototopical quinolone antibiotics and aminoglycoside antibiotics for the treatment of otitis externa or otitis media in patients with tympanostomy tubes.
- In patients with acute otitis media and tympanostomy tubes, there is no new comparative evidence evaluating differences between antibiotic/corticosteroid combinations. Similarly, there is no new comparative evidence evaluating differences between ototopical antibiotic formulations.
- Evidence comparing antibiotics alone to antibiotic/corticosteroid combinations for treatment of otitis media in patients with tympanostomy tubes is mixed. Evidence from 2 randomized controlled trials (RCTs) demonstrated that compared to ototopical ciprofloxacin, ototopical ciprofloxacin/fluocinolone improves time to resolution of otorrhea by approximately 2-3 days. However, there is no evidence which compares ciprofloxacin/fluocinolone to current medications which are FDA approved for otitis media (including ofloxacin solution, ciprofloxacin/dexamethasone suspension, and ciprofloxacin intratympanic injection). Evidence from a recent systematic review included 2 other RCTs which compared ofloxacin to ciprofloxacin/dexamethasone.[1] There was low quality evidence that treatment with ciprofloxacin/dexamethasone improved resolution of their otorrhea within 2 weeks compared to ofloxacin.[1] However, data at 2-4 weeks failed to achieve statistical significance.[1] Evidence was significantly limited by poor study quality and high risk of publication bias.[1]

Recommendations:

- There is no new comparative evidence that changes the previous conclusions. No further review or research needed at this time. Continue to have at least one preferred product for treatment of acute otitis media in patients with tympanostomy tubes and at least one ototopical aminoglycoside antibiotic as an option for otitis externa.
- Review comparative drug costs in the executive session.

Previous Conclusions:

- There is insufficient evidence that one ototopical antibiotic or antibiotic/corticosteroid combination has superior clinical efficacy or comparative effectiveness over another product for clinical resolution of acute otitis externa.
- There is insufficient evidence that either ofloxacin or ciprofloxacin/dexamethasone, the only ototopical drugs with FDA indications for treating otitis media specifically in patients with tympanostomy tubes, is more efficacious or safer than the other for this indication. Since these patients have received multiple systemic antibiotics for acute otitis media prior to getting tympanostomy tube placement, higher rates of antibiotic resistance may be noted in these patients and the use of a broad spectrum quinolone antibiotic is appropriate. There is insufficient evidence for all other ototopical antibiotics or antibiotic/corticosteroid combinations for this indication.
- There is low quality evidence that ototopical quinolone antibiotics or quinolone/corticosteroid combinations may be safer than ototopical aminoglycoside antibiotics in patients with tympanostomy tubes due to potential risk for adverse effects from systemic absorption of the aminoglycoside in the inner ear.

Previous Recommendations:

- Keep either ofloxacin or ciprofloxacin/dexamethasone as a preferred product for treatment of acute otitis media in patients with tympanostomy tubes.
- Keep at least one ototopical aminoglycoside antibiotic as an option for otitis externa.
- Maintain finafloxacin as non-preferred due to its limited indication for otitis externa only and lack of comparative evidence, unless it is cost-effective.
- Review comparative drug costs in the executive session.

Methods:

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

A 2015 systematic review examined updated evidence supporting efficacy and safety of interventions for the treatment of otitis externa.[3] A prior review published in 2007 had determined that otic antibiotic formulations (with or without corticosteroids) were likely to be beneficial for the treatment of otitis externa but there was insufficient evidence to determine differences between formulations.[3] Systematic reviews and randomized controlled trials published through October 2013 were included in the review if they had at least 20 participants, follow-up rate of greater than 80%, and a duration of at least 1 month.[3] This duration was chosen because patients with otitis externa often have a high rate of recurrent or chronic infection. Pharmacological interventions included oral antibiotics, topical acetic acid, topical aluminium acetate, topical antibacterials, topical antifungals, topical corticosteroids, and combinations of these

agents.[3] Only one trial examining the comparative efficacy of antibiotic or combination antibiotic/corticosteroid otic formulations met inclusion criteria with at least 1 month of follow-up.[3] This trial included patients with moderate to severe chronic or acute otitis externa (n=38, including 55 ears) who were randomized to triamcinolone-neomycin or hydrocortisone-neomycin-polymixin B for 10 days.[3] Overall, patients randomized to triamcinolone-neomycin had a higher cure rate at 1 month than patients who received hydrocortisone-neomycin-polymixin B (79% vs. 48%; p<0.01).[3] Data was limited by small sample size, lack of reported outcome definitions, and potential for bias due to unclear randomization methods and unbalanced baseline characteristics. Overall, evidence insufficient to determine differences between formulations.[3] Other randomized controlled trials included in this systematic review compared otic antibiotic formulations to topical acetic acid/corticosteroid, acetic acid alone, and aluminum acetate formulations. There was insufficient evidence to determine differences between aluminum acetate and otic antibiotic formulations.[3] One RCT (n=213) provided low quality evidence of no difference in efficacy between dexamethasone/neomycin/polymyxin drops and triamcinolone/acetic acid drops.[3] Upon comparison to acetic acid alone, dexamethasone/neomycin/polymyxin drops for 21 days reduced rate of recurrence at day 42 (45% vs 21%, OR 3.12, 95% CI 1.37 to 7.09; p=0.0068; moderate quality evidence).[3] Authors conclude that based on updated evidence, otic antibiotics are likely to be effective for treatment of otitis externa, but there is insufficient evidence to determine differences in efficacy or safety between otic antibiotics.[3]

A Cochrane systematic review examined the efficacy and safety of interventions for the treatment of post-procedure otorrhea in children with recent placement of tympanostomy tubes.[1] Interventions included antibiotic eardrops, combined antibiotic/corticosteroid eardrops, corticosteroid eardrops, and oral antibiotics.[1] Of the nine studies included in the review, only 3 RCTs examined comparative efficacy between antibiotic eardrops and antibiotic/corticosteroid eardrops.[1] Two studies (n=590) examined comparative efficacy of ofloxacin versus ciprofloxacin/dexamethasone eardrops, and one study (n=331) compared ciprofloxacin to ciprofloxacin/fluocinolone acetonide. Overall evidence was rated as low or insufficient and was significantly limited by poor study quality and risk for publication bias.[1] The review identified multiple completed studies comparing ototopical antibiotics and antibiotic/corticosteroid combinations whose results remain unpublished.[1] There was low quality evidence that compared to ofloxacin, children treated with combination ciprofloxacin/dexamethasone were more likely to have resolution of their otorrhea within 2 weeks (ARR 15%; RR 1.76, 95% CI 1.33 to 2.31, I^2=0%).[1] In addition, the duration of ear discharge was shorter with ciprofloxacin/dexamethasone eardrops compared to ofloxacin (average difference of 1 to 2 days).[1] However, resolution of otorrhea at 2 to 4 weeks failed to achieve statistical significance (RR 1.09, 95% CI 0.90 to 1.31; I^2= 84%).[1] Comparative safety was examined in 3 studies including 1023 children randomized to combination antibiotic/corticosteroid or antibiotic eardrops alone.[1] Differences in rate of adverse effects was not significantly different between groups (low quality evidence; RR 0.86, 95% CI 0.55 to 1.32; I^2=0%), and serious complications related to middle ear infection, hearing, or tube blockage were reported infrequently.[1]

New Guidelines:
No recent guidelines were identified which discuss use of otic antibiotics for treatment of otitis externa or otitis media in patients with tympanostomy tubes.

New Formulations:
Otiprio® (ciprofloxacin) otic suspension approved December 2015 for otitis media with effusion following tympanostomy tube placement.[4] The formulation exists as a liquid at room temperature and a gel upon exposure to body temperature.[4] It was approved on the basis of 2 phase 3 randomized, double-blinded, placebo-controlled clinical trials in 532 pediatric patients (mean age 1.5 years) with otitis media with effusion undergoing tympanostomy tube placement. Ciprofloxaxin was given as a single 0.1 mL (6 mg) intratympanic injection during surgery following suctioning of middle ear effusion.[4] The primary outcome evaluated treatment failure within 15 days (defined as presence of otorrhea, antibacterial use post-surgery, or loss-to-follow-up).[4] In both studies, more patients treated with sham injection experienced treatment failure compared to patients treated with ciprofloxacin (ARR 24%, 95% CI 12 to 36%, p<0.001 and ARR 20%,

95% CI 8 to 32%, p<0.001).[4] Most frequent adverse reactions occurring in more than 3% of the population and more commonly than placebo were nasopharyngitis, irritability, and rhinorrhea.[4]

Otovel® (ciprofloxacin 0.3%/fluocinolone 0.025%) otic solution approved in April 2016 for pediatric patients (age 6 months and older) with otitis media and tympanostomy tubes.[5] It is dosed as one vial (0.25 mL) instilled into the ear canal twice daily for 7 days.[5] It was approved on the basis of 2 phase 3 RCTs in 662 pediatric patients.[5] Compared to ciprofloxacin alone, the time to otorrhea cessation was improved by a mean difference of 3.9 days and 1.9 days in each study.[5] In both studies, the proportion of patients with resolution of otorrhea at 22 days was significantly improved with combination ciprofloxacin/fluocinolone (79% and 78%) compared to ciprofloxacin alone (67% and 69%) or fluocinolone alone (48% and 43%).[5] Adverse reactions were infrequent and similar across all groups.[5] The most commonly reported adverse reaction occurring in more than 2% of the population was otorrhea.[5]

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

References:

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. *Cochrane Database Syst Rev.* 2016;11:CD011684.
2. Spektor Z, Pumarola F, Ismail K, et al. Efficacy and Safety of Ciprofloxacin Plus Fluocinolone in Otitis Media With Tympanostomy Tubes in Pediatric Patients: A Randomized Clinical Trial. *JAMA otolaryngology-- head & neck surgery.* 2016.
3. Hajioff D MS. Otitis externa. Systematic review 510. BMJ Clinical Evidence. http://clinicalevidence.bmj.com/x/systematic-review/0510/overview.html. Accessed February 24, 2017.
4. Otiprio (ciprofloxacin) otic suspension [package insert]. San Diego, CA: Otonomy, Inc; December 2015.
5. Otovel (ciprofloxacin and fluocinolone acetonide) otic solution [package insert]. Atlanta, GA: Arbor Pharmaceuticals, LLC; April 2016.

Appendix 1: Current Preferred Drug List

Formulation	Brand	Generic	PDL
VIAL	OTIPRIO	CIPROFLOXACIN	N
DROPS SUSP	CIPRODEX	CIPROFLOXACIN HCL/DEXAMETH	N
VIAL	OTOVEL	CIPROFLOXACIN HCL/FLUOCINOLONE	N
DROPS SUSP	CIPRO HC	CIPROFLOXACIN/HYDROCORTISONE	N
SOLUTION	NEOMYCIN-POLYMYXIN-HYDROCORT	NEOMYCIN/POLYMYXIN B SULF/HC	N
DROPS SUSP	NEOMYCIN-POLYMYXIN-HC	NEOMYCIN/POLYMYXIN B SULF/HC	Y
DROPS SUSP	COLY-MYCIN S	NEOMYCIN SU/COLIST/HC/THONZON	Y
DROPS	OFLOXACIN	OFLOXACIN	Y

Appendix 2: New Comparative Clinical Trials

A total of 43 citations were manually reviewed from the initial literature search. After further review, 42 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or intervention (e.g., otic antibiotics which are not approved in the United States). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Pooled Results
Spektor Z, et al.[2] 2 identical, phase 3, MC, DB, RCTs N=662	1. Ciprofloxacin 0.3% and fluocinolone 0.025% solution 2. Ciprofloxacin 0.3% solution 3. Fluocinolone 0.025% solution Otic solutions were given twice daily for 7 days	Children with acute otitis media with tympanostomy tubes and otorrhea for >3 weeks	Time to cessation of otorrhea	1. 4.23 days (95% CI 3.65 to 4.94) 2. 6.95 days (95% CI 5.66 to 8.20) 3. NE (95% CI 16.67-NE) Mean difference 2.72 days (95% CI not reported), p<0.001

Abbreviations: DB = double-blind; MC = multicenter; NE = not estimable; RCT = randomized clinical trial

Appendix 3: Abstracts of Comparative Clinical Trials

Spektor Z, Pumarola F, Ismail K, et al. Efficacy and Safety of Ciprofloxacin Plus Fluocinolone in Otitis Media With Tympanostomy Tubes in Pediatric Patients: A Randomized Clinical Trial. *JAMA otolaryngology-- head & neck surgery.* 2016.

Importance: Acute otitis media with tympanostomy tubes (AOMT) in children commonly presents with otorrhea and negatively affects their daily activities. Objective: To evaluate the efficacy and safety of topical ciprofloxacin, 0.3%, plus fluocinolone acetonide, 0.025%, otic solution relative to ciprofloxacin, 0.3%, otic solution alone and fluocinolone acetonide, 0.025%, otic solution alone in the treatment of AOMT in children. Design, Setting, and Participants: Two twin multicenter, randomized, double-blind clinical trials with identical designs were conducted from June 24, 2011, through June 23, 2014, at ear, nose, and throat pediatric practices, general practices, hospitals, and clinical research centers. The study population comprised 662 children (331 in each trial) with AOMT in at least 1 ear who presented with moderate or severe purulent otorrhea for 3 weeks or less. Data analyses were performed on an intention-to-treat basis. Interventions: Patients were randomly assigned to receive ciprofloxacin plus fluocinolone, ciprofloxacin alone, or fluocinolone alone twice daily for 7 days and were evaluated on days 1 (baseline), 3 to 5 (undergoing therapy), 8 to 10 (end of therapy), and 18 to 22 (test of cure). Main Outcomes and Measures: The primary efficacy measure was time to cessation of otorrhea. The principal secondary end point was sustained microbiological cure, defined as eradication or presumed eradication at end-of-therapy and test-of-cure visits.
Results: A total of 662 children participating in the 2 studies were randomized to receive ciprofloxacin plus fluocinolone (n = 223), ciprofloxacin alone (n = 221), or fluocinolone alone (n = 218). The median age was 2.5 years (range, 0.6-12.7 years). The median time to cessation of otorrhea was 4.23 days (95% CI, 3.65-4.95 days) in patients receiving ciprofloxacin plus fluocinolone compared with 6.95 days (95% CI, 5.66-8.20 days) in those receiving ciprofloxacin and not estimable findings in those receiving fluocinolone alone (P < .001). The clinical cure rate at the test-of-cure visit was 80.6% in the ciprofloxacin plus fluocinolone group, 67.4% in the ciprofloxacin group (difference, 13.2%; 95% CI, 5.0%-21.4%; P = .002), and 47.6% in the fluocinolone group (difference, 33.0%; 95% CI, 24.0%-42.0%; P < .001). The sustained microbiological cure rate was 79.7% in the ciprofloxacin plus fluocinolone group vs 67.7% in the ciprofloxacin group (difference, 12.0%; 95% CI, 0.8%-23.0%; P = .04) and 37.6% in the fluocinolone group (difference, 42.1%; 95% CI, 29.3%-54.8%; P < .001). Only 7 (3.1%) of the patients receiving

ciprofloxacin plus fluocinolone, 8 (3.6%) of the patients receiving ciprofloxacin, and 10 (4.7%) of the patients receiving fluocinolone presented with adverse events related to study medication.
Conclusions and Relevance: The combination of ciprofloxacin plus fluocinolone is more effective than treatment with ciprofloxacin or fluocinolone alone for AOMT, and it is safe and well tolerated in children. Trial Registration: clinicaltrials.gov Identifiers: NCT01395966 and NCT01404611.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

1	exp Colistin/	3073
2	exp Neomycin/	8980
3	thonzonium.mp.	4
4	exp Polymyxin B/	2916
5	exp ciprofloxacin/	11767
6	exp ofloxacin/	6365
7	exp Anti-Bacterial Agents/	630268
8	exp Otitis/	26950
9	exp Labyrinthitis/	663
10	exp Otitis Media, Suppurative/	2178
11	8 or 9 or 10	26950
12	1 or 2 or 3 or 4 or 5 or 6 or 7	630366
13	11 and 12	5611
14	limit 13 to yr="2015 -Current"	162
15	limit 14 to (english language and humans)	132
16	limit 15 to (clinical study or clinical trial, all or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	35

Trade Name (generic)

Intrarosa (prasterone) | Indication not funded

Indications

- Prasterone is indicated for treatment of moderate to severe postmenopausal dyspareunia

Dosage

- One 6.5 mg suppository inserted vaginally once daily at bedtime

Background

- Prasterone (or dehydroepiandrosterone, DHEA) is an inactive endogenous steroid that is transformed to active androgens and estrogens. Its mechanism of action in postmenopausal women with vulvar and vaginal atrophy is still being elucidated.
- Postmenopausal decline of estrogen and DHEA leads to hormone deficiency-related signs and symptoms in the vagina, including vulvovaginal atrophy and dyspareunia.

Efficacy

FDA approval of intravaginal prasterone 6.5 mg once daily was based on two twelve-week, randomized, double-blind, placebo-controlled, phase 3 clinical trials in postmenopausal, women who self-identified as having moderate to severe dyspareunia as the most bothersome symptom of vulvovaginal atrophy and met criteria for vulvovaginal atrophy (i.e. superficial cells ≤5% on vaginal smear and a vaginal pH >5). Women included were predominantly white and 40 to 80 years of age. Co-primary endpoints in these trials are listed in the **Table**. Symptom improvement was evaluated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Overall, prasterone improved symptoms by less than half a point compared to placebo. The clinical significance of a 0.35 to 0.4 point change has not been determined. Statistically significant differences were also documented for the percentage of parabasal cells, percentage of superficial cells, and vaginal pH, though the clinical significance of these differences remains unclear.

Table. Least square mean differences between prasterone and placebo for the co-primary outcomes for each trial

Co-primary endpoints	Labrie et al (2016) N=325 prasterone; 152 placebo	Archer et al (2015) N=81 prasterone; 77 placebo	P-value
Moderate to severe dyspareunia, as assessed by patients using a vaginal atrophy symptoms questionnaire	–0.35	–0.40	P=0.0002 and 0.0132, respectively
Percentage parabasal cells	–27.7	–45.8	P<0.0001 for both
Percentage superficial cells	8.44	4.7	P<0.0001 for both
Vaginal pH (units)	–0.66	–0.83	P<0.0001 for both

Safety

- **Contraindications:** Undiagnosed abnormal genital bleeding
- **Warnings and precautions:** History of breast cancer
- **Common adverse reactions:** Vaginal discharge and abnormal Pap smear

Evidence Gaps/Limitations

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

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Intrarosa (prasterone) [prescribing information]. Quebec City, Canada: Endoceutics Inc; November 2016.
2. Archer DF, Labrie F, Bouchard C, et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). *Menopause (New York, N.Y.)*. 2015;22(9):950-963.
3. Labrie F, Archer DF, Koltun W, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause (New York, N.Y.)*. 2016;23(3):243-256.

Abbreviated Drug Review

Trade Name (generic)	
EUCRISA (crisaborole) topical ointment	Indication not funded

Indications

- Topical treatment of mild to moderate atopic dermatitis (AD) in patients ≥2 years of age.

Dosage

- 2% (20 mg/gram) topical ointment
- Thin layer applied topically twice daily to affected areas (not for ophthalmic, oral, or intravaginal use)

Background

- Crisaborole is a new molecular entity that inhibits phosphodiesterase 4, resulting in increased intracellular cAMP levels. Its mechanism of action is not well defined.
- Other drug treatments for AD include topical corticosteroids and topical calcineurin inhibitors.

Efficacy

- In two identically designed, multicenter, double-blind, phase 3 studies (AD-301 and AD-302), 1522 United States patients 2 to 79 years old with mild to moderate AD were randomly assigned 2:1 to crisaborole or vehicle-control applied twice daily for 28 days.
- Baseline characteristics:
  - 86.3% were age 2 to 17 years, 56% were male, 61% were White, 28% were Black
  - Treatable body surface area was 5% to 95% (mean 18.3%)
  - 38.5% had an Investigator's Static Global Assessment (ISGA) score of 2 (indicating mild severity) and 61.5% had a score of 3 (indicating moderate severity)
- Primary end point was the proportion of patients with an ISGA score at day 29 of clear (0) or almost clear (1) skin with at least a 2-grade improvement from baseline:
  - Trial AD-301: 32.8% of crisaborole group (n=503) vs. 25.4% of vehicle group (n=256), p=0.038; NNT = 14
  - Trial AD-302: 31.4% of crisaborole group (n=513) vs. 18% of vehicle group (n=250), p<0.001; NNT = 8

Safety

- **Adverse reactions:** Application site pain (3%), contact urticarial (<1%)
- **Contraindications:** Known hypersensitivity
- **Warnings and precautions**: Hypersensitivity reactions

Evidence Gaps/Limitations

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

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Eucrisa (crisaborole) [prescribing information]. Palo Alto, CA: Anacor Pharmaceuticals, Inc; December 2016.
2. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *Journal of the American Academy of Dermatology*. 2016;75(3):494-503.

Trade Name (generic)	
Ameluz (aminolevulinic acid hydrochloride) gel, 10%	Indication not funded

Indications

- Aminolevulinic acid (AA) gel plus BF-RhodoLED (BF-R) lamp is indicated for lesion- and field-directed treatment of mild-to-moderate actinic keratosis (AK) on the face and scalp.

Dosage

- 10% gel applied topically, 1 mm thick by a health care provider to a single or field of AK lesions (not to exceed an area of 20 cm^2 and 2 grams of gel [one tube] at any one time), followed by occlusion for 3 hours, and then by red light photodynamic therapy (PDT) with the BF-R lamp; retreated in 3 months if not resolved

Background

- AA has been prescribed as a 20% topical solution (Levulan Kerastick) plus BLU-U Blue Light PDT Illuminator since 1999 for minimally to moderately thick AK of the face or scalp.
- AA is a prodrug metabolized to protoporphyrin IX (PpIX), a photoactive compound that accumulates in the skin. Upon photoactivation of PpIX, reactive oxygen species are formed which destroy cells within the AK lesion.
- AK lesions are caused by exposure to ultraviolet light and are more common in patients with fair skin (Fitzpatrick skin types I-III). In a small percentage of patients, lesions may progress to squamous cell carcinoma.

Efficacy

According to labeling, three randomized, multicenter, double-blind, vehicle-controlled clinical trials evaluated the efficacy of AA 10% gel plus PDT with a red light lamp. Patients (n=212 total) had 4 to 8 mild to moderate AK lesions on the face and/or bald scalp, ranged from 49 to 87 years old (mean 71 years), and most had Fitzpatrick skin types I, II, or III (scale I to VI). About 86% were male, and all were Caucasian. The treatment regimen included lesion preparation with alcohol, AA application, occlusion for 3 hours, removal of residual gel, then illumination with red light source (about 630 nm peak; 37 J/cm^2 dose) in Trials 1 and 2 or BF-R (635 nm; 37 J/cm^2) in Trial 3. Multiple light sources were used in Trial 1 and 2, and the published subgroup analyses by light source did not include comparative statistical analyses or sufficient data to confirm data presented in labeling. Patients without complete clearance of lesions after 12 weeks received a second course of identical therapy (42% of patients). Results for the primary endpoint (patients with complete clearance at 12 weeks after the last PDT) for AA versus vehicle, respectively, were:

Trial 1: 85% (n=106/125) vs. 13% (n=5/39); NNT=2 **Trial 2:** 84% (n=27/32) vs. 13% (n=2/16); NNT=2 **Trial 3:** 91% (n=50/55) vs. 22% (n=7/32); NNT=2

Safety

- **Contraindications:** Porphyria, photodermatoses, hypersensitivity to porphyrins or any AA gel component (including soybean phosphatidylcholine)
- **Warnings and precautions:** Risk of eye injury with BF-R lamp (wear eye protection); photosensitivity (protect treated areas from sunlight and prolonged, intense light for 48 hours); photoreaction with other photosensitizing agents; bleeding in patients with coagulation disorders; ophthalmic and mucous membrane reactions (avoid gel contact in these areas)
- **Common adverse reactions:** Application site reactions (e.g. erythema, pain/burning, irritation, edema, pruritus, exfoliation, scab, or induration), chills, headache, or skin exfoliation
- **Specific populations:** Safety in patients less than 18 years of age is not established
- **Toxicology:** May cause genotoxic effects

Evidence Gaps/Limitations

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

Recommendation

Restrict use to OHP-funded conditions through Prior Authorization for physician administered and pharmacy claims.

References

1. Ameluz (aminolevulinic acid hydrochloride) [prescribing information]. Wakefield, MA: Biofrontera Inc; May 2016
2. Dirschka T, Radny P, Dominicus R, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. *Br J of Dermatol*. 2012;166(1):137-146.
3. Reinhold U, Dirschka T, Ostendorf R, et al. A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) vs. placebo in the field-directed treatment of mild-to-moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED(®) lamp. *Br J Dermatol*. 2016;175(4):696-705.
4. Szeimies RM, Radny P, Sebastian M et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. *Br J Dermatol.* 2010; 163:386-394.

Abbreviated Drug Review

Trade Name (generic)

Levulan Kerastick (aminolevulinic acid HCl) for Topical Solution, 20% | Indication not funded

Indications

- Aminolevulinic acid (AA) topical solution plus BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratosis (AK) of the face or scalp.

Dosage

- Apply 20% topical solution twice to AK lesions on face or scalp (not both simultaneously), and then, 14 to 18 hours later, illuminate lesions with the BLU-U illuminator; unresolved lesions may be retreated in 8 weeks. Must be applied by qualified clinician.

Background

- AA 20% topical solution plus BLU-U illumination has been prescribed in the U.S. since 1999 for minimally to moderately thick AK of the face or scalp.
- AA is a prodrug metabolized to protoporphyrin IX (PpIX), a photoactive compound that accumulates in the skin. Reactive oxygen species, which develop when oxygen is in the presence of photoactivated PpIX, destroy cells.
- Off-label uses of AA have included the treatment of basal cell carcinoma, Bowen's disease, and anogenital warts.

Efficacy

Two identically designed, randomized, multicenter, investigator-blinded, vehicle-controlled, phase 3 clinical trials (ALA-018, ALA-019) evaluated the efficacy of AA 20% gel plus BLU-U illumination vs vehicle plus BLU-U. The studies randomized (3:1) subjects (n=243 total) who had 4 to 15 Grade 1 (slightly palpable) or Grade 2 (moderately thick) AK lesions on the face or on the scalp. Subjects ranged from 34 to 89 years old (mean 66 years), and most subjects had fair skin with Fitzpatrick skin types I, II, or III (scale I to VI). About 85% of subjects were male, and all were Caucasian. The treatment regimen included two applications of AA then illumination with BLU-U (1000 seconds for a nominal exposure of 10 J/cm^2) 14 to 18 hours later. The primary endpoint was percent of patients with complete clearance of lesions 8 weeks after treatment. Results were analyzed with intent-to-treat analysis with missing data imputed using last observation carried forward.

	ALA-018				ALA-019			
Lesion location	AA (n=88)	Vehicle (n=29)	Risk difference (95% CI), p-value	NNT	AA (n=93)	Vehicle (n=33)	Risk difference (95% CI), p-value	NNT
Face	68% (n=72)	10% (n=21)	58% (43 to 76%), p<0.001	2	70% (n=67)	21% (n=20)	49% (28 to 71%) p<0.01	2
Scalp	69% (n=16)	25% (n=8)	44% (6 to 81%), p=0.099	NS	46% (n=26)	0% (n=13)	46% (27 to 65%), p<0.01	3

Safety

Common adverse reactions: Erythema, edema, stinging/burning, scaling/crusting, hypo/hyperpigmentation, itching, erosion, wheal/flare, vesiculation, ulceration, bleeding/ hemorrhage, pain, pustules, tenderness, scabbing, dysesthesia, skin disorder not otherwise specified
Contraindications: Patients with cutaneous photosensitivity at wavelengths of 400 to 450 nm, porphyria or porphyrins allergies, sensitivity to Levulan components
Warnings and precautions: Protect treated lesions from bright indoor light and sunlight until BLU-U treatment or ≥40 hours after AA application; sunscreen does not protect against photosensitivity reactions; perform AA application by a qualified clinician; do not apply AA to eyes, mucous membranes, or perilesional skin; applying AA under occlusion may cause excessive irritation; AA has not been tested in patients who are <18 years old or who have coagulation defects; concomitant use of other known photosensitizing agents (e.g., thiazide diuretics, sulfonylureas) might increase the photosensitivity reaction of AA-treated AK; use AA cautiously in nursing mothers; use AA in pregnant women only if clearly needed

Evidence Gaps/Limitations

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

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Levulan (aminolevulinic acid hydrochloride) [prescribing information]. Wilmington, MA: DUSA Pharmaceuticals; March 2010.
2. Center for Drug Evaluation and Research. Medical Review: Application number 20-965. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed March 2, 2017.

Trade Name (generic)

Rhofade (oxymetazoline) cream 1% for topical use

Indications

Oxymetazoline topical therapy is indicated for persistent facial erythema associated with rosacea in adults

Dosage

A pea-sized amount applied once daily to the entire face in a thin layer, avoiding the eyes and lips

Background

Oxymetazoline is an alpha1A adrenoceptor agonist and acts as a vasoconstrictor

Efficacy

The FDA approved once-daily oxymetazoline cream (1%) based on two identical, double-blind, vehicle-controlled clinical trials that randomized (1:1) predominantly female (79%) and Caucasian (90%) subjects (n=885) who were aged ≥18 years. Clinicians and subjects graded disease severity using a 5-point clinician erythema assessment (CEA) scale and a 5-point subject self-assessment (SSA) scale, respectively, on which subjects scored either "moderate" or "severe" on both scales. CEA and SSA were measured at 3, 6, 9, and 12 hours post-dose on Days 1, 15, and 29 of the 29-day study. Following is the primary endpoint data (proportions of subjects with ≥2-grade reduction in erythema from baseline on both the CEA and SSA measured at hours 3, 6, 9, and 12 on Day 29) for both trials:

	Trial 1		Trial 2	
Time-point on Day 29	**Oxymetazoline (n=222)**	**Vehicle (n=218)**	**Oxymetazoline (n=224)**	**Vehicle (n=221)**
Hour 3	12%	6%	14%	7%
Hour 6	16%	8%	13%	5%
Hour 9	18%	6%	16%	9%
Hour 12	15%	6%	12%	6%

Safety

Common adverse reactions: Application site dermatitis, pruritus, erythema, and pain; worsening inflammatory lesions of rosacea

Warnings and precautions: Use cautiously in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, Sjögren's syndrome, severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, or uncontrolled hypertension or hypotension; may affect blood pressure and increase risk of angle closure glaucoma in patients with narrow-angle glaucoma; advise patients who have signs and symptoms of acute narrow-angle glaucoma or potentiation of vascular insufficiency and patients who have worsening cardiovascular disease, orthostatic hypotension, or uncontrolled hypertension or hypotension to seek medical care; use cautiously drugs such as beta-blockers, anti-hypertensives, and cardiac glycosides, as well as alpha1 adrenergic receptor antagonists and MAO inhibitors.

Avoid use: Pediatric patients <18 years of age

Evidence Gaps/Limitations

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

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Rhofade (oxymetazoline cream) [Prescribing Information]. Irvine, CA; Allergan, January 2017.

Drug Product

Belviq (lorcaserin)	Indication not funded

Indications

- Indicated as an adjunct to reduced-calorie diet and increased physical activity in adults who are either obese (BMI ≥30 kg/m2) or overweight (BMI ≥27 kg/m2) with at least one weight-related comorbidity (e.g., type 2 diabetes mellitus [DM], dyslipidemia, or hypertension).

Dosage

- 10 mg oral tablet twice daily
- 20 mg film-coated, extended-release tablet once daily
- Discontinuation of lorcaserin is recommended at week 12 if ≥5% of body weight has not been lost.

Background

- Although lorcaserin's exact mechanism of action is unknown, this first-in-class agent is believed to curb appetite by selectively activating serotonin 2C receptors on neurons in the hypothalamus which are involved in appetite control.

Efficacy

FDA approval of lorcaserin 10 mg twice daily was based on three randomized (1:1), double-blind, placebo-controlled trials: one in adults with inadequately controlled DM (BLOOM-DM) and two in adults without DM (BLOOM and BLOSSOM). All subjects received diet and exercise counseling on the first treatment day and every 4 weeks thereafter. BLOOM and BLOSSOM enrolled subjects who were 18 to 65 years old and either overweight (BMI 27-29.9 kg/m2) with at least one weight-related comorbid condition or obese (BMI 30-45 kg/m2). Most subjects were Caucasian (67%) and approximately 80% were women. BLOOM-DM enrolled subjects who were 21 to 65 years old, had a BMI ≥27 kg/m2, HbA1c of 7-10%, and were taking metformin or a sulfonylurea. Most were Caucasian (61%) and 54% were women. The primary outcome for all of the studies was weight loss at 1 year as assessed by the difference between the lorcaserin groups versus placebo for the following parameters (modified intent-to-treat and last observation carried forward):

Difference from placebo	BLOOM and BLOSSOM combined (n=3098 lorcaserin; 3038 placebo)	BLOOM-DM (n=251 lorcaserin; 248 placebo)
Percent of patients losing ≥5% body weight	24.5 (95% CI 22.2 to 26.8, p<0.001)	21.3 (95% CI 13.8 to 28.9, p<0.001)
Percent of patients losing ≥10% body weight	13.8 (95% CI 12 to 15.5, p<0.001)	11.9 (95% CI 6.7 to 17.1, p<0.001)
Adjusted mean change in weight (kg)	–3.3 (95% CI –3.6 to –2.9, p<0.001)	–3.1 (95% CI –4 to –2.2, p<0.001)

Attrition rate: 50% BLOOM, 45% BLOSSOM, and 36% BLOOM-DM

Safety

Common adverse reactions (>5%): Headache, dizziness, fatigue, nausea, dry mouth, and constipation for non-DM patients. Hypoglycemia, headache, back pain, cough, and fatigue for DM patients.
Contraindications: Pregnancy or prior hypersensitivity to lorcaserin
Warnings and precautions: May increase risk of serotonin syndrome or neuroleptic malignant syndrome-like reactions, valvular heart disease, psychiatric disorders, hypoglycemia, bradycardia, hematological changes, prolactin elevation, and pulmonary hypertension. Monitoring for these adverse effects is recommended. Use with caution in patients with heart failure, bradycardia, history of heart block greater than first degree, predisposition to priapism, moderate renal failure, or severe hepatic impairment. Caution patients about impaired cognitive function and priapism. Use with extreme caution with drugs affecting serotonergic neurotransmitter systems and with CYP2D6 substrates.
Avoid use in: Patients with severe renal impairment and pediatric patients.
Carcinogenesis: Increased incidence of mammary fibroadenoma was observed in female rats at doses comparable to the human FDA-approved dose.

Evidence Gaps/Limitations

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

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Belviq (lorcaserin) [Prescribing Information]. Zofingen, Switzerland: Arena Pharmaceuticals GmbH. December 2014.
2. FDA Center for Drug Evaluation and Research Summary Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022529Orig1s000SumR.pdf. Accessed February 5, 2017.